CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206038Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 206038
Product Name: ORKAMBI (lumacaftor-ivacaftor)

PMR/PMC Description: Conduct a 24 month oral carcinogenicity study with lumacaftor in rats

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	
Final Report Submission:	07/31/2015
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

   Approximately one half of cystic fibrosis patients are homozygous for the *F508del CFTR* mutation and there is unmet medical need for this population. The lumacaftor-ivacaftor combination received Breakthrough Designation for this patient population on 12/5/2012. The sponsor proposed, and the division agreed, that the two-year carcinogenicity study in rats could be completed post-approval (see meeting minutes dated 3/20/2013 and communication dated 8/5/2013). The remaining nonclinical program was complete at the time of NDA submission, including the 6-month carcinogenicity study in transgenic mice. The carcinogenicity studies involve patient safety.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   This ongoing two-year study in rats is designed to assess the potential tumorigenicity of lumacaftor (b) (4) .

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The agreed upon study is a GLP-compliant two-year carcinogenicity study in rats. The design of the study received CDER Executive Carcinogenicity Assessment Committee (ECAC) concurrence via the Special Protocol Assessment process.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

SALLY M SEYMOUR
06/26/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 11, 2015
To:	Badrul Chowdhury, M.D. Director **Division of Pulmonary, Allergy and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, MSN, FNP-BC, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Matthew Falter. Pharm.D., R.Ph. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ORAKAMBI (lumacaftor/ivacaftor)
Dosage Form and Route:	Tablets for oral use
Application Type/Number:	NDA 206038
Applicant:	Vertex Pharmaceuticals Incorporated

1 INTRODUCTION

On November 5, 2014, Vertex Pharmaceutricals Inc., submitted for the Agency's review a New Drug Application for Orakambi (lumacaftor/ivacaftor). The proposed indication for ORAKAMBI Orakambi (lumacaftor/ivacaftor) tablets for oral use is for the treatment of cystic fibrosis (CF) in patients 12 years and older who are homozygous for the F450del mutation in the CFTR gene.

Fast Track designation was granted to lumacaftor by the FDA on January 17, 2008. Lumacaftor in combination with ivacaftor was granted Breakthrough Therapy designation on December 7 2012. Lumacaftor was granted Orphan Drug Designation on March 2, 2010. The combination of lumacaftor and ivacaftor was granted Orphan Drug Designation and Fast Track Designation status on June 30, 2014, based on the significant unmet medical need for more effective treatment of patients with CF.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on November 19, 2014, and November, 25, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Orakambi (lumacaftor/ivacaftor) tablets for oral use.

2 MATERIAL REVIEWED

- Draft Orakambi (lumacaftor/ivacaftor) PPI received on November 5, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 5, 2015.
- Draft Orakambi (lumacaftor/ivacaftor) Prescribing Information (PI) received on November 5, 2014, and amended on March 18, 2015, and received by DMPP and OPDP on June 5, 2015.
- Approved KALYDECO (ivacaftor) oral tablets comparator labeling dated March 4, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
06/11/2015

MATTHEW J FALTER
06/11/2015

MELISSA I HULETT
06/11/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **June 10, 2015**

To: **Leila Hann**
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: **Matthew Falter, Pharm.D.**
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: **Kathleen Klemm, Pharm.D., RAC**
Group Leader, OPDP

Subject: **OPDP Labeling Consult Response**
NDA # 206038
ORKAMBI™ (lumacaftor/ivacaftor) tablets, for oral use

In response to DPARP's, November 25, 2014, consult request, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and Carton/Container labeling for ORKAMBI™ (lumacaftor/ivacaftor) tablets, for oral use (Orkambi).

OPDP has reviewed the proposed PI. Our comments on the proposed PI are based on the proposed draft-marked up labeling titled "206038 Orkambi uspi 060515 clean.docx", which was sent via e-mail from DPARP to OPDP on April 5, 2015. OPDP comments on the proposed PI are provided directly in the marked-up document attached (see below).

In addition, we have the following general comment regarding the proposed PI:

- We note the following phrases used throughout the proposed PI (underlined emphasis added):

(b) (4)

We reference the pharmacology and toxicology review by Dr. Andrew Goodwin submitted into DARRTS on June 4, 2015.

OPDP is concerned, from a promotional perspective, that (b) (4)

(b) (4)

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For these reasons, OPDP recommends that (b) (4) not be included in the proposed PI for Orkambi.

OPDP has reviewed the proposed Carton and Container Labeling submitted by the applicant and available in the EDR at:

- \\cdsesub1\evsprod\nda206038\0002\m1\us\orkambi-us-blister-draft.pdf
- \\cdsesub1\evsprod\nda206038\0002\m1\us\orkambi-us-blister-holder-draft.pdf
- \\cdsesub1\evsprod\nda206038\0002\m1\us\orkambi-us-inner-carton-draft.pdf
- \\cdsesub1\evsprod\nda206038\0002\m1\us\orkambi-us-outer-carton-draft.pdf

OPDP does not have any comments on the proposed Carton and Container labels at this time.

OPDP's review and comments on the proposed PPI was conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be provided under separate cover and submitted into DARRTS at a later date.

Thank you for the opportunity to comment on the proposed labeling. If you have any questions regarding this review, please contact me at matthew.falter@fda.hhs.gov or at 6-2287.

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/s/

MATTHEW J FALTER
06/10/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 28, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 206038
Product Name and Strength:	Orkambi (Lumacaftor and Ivacaftor) Tablets, 200 mg/125 mg
Product Type:	Multi-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Vertex Pharmaceuticals Incorporated
Submission Date:	November 5, 2014
OSE RCM #:	2014-2321
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Associate Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, and prescribing information, for Orkambi for risk of medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). DPARP requested this as part of their evaluation for NDA 206038.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Ivacaftor is currently marketed as Kalydeco; however, Lumacaftor is not currently marketed. This NDA was granted the Fast Track Status, Orphan Drug Status, and Breakthrough Designation Status.

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors.

DMEPA finds the proposed container label and carton labeling acceptable. However, the prescribing information can be improved to decrease possible confusion.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information can be clarified to mitigate confusion.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 RECOMMENDATIONS FOR THE REVIEW DIVISION

A. Full Prescribing Information- Dosage and Administration

1. Consider revising the Dosage and Administration section from "Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours (b) (4) with fat containing food..." to read: "Adults and pediatric patients age 12 years and older: two tablets taken orally every 12 hours with fat containing food…." As currently presented the (b) (4) may lead to confusion in determining the correct dose.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Orkambi that Vertex Pharmaceuticals submitted on November 5, 2014.

Table 2. Relevant Product Information for Orkambi	
Initial Approval Date	N/A
Active Ingredient	Lumacaftor and Ivacaftor
Indication	Treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg/125 mg
Dose and Frequency	Two tablets every 12 hours
How Supplied	Pink, oval shaped tablets, printed with "2V125" in black ink on one side and plain on the other, and is packaged as follows: 112–count tablet box containing a 4 week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip)
Storage	Store at 20 25°C (68 77°F); excursions permitted to 15 30°C (59 86°F)

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/s/

LISSA C OWENS
05/28/2015

LUBNA A MERCHANT
05/28/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 25, 2015

TO: Leila Hann, Regulatory Project Manager
Robert Lim, M.D., Medical Officer
Anthony Durmowicz, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206038

APPLICANT: (b) (4)

DRUG: lumacaftor-ivacaftor (Orkambi™)

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review

INDICATION: Treatment of patients with cystic fibrosis (CF) who are homozygous for *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

CONSULTATION REQUEST DATE:	January 2, 2015
INSPECTION SUMMARY GOAL DATE (original):	March 25, 2015
INSPECTION SUMMARY GOAL DATE (revised):	April 6, 2015
DIVISION ACTION GOAL DATE	May 25, 2015
PDUFA DATE:	July 5, 2015

I. BACKGROUND:
The sponsor proposes that the combination treatment of lumacaftor and ivacaftor for cystic fibrosis in patients homozygous for the *F508del-CFTR* mutation leads to increased epithelial cell chloride transport, exceeding the benefit of each drug agent alone. The confirmatory diagnosis of cystic fibrosis includes (1) a sweat chloride value greater than 60 mmol/L by quantitative pilocarpine iontophoresis or two documented cystic fibrosis-causing mutations, and (2) chronic sinus-pulmonary disease, gastrointestinal or nutritional abnormalities.

Two adequate and well-controlled clinical trials (VX12-809-103 and VX12-809-104) were submitted in support of the applicant's NDA.

Study VX12-809-103
Study VX12-809-103 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. The primary study objective was to evaluate the efficacy of lumacaftor in combination with ivacaftor at Week 24 in subjects with cystic fibrosis (CF) who are homozygous for the *F508del* mutation on the *CF transmembrane conductance regulator (CFTR)* gene. Patients were randomized into one of the following three treatment arms: (1) Treatment Arm A: 600 mg lumacaftor once daily (qd) + 250 mg ivacaftor every 12 hours (q12h); (2) Treatment Arm B: 400 mg lumacaftor q12h + 250 mg ivacaftor q12h or (3) Treatment Arm C: lumacaftor placebo q12h + ivacaftor placebo q12h. The primary study efficacy endpoint was the absolute change in percent predicted forced expiratory volume in 1 second (FEV1) from baseline at Week 24.

Protocol VX12-809-104
Study VX12-809-104 was also a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. The primary study objective was to evaluate the efficacy of lumacaftor in combination with ivacaftor at Week 24 in subjects with cystic fibrosis (CF)

who are homozygous for the *F508del* mutation on the *CF transmembrane conductance regulator (CFTR)* gene. The study period and the 1:1:1 randomization treatment arm methodologies were similar to VX12-809-103. The primary study efficacy endpoint was also the absolute change in percent predicted forced expiratory volume in 1 second (FEV1) from baseline at Week 24.

The three sites that were selected for audit had a large number of enrolled subjects or large treatment effects.

II. RESULTS:

Name of CI Location	**Study Site/Protocol/Number of Subjects Enrolled (n)**	**Inspection Date**	**Classification***
Cori Daines, M.D. Division of Pulmonology, Allergy and Immunology Department of Pediatrics University of Arizona Medical Center 1501 N. Campbell Ave. Tucson, AZ 85724	Site #091 Protocol VX12-809-103 Subjects=12	January 26-29, 2015	Preliminary: NAI
Karen Sharrock McCoy, M.D. Nationwide Children's Hospital 700 Children's Drive Columbus, OH 43205	Site #006 Protocol VX12-809-104 Subjects=22	February 13-27, 2015	Preliminary: VAI
Michael William Konstan, M.D. Rainbow Babies and Children's Hospital 11100 Euclid Avenue Cleveland, OH 44106	Site #009 Protocol VX12-809-104 Subjects=22	February 2-13, 2015	VAI
Sponsor: Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210	Protocols VX12-809-103 and VX12-809-104	February 11-17, 2015	NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Cori Daines, M.D, Protocol VX12-809-103/Site #091
Tuczon, AZ

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from January 26 to 29, 2015.

A total of 16 subjects were screened, 12 subjects were enrolled and randomized. Twelve subjects completed the study. An audit of 12 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Karen Sharrock McCoy, M.D., Protocol VX12-809-104/Site #006
Columbus, OH

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from February 13 to 27, 2015. A total of 24 subjects were screened, 22 subjects were enrolled, randomized and completed the study. An audit of 22 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the investigational plan. Specifically,

Subject 04-006-012 was hospitalized and administered prednisone greater than 10 mg PO daily while on the study medication for the following times: (a) 40 mg on (b) (6) at (b) (6) hours, (b) 30 mg on (b) (6) at (b) (6) hours, (c) 30 mg on (b) (6) at (b) (6) hours, (d) 30 mg on (b) (6) at (b) (6) hours, (e) 30 mg on (b) (6) at (b) (6) hours, (f) 30 mg on (b) (6) at (b) (6) hours, and (g) 20 mg on (b) (6) at (b) (6) hours.

Dr. McCoy responded adequately to the Form FDA 483 on March 11, 2015. In her response, Dr. McCoy stated that prednisone (doses greater than 10 mg daily) was added to the prohibited medication list on June 10, 2003. The prohibited medication list had been revised three times during the period of March 21 to June 4, 2013. The June 10, 2013 list was the fourth revision and was communicated to the site by e-mail, not protocol amendment or administrative letter. She believes that subject safety was not compromised, since this actually decreased drug exposure due to increased CYP3A ivacaftor-lumacaftor metabolism.

c. Assessment of data integrity:
Despite the above isolated violation, data submitted by this clinical site appear acceptable in support of this specific indication.

3. Michael W. Konstan, M.D., Protocol VX12-809-104/Site #009
Cleveland, OH

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from February 2 to 13, 2015. A total of 23 subjects were screened, 22 subjects were enrolled and randomized. Twenty-one subjects completed the study. An audit of 22 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the investigational plan. Specifically:

(1) While Subject 04-009-04 was hospitalized, he received a study-prohibited medication (two doses of voriconazole).
(2) Two SAEs were not reported to sponsor within 24 hours, related to unplanned hospitalizations for the following patients:
   a. Subject 04-009-04 was admitted on (b) (6) This SAE was reported to the sponsor on (b) (6)
   b. Subject 04-009-20 was admitted on (b) (6) This SAE was reported to the sponsor on (b) (6)

OSI Comment: These observations do not have an impact on data integrity.

Dr. Konstan responded adequately to the Form FDA 483 on March 4, 2015.

c. Assessment of data integrity:
Despite the above isolated regulatory deficiencies that were not considered critical, data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR
4. Vertex Pharmaceuticals Incorporated
Boston, MA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from February 11-17, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
The sponsor generally maintained adequate oversight of the clinical trial. For the most part, monitoring of the investigator sites was adequate. There was no evidence of under-reporting of adverse events. Stringent monitoring of eight compliant sites was undertaken due to past history of non-compliance.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:
The sponsor monitoring of sites appeared to be reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two adequate and well-controlled clinical trials (VX12-809-103 and VX12-809-104) were submitted in support of the applicant's NDA. Three domestic sites (Dr. Cori Daines for Study 103, Dr. Karen McCoy for Study 104, and Dr. Michael Konstan for Study 104) were selected for audit. The Sponsor (Vertex) was also inspected for this NME application.

The preliminary classification for Dr. Daines is No Action Indicated (NAI). The preliminary classification of Dr. McCoy is Voluntary Action Indicated (VAI). The final regulatory classification for Dr. Konstan is Voluntary Action Indicated. The final regulatory classification of the sponsor audit is No Action Indicated.

Note: *The inspectional observations noted above for Drs. Daines and McCoy are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and/or review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.*

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/s/

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03/26/2015

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03/26/2015

KASSA AYALEW
03/26/2015

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 206038
Brand Name	ORKAMBI™
Generic Name	Lumacaftor/Ivacaftor
Sponsor	Vertex Pharmaceuticals Incorporated
Indication	Treatment of cystic fibrosis
Dosage Form	Oral tablet (200 mg lumacaftor and 125 mg ivacaftor in a fixed dose combination tablet)
Drug Class	CFTR trafficking enhancer
Therapeutic Dosing Regimen	Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose) with fat containing food **For moderate hepatic impairment:** two tablets in the morning and 1 tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) **For severe hepatic impairment:** Maximum dose of one tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	No maximum tolerated dose was established in humans
Submission Number and Date	SDN 003, 10 December 2014
Review Division	DPARP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study was conducted in 2 parts (Parts A and B). Part B was initiated once the supratherapeutic dose had been selected from Part A. No significant QTc prolongation effect of Lumacaftor (LUM) and Ivacaftor (IVA) combination at the therapeutic (LUM 600 mg qd/IVA 250 mg q12h) and supratherapeutic (LUM 1000 mg qd/IVA 450 q12h) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between LUM 600 mg qd/IVA 250 mg q12h and placebo, and between LUM 1000 mg qd/IVA 450 q12h and placebo were below 10 ms, the threshold for

regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

Part A was a sequential, double-blind, randomized, placebo-controlled, multiple-dose escalation study, 30 subjects received lumacaftor 600, 1000, and 1200 mg daily (qd).

Part B was a parallel, double-blind, randomized, placebo- and active-controlled, multiple-dose, single-center ECG study, 170 subjects received LUM 600 mg qd/IVA 250 mg q12h, LUM 1000 mg qd/IVA 450 q12h, moxifloxacin and placebo. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for LUM 600 mg qd/IVA 250 mg q12h and LUM 1000 mg qd/IVA 450 q12h, and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
LUM 600 mg qd/IVA 250 mg q12h	12	-2.1	(-5.6, 1.5)
LUM 1000 mg qd/IVA 450 q12h	12	1.1	(-3.1, 5.3)
Moxifloxacin 400 mg*	3	9.4	(6.7, 12.1)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 5.7 ms.

The supratherapeutic dose (1000 mg Lumacaftor *qd* + 450 mg Ivacaftor *q12h*) produces lumacaftor mean C_{max} value marginally higher than the mean C_{max} for the therapeutic dose (600 mg Lumacaftor *qd* + 250 mg Ivacaftor *q12h*) tested in this TQT study (41.1 vs. 35.9 μg/mL). The proposed dose in the label for the general patient population is 400 mg Lumacaftor *q12h* + 250 mg Ivacaftor *q12h.* Thus, the lumacaftor concentrations achieved by the supratherapeutic dose would be above that achieved by the dose proposed in the label.

Since lumacaftor is partly eliminated via CYP3A metabolism, the inhibitory effect of strong CYP3A inhibitor may represent a high clinical exposure scenario. However, in a DDI study, the co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Ivacaftor has already been studied in a thorough QT study and did not show a clinically relevant effect on the QTc interval.

Moreover, since lumacaftor is eliminated by hepatic routes (metabolism and secretion) hepatic impairment may also represent a high clinical exposure scenario. Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child Pugh Class B) had approximately 30% higher C_{max} compared with healthy subjects matched for demographics. But the proposed label suggested a

reduced dose of 2 tablets in the morning and 1 tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) for these patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child Pugh Class A) on PK of lumacaftor given in combination with ivacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Studies have not been conducted in patients with severe hepatic impairment (Child Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. The proposed label suggested to use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg /ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment. Thus, the supratherapeutic dose tested in this TQT study generally covers the concentrations of lumacaftor expected in high clinical exposure scenario with dosing adjustements proposed in the label.

2 PROPOSED LABEL

12.2 PHARMACODYNAMICS

(b) (4)

The effect of multiple doses of lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h on QTc interval was evaluated in a randomized, placebo- and active controlled (400 mg moxifloxacin), parallel, thorough QT study in 168 healthy subjects. No meaningful changes in QTc interval were observed with either lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h dose groups.

2.1 QT-IRT RECOMMENDATIONS

The proposed labeling is reasonable. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Lumacaftor is being developed to treat cystic fibrosis. It compensates for a lost phenylalanine in the cystic fibrosis transmembrane conductance regulator (CFTR), permitting its trafficking.

3.2 MARKET APPROVAL STATUS

Lumacaftor is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

No effect was seen in a hERG assay at 5 μM. No effect was seen on the ECG in dogs.

3.4 PREVIOUS CLINICAL EXPERIENCE

Several hundred subjects have been exposed. Cardiovascular adverse events have not been prominent.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of lumacaftor's and ivacaftor's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 79521. The sponsor submitted the study report VX12-809-008 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Placebo- and Active-Controlled, Double-Blind, Parallel, Electrocardiogram Study to Evaluate the Effect of Lumacaftor in Combination With Ivacaftor on the QT/QTc Interval in Healthy Subjects

4.2.2 Protocol Number

VX12-809-008

4.2.3 Study Dates

Study initiation: 07 June 2013

Study completion: 11 March 2014

4.2.4 Objectives

Primary Objectives:

PartA: to evaluate the safety and tolerability of multiple ascending doses of lumacaftor administered for 7 days in healthy subjects

PartB: to evaluate the effects of a therapeutic and a supratherapeutic dose of lumacaftor in combination with ivacaftor administered for 7 days on the QT/QTc interval in healthy subjects

Secondary Objectives:

PartA: To evaluate the pharmacokinetics (PK) of lumacaftor and its metabolite, M28 (M28-lumacaftor), following multiple ascending doses of lumacaftor administered for 7 days in healthy subjects

PartB

- To evaluate assay sensitivity (i.e., to evaluate the effect of a positive control, a single, oral, 400-mg dose of AVELOX® [moxifloxacin] administered on Day 14, on the QT/QTc interval in healthy subjects)
- To assess the effects of a therapeutic dose and a supratherapeutic dose of lumacaftor in combination with ivacaftor on non-QT interval electrocardiogram (ECG) parameters (heart rate [HR], RR, PR, and QRS intervals) in healthy subjects

- To determine the lumacaftor, M28-lumacaftor, ivacaftor, and ivacaftor major metabolites, M1 and M6 (M1-ivacaftor and M6-ivacaftor) plasma concentration-effect relationship for the QT/QTc interval and the magnitude of the relationship, if any exist
- To evaluate the PK of lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor at therapeutic and supratherapeutic doses of lumacaftor in combination with ivacaftor in healthy subjects
- To evaluate the safety and tolerability of therapeutic and supratherapeutic systemic exposure to lumacaftor in combination with ivacaftor in healthy subjects

4.2.5 Study Description

4.2.5.1 Design

This study was conducted in 2 parts (Parts A and B). Part B was initiated once the supratherapeutic dose had been selected from Part A.

Part A was a sequential, double-blind, randomized, placebo-controlled, multiple-dose escalation, single-center study investigating the safety and tolerability of lumacaftor administered for 7 days to healthy male and female subjects. Part A was to consist of a maximum of 4 cohorts, but only 3 cohorts were completed. The doses for Cohorts 1, 2, and 3 were lumacaftor (LUM) 600, 1000, and 1200 mg daily (qd). However, review of the data from Cohort 2 and Cohort 3 indicated that drug exposure had been saturated at the 1000-mg dose level. Initiation of Cohort 4 was therefore unwarranted, and the lumacaftor dose used in Cohort 2 (i.e., LUM 1000 mg qd for 7 days) was selected as the supratherapeutic dose for Part B.

Part B of the study was a parallel, double-blind, randomized, placebo- and active-controlled, multiple-dose, single-center ECG study investigating the effect of lumacaftor in combination with ivacaftor on QT/QTc intervals in healthy male and female subjects. Cohorts A and B received a total of 14 days of double-blinded study drug treatment: Cohort A received the therapeutic dose for 7 days (Days 1 through 7) followed by the supratherapeutic dose for an additional 7 days (Days 8 through 14) while Cohort B received placebo for 14 days. Cohort C received a single dose of open-label moxifloxacin on Day 14. All cohorts were dosed in 14 days. Cohort C received a single dose of open-label moxifloxacin on Day 14.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Lumacaftor:

Part A: 600 mg qd (Cohort 1)
1000 mg qd (Cohort 2)
1200 mg qd (Cohort 3)
Part B: 600 mg qd (Therapeutic Dose)
1000 mg qd (Supratherapeutic Dose)

Ivacaftor:
Part B: 250 mg q12h (Therapeutic Dose)
450 mg q12h (Supratherapeutic Dose)

Lumacaftor-matching placebo:
Parts A and B :0 mg qd

Ivacaftor-matching placebo:
Part B: 0 mg q12h

Moxifloxacin (AVELOX):
Part B: 400 mg (single dose, Day 14)

4.2.6.2 Sponsor's Justification for Doses

9.2.2.3 Rationale for Part B: Therapeutic Dose

The therapeutic dose was chosen to cover the exposures predicted to be obtained at the clinical doses selected for the pivotal Phase 3 studies of lumacaftor: LUM 600 mg qd/ IVA 250 mg q12h and LUM 400 mg q12h/IVA 250 mg q12h.

Because the LUM 600 mg qd dose produces the higher Cmax and, in general, drug effect on QT/QTc interval is directly associated with drug concentrations, LUM 600 mg qd was chosen as the therapeutic lumacaftor dose for Part B. However, due to differences in the exposures observed between healthy subjects and subjects with CF (see next paragraph), the therapeutic dose in Part B may have been adjusted based on the actual exposures observed in healthy subjects in Part A in order to cover the exposures predicted to be obtained at the clinical doses selected for the pivotal Phase 3 studies. Review of the data indicated that this adjustment was not necessary. The dose of ivacaftor was 250 mg q12h in both Phase 3 study regimens and was the therapeutic ivacaftor dose chosen for Part B.

Based on the cross-study comparison of the PK data, subjects with CF appear to have approximately 2-fold lower AUC of lumacaftor compared to healthy subjects. It was not known if the same trend would hold at higher doses. However, it was expected that lumacaftor and M28-lumacaftor exposures (Cmax and AUC0-24h) in healthy subjects following 7-day dosing of LUM 600 mg qd in combination with ivacaftor would likely be higher or at least similar to those obtained in subjects with CF at the same dose.

Exposures to ivacaftor, M1-ivacaftor, and M6-ivacaftor in subjects with CF are similar compared to those in healthy subjects. However, there is a drug-drug interaction between lumacaftor and ivacaftor; when lumacaftor and ivacaftor were administered in combination, plasma exposures of ivacaftor and M1-ivacaftor decreased by 81% and 72% compared to when ivacaftor was administered alone. (Exposures to lumacaftor, M28-

lumacaftor, and M6-ivacaftor when lumacaftor and ivacaftor were administered in combination were comparable to those when lumacaftor was administered alone.) This interaction was observed in both healthy subjects and in subjects with CF. Therefore, the exposures of ivacaftor, M1-ivacaftor, and M6-ivacaftor in healthy subjects following administration of lumacaftor in combination with ivacaftor for 7 days were predicted to be similar to the steady-state exposures observed in subjects with CF following therapeutic doses of the combination.

9.2.2.4 Rationale for Part B: Supratherapeutic Dose

The supratherapeutic dose of lumacaftor (1000 mg qd) was based on safety, tolerability, and PK data from Part A and was selected to cover the potential increase in exposures due to special population or any drug-drug interactions.

The supratherapeutic dose of ivacaftor was 450 mg q12h. This was the highest dose tested in previous ivacaftor studies and was the supratherapeutic dose used in the ivacaftor thorough QT study. Due to the CYP3A induction by lumacaftor, the exposures for ivacaftor and M1-ivacaftor at 450 mg q12h when administered in combination with lumacaftor were expected to be markedly lower than those observed when IVA 450 mg q12h is administered alone. However, the M6-ivacaftor exposure was expected to be very similar in both cases.

Therefore, the supratherapeutic dose of ivacaftor in combination with lumacaftor was not expected to exceed the highest dose previously tested in ivacaftor monotherapy and provided a safety margin for both ivacaftor and its major metabolites.

Source: Sponsor's study report, Page 52-53

Reviewer's Comment: The approach to dose selection for lumacaftor appears reasonable. It is unclear why ivacaftor is included in this study. Ivacaftor has already been studied in a thorough QT study and did not show a clinically relevant effect on the QTc interval. Part A of the study showed that lumacaftor Cmax was dose proportional with a dose of 1000 mg qd producing 1.7-fold the C_{max} produced by lumacaftor 600 mg qd dose (60.4 vs. 35.6 μg/mL). But in part B, when lumacaftor was used in combination with ivacaftor, when the therapeutic dose regimen (LUM 600 mg qd/IVA 250 mg q12h) was changed to the supratherapeutic regimen (LUM 1000 mg qd/IVA 450 mg q12h) there was only marginally higher Cmax for 1000 mg qd dose compared to 600 mg qd dose of lumacaftor (41.1 vs. 35.9 μg/mL).

4.2.6.3 Instructions with Regard to Meals

Study drug was administered with a standard meal.

Reviewer's Comment: Acceptable. Food has been demonstrated to increase exposure of both lumacaftor and ivacaftor and the proposed label also suggests administration with fat-containing food.

4.2.6.4 ECG and PK Assessments

PK Assessment:

Part A

On Day 1, a plasma sample was collected before study drug dosing. On Day 7, plasma samples were collected before study drug dosing and 1, 2, 3, 4, 6, 8, 10, and 12 hours after study drug dosing. On Days 8 through 11, plasma samples were also collected 24 (Day 8), 48 (Day 9), 72 (Day 10), and 96 (Day 11) hours after study drug dosing.

Part B

All PK sampling times were relative to the nominal dose time of the study drug(s) with a window of ± 15 minutes for the actual dose time. On Days 7 (Cohorts A and B) and 14 (all cohorts), plasma samples were collected before study drug dosing and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after study drug dosing. Additional plasma samples matching the 0- to 24-hour time points (on Days 7 and/or 14) were collected on Day -1 (i.e., at -24, -23.5, -23, -22, -21, -20, -18, -15, -12, and 0 hours before the first dose of study drug on Day 1).

ECG Assessment:

Part A

Not applicable

Part B

Continuous 12-lead ECG recordings were obtained for 24 hours. On Days 7 (Cohorts A and B) and 14 (all cohorts), a 24-hour time-matched triplicate ECG was extracted from continuous 12-lead ECG recordings -0.5, 0.5, 1, 2, 3, 4, 6, 9, 12, and 23.5 hours after study drug dosing. Time-matched predose (i.e., baseline) ECGs were extracted on Day -1.

Source: Sponsor's study report, Page 7

Reviewer's Comment: The timing of ECG/PK assessments is adequate to capture potential effects at T_{max} and delayed effects over 24 hours.

4.2.6.5 Baseline

The sponsor used the time-matched pre-dose QTc values on Day -1 as baseline.

4.2.7 ECG Collection

Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Part A

A maximum of approximately 40 subjects (10 subjects each in up to 4 cohorts) were planned to be enrolled (LUM or placebo; randomized 4:1). As Cohort 4 was unwarranted, a total of 30 subjects were randomized, received at least 1 dose of study drug, and were included in the Safety Set: in Cohort 1, 10 subjects were randomized to either LUM 600 mg qd (8 subjects) or placebo (2 subjects); in Cohort 2, 10 subjects were randomized to either LUM 1000 mg qd (8 subjects) or placebo (2 subjects); in Cohort 3, 10 subjects were randomized to either LUM 1200 mg qd (8 subjects) or placebo (2 subjects).

Part B

Approximately 165 subjects were planned to be enrolled (Cohort A [LUM/IVA], Cohort B [placebo], or Cohort C [moxifloxacin]; randomized 1:1:1). A total of 170 subjects were randomized and included in the All Subjects Set: 55 subjects in Cohort A; 58 subjects in Cohort B; 57 subjects in Cohort C. The Safety Set and FAS included 55 subjects in Cohort A, 58 subjects in Cohort B, and 55 subjects in Cohort C. The Complete Case Set (CCS) included 50 subjects in Cohort A, 58 subjects in Cohort B, and 55 subjects in Cohort C.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

PartA

Not applicable

PartB

The primary endpoint was time-matched baseline-adjusted QTcF mean differences between LUM 600 mg qd/ IVA 250 mg q12h on 7 days and LUM 1000 mg qd/IVA 450 mg q12h on Day 14. The upper limits of the 2-sided 90% CI for the least squares mean differences from placebo for the time-matched, baseline-adjusted QTcF interval for the therapeutic and supratherapeutic dose regimens did not exceed 10 ms, indicating that lumacaftor and ivacaftor combination therapy does not prolong the QTc interval to a clinically significant degree at the therapeutic and supratherapeutic dose levels.

Table 2: Sponsor's Results of ΔΔQTcF on Day 7 Between the Therapeutic Dose and Placebo and on Day 14 Between the Supratherapeutic Dose and Placebo (Part B)

		Day 7		Day 14	
Time Point	Statistics	Cohort B Period 1 Placebo [N = 58]	Cohort A Period 1 LUM 600 mg qd/ IVA 250 mg q12h [N = 50]	Cohort A Period 2 LUM 1000 mg qd/ IVA 450 mg q12h [N = 36]	Cohort B Period 2 Placebo [N = 56]
0.5 Hours Predose	n	58	45	33	56
	LS Mean	-0.3	-2.7	-0.7	-0.6
	2-sided 95% CI	(-3.3, 2.7)	(-5.9, 0.6)	(-4.2, 2.9)	(-3.4, 2.2)
	LS Mean Diff vs Placebo	NA	-2.4	-0.1	NA
	2-sided 90% CI	NA	(-6.0, 1.3)	(-3.8, 3.7)	NA
0.5 Hours Postdose	n	58	45	33	55
	LS Mean	-2.5	-5.9	-4.4	-2.7
	2-sided 95% CI	(-5.4, 0.5)	(-9.1, -2.6)	(-7.9, -0.9)	(-5.5, 0.1)
	LS Mean Diff vs Placebo	NA	-3.4	-1.7	NA
	2-sided 90% CI	NA	(-7.1, 0.3)	(-5.4, 2.1)	NA
1 Hour Postdose	n	58	45	33	55
	LS Mean	-2.4	-6.9	-4.4	-2.2
	2-sided 95% CI	(-5.3, 0.6)	(-10.1, -3.6)	(-8.0, -0.9)	(-5.0, 0.5)
	LS Mean Diff vs Placebo	NA	-4.5	-2.2	NA
	2-sided 90% CI	NA	(-8.2, -0.8)	(-5.9, 1.5)	NA
2 Hours Postdose	n	57	47	34	55
	LS Mean	-5.5	-8.0	-5.5	-3.5
	2-sided 95% CI	(-8.4, -2.5)	(-11.3, -4.8)	(-9.0, -2.0)	(-6.3, -0.7)
	LS Mean Diff vs Placebo	NA	-2.6	-2.0	NA
	2-sided 90% CI	NA	(-6.2, 1.1)	(-5.8, 1.7)	NA
3 Hours Postdose	n	56	46	33	54
	LS Mean	-4.0	-9.5	-5.7	-3.4
	2-sided 95% CI	(-7.0, -1.0)	(-12.8, -6.3)	(-9.2, -2.1)	(-6.2, -0.6)
	LS Mean Diff vs Placebo	NA	-5.5	-2.2	NA
	2-sided 90% CI	NA	(-9.2, -1.8)	(-6.0, 1.5)	NA

4 Hours Postdose	n	55	46	33	53
	LS Mean	-3.2	-7.0	-3.1	-2.1
	2-sided 95% CI	(-6.1, -0.2)	(-10.3, -3.8)	(-6.6, 0.4)	(-4.9, 0.7)
	LS Mean Diff vs Placebo	NA	-3.9	-1.0	NA
	2-sided 90% CI	NA	(-7.6, -0.2)	(-4.8, 2.7)	NA
6 Hours Postdose	n	55	47	33	53
	LS Mean	-3.6	-6.4	-5.6	-4.2
	2-sided 95% CI	(-6.6, -0.7)	(-9.6, -3.2)	(-9.1, -2.1)	(-7.0, -1.4)
	LS Mean Diff vs Placebo	NA	-2.8	-1.4	NA
	2-sided 90% CI	NA	(-6.4, 0.9)	(-5.1, 2.4)	NA
9 Hours Postdose	n	54	43	31	52
	LS Mean	-6.7	-11.8	-7.5	-4.1
	2-sided 95% CI	(-9.7, -3.7)	(-15.1, -8.6)	(-11.1, -4.0)	(-6.9, -1.3)
	LS Mean Diff vs Placebo	NA	-5.1	-3.4	NA
	2-sided 90% CI	NA	(-8.8, -1.4)	(-7.2, 0.4)	NA
12 Hours Postdose	n	56	46	32	53
	LS Mean	-5.2	-7.2	-5.0	-6.5
	2-sided 95% CI	(-8.2, -2.2)	(-10.5, -4.0)	(-8.6, -1.5)	(-9.3, -3.7)
	LS Mean Diff vs Placebo	NA	-2.0	1.5	NA
	2-sided 90% CI	NA	(-5.7, 1.7)	(-2.3, 5.2)	NA
23.5 Hours Postdose	n	55	48	35	53
	LS Mean	-0.7	-1.8	-3.9	-2.2
	2-sided 95% CI	(-3.7, 2.3)	(-5.0, 1.5)	(-7.4, -0.4)	(-5.0, 0.6)
	LS Mean Diff vs Placebo	NA	-1.1	-1.7	NA
	2-sided 90% CI	NA	(-4.7, 2.6)	(-5.4, 2.0)	NA

Sources: Table 14.3.6.1.1b and Table 14.3.6.2.1b.
CI: confidence interval; Diff: difference; ECG: electrocardiogram; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; MMRM: mixed-effects model for repeated measures; N: data set sample size; n: number of subjects: NA: not applicable; q12h: every 12 hours; qd: daily.
Notes: Triplicate ECGs at each visit are averaged. The MMRM model includes the following categorical variables as fixed effects: treatment, time, and treatment-by-time interaction; and subject as a random effect, with time-matched QTcF interval on Day -1 as a covariate. The correlation for the vector of time-matched changes from baseline within a subject was modeled using an AR(1) structure.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.8.2.2 Assay Sensitivity

The lower limit of the 2-sided 97.5% CI for the LS mean difference from placebo for the baseline-adjusted QTcF interval for moxifloxacin ranged from 0.0 to 3.0 ms. The lower limit did not exceed 5 ms at any time point, indicating that assay sensitivity was not demonstrated according to the criteria specified in the protocol. However, assay sensitivity was established according to ICH E14 criteria via an ad-hoc analysis.

Table 3: Sponsor's Results of ΔΔQTcF on Day 14 Between the Moxifloxacin Placebo (Part B)

Visit (Time Point)	Statistics	Cohort B Period 2 Placebo [N = 56]	Cohort C Moxifloxacin 400 mg [N = 55]
Day 14 (2 Hours Postdose)	n	55	55
	LS Mean	-2.5	2.5
	2-sided 95% CI	(-5.5, 0.5)	(-0.6, 5.5)
	LS Mean Difference versus Placebo	NA	5.0
	2-sided 97.5% CI	NA	(0.0, 9.9)
Day 14 (3 Hours Postdose)	n	54	55
	LS Mean	-2.4	5.5
	2-sided 95% CI	(-5.5, 0.6)	(2.4, 8.6)
	LS Mean Difference versus Placebo	NA	7.9
	2-sided 97.5% CI	NA	(3.0, 12.9)
Day 14 (4 Hours Postdose)	n	53	54
	LS Mean	-0.9	6.4
	2-sided 95% CI	(-4.0, 2.2)	(3.3, 9.5)
	LS Mean Difference versus Placebo	NA	7.3
	2-sided 97.5% CI	NA	(2.3, 12.2)
Day 14 (6 Hours Postdose)	n	53	54
	LS Mean	-3.1	2.6
	2-sided 95% CI	(-6.2, -0.1)	(-0.5, 5.7)
	LS Mean Difference versus Placebo	NA	5.7
	2-sided 97.5% CI	NA	(0.7, 10.7)

Source: Table 14.3.6.3.1.1b.
CI: confidence interval; ECG: electrocardiogram; LS: least squares; MMRM: mixed-effects model for repeated measures; N: data set sample size; n: number of subjects; NA: not applicable.
Notes: Triplicate ECGs at each visit are averaged. The MMRM model includes the following categorical variables as fixed effects: treatment, time, and treatment-by-time interaction; and subject as a random effect, with time-matched QTcF interval on Day -1 as a covariate. The correlation for the vector of time-matched changes from baseline within a subject was modeled using an AR(1) structure.

Source: Clinical Study Report, Section 114.1.2, Table 11-6, page 59/12832

Reviewer's Comments: The sponsor's used 2-sided 97.5% CI the LS mean difference from placebo for the baseline-adjusted QTcF interval for moxifloxacin ranged from 0.0 to 3.0 ms. This review used 2-sided 90% CI and the lower bound is greater than 5 ms.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. One subject's absolute QTc was >480 ms. No subject's ΔQTc was >60 ms.

4.2.8.3 Safety Analysis

Part A:

The data suggest that lumacaftor, at the dose levels evaluated in Part A of this study, was associated with a decline in ppFEV1 of approximately 6 percentage points in the overall active treatment group, which was evident within 4 hours of the first dose and which persisted, with only subtle improvement for most subjects, through Day 7. The higher doses of lumacaftor were associated with an increased incidence of respiratory AEs (namely, throat tightness, dyspnea, and respiration abnormal). These AEs were mild in severity and resolved without treatment, in most cases within 1 to 3 days.

Part B:

There were no SAEs and the majority of AEs were mild or moderate in severity, although a higher rate of discontinuation was observed compared to the placebo cohort (16.4% [therapeutic dose regimen] and 18.4% [supratherapeutic dose regimen] versus 0% in the placebo cohort) during Part B. A collection of AEs assigned to Period 1 led to treatment discontinuation, whereas the majority of AEs assigned to Period 2 that led to treatment discontinuation were limited to rash generalized and transaminases increased.

A higher proportion of subjects with lumacaftor and ivacaftor combination therapy had AEs of chest discomfort in Part B. With 1 exception, all the AEs of chest discomfort were mild in severity and all resolved without treatment and without study interruption.

4.2.8.4 Clinical Pharmacology

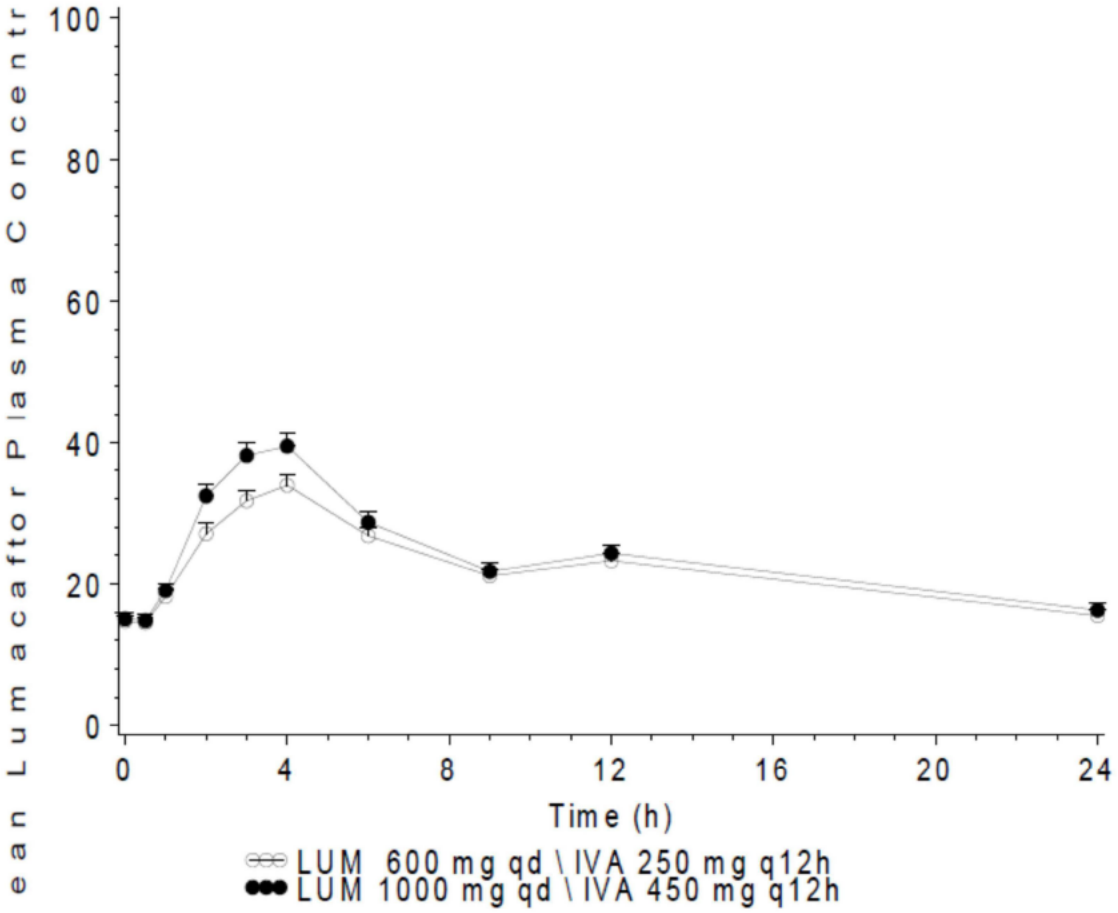
4.2.8.4.1 Pharmacokinetic Analysis

Sponsor's mean concentration-time profiles for lumacaftor, ivacaftor and the associated metabolites (M28 for lumacaftor, and M1 and M6 for ivacaftor) after the therapeutic dose regimen (Days 1 through 7) on Day 7 and the supratherapeutic dose regimen (Days 8 through 14) on Day 14 are shown in Figure 1. The PK results for these drugs and metabolites are presented in Table 4 and Table 5. The mean lumacaftor AUC_{τ} was similar (525 to 566 μg·h/mL) and C_{max} increased marginally (35.9 to 41.1 μg/mL) when the therapeutic dose regimen was changed to the supratherapeutic dose regimen. The mean AUC_{τ} and C_{max} for M28 (lumacaftor metabolite) were increased by approximately 40% when the therapeutic dose regimen was changed to the supratherapeutic dose regimen. The mean AUC_{τ} and C_{max} were increased by approximately 30-40% for ivacaftor and M1 (ivacaftor metabolite) and by 5-60% for M6 (ivacaftor metabolite) when the therapeutic dose regimen was changed to the supratherapeutic dose regimen (ivacaftor dose was increased by 80%).

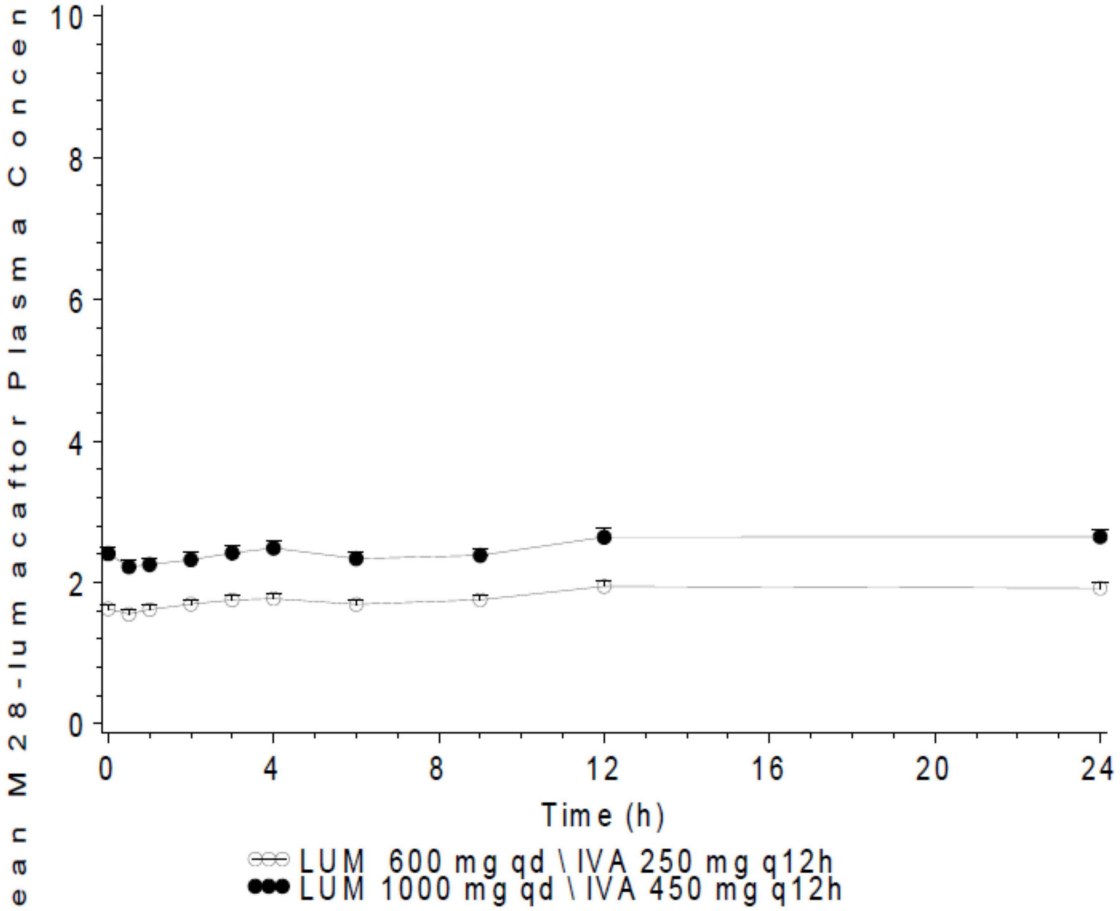
Sponsor's mean concentration-time profiles for moxifloxacin after administration of a single dose of 400 mg are shown in Figure 2. The PK results for moxifloxacin are presented in Table 6.

Figure 1: Sponsor's Mean Plasma Concentration-Time Profiles for A) Lumacaftor, B) M28 (Lumacaftor metabolite), C) Ivacaftor, D) M1 (Ivacaftor metabolite), and E) M6 (Ivacaftor metabolite), after Administration of Lumacaftor in Combination with Ivacaftor at therapeutic (600 mg Lumacaftor *qd* + 250 mg Ivacaftor *q12h*) and supratherapeutic (1000 mg Lumacaftor *qd* + 450 mg Ivacaftor *q12h*) doses.

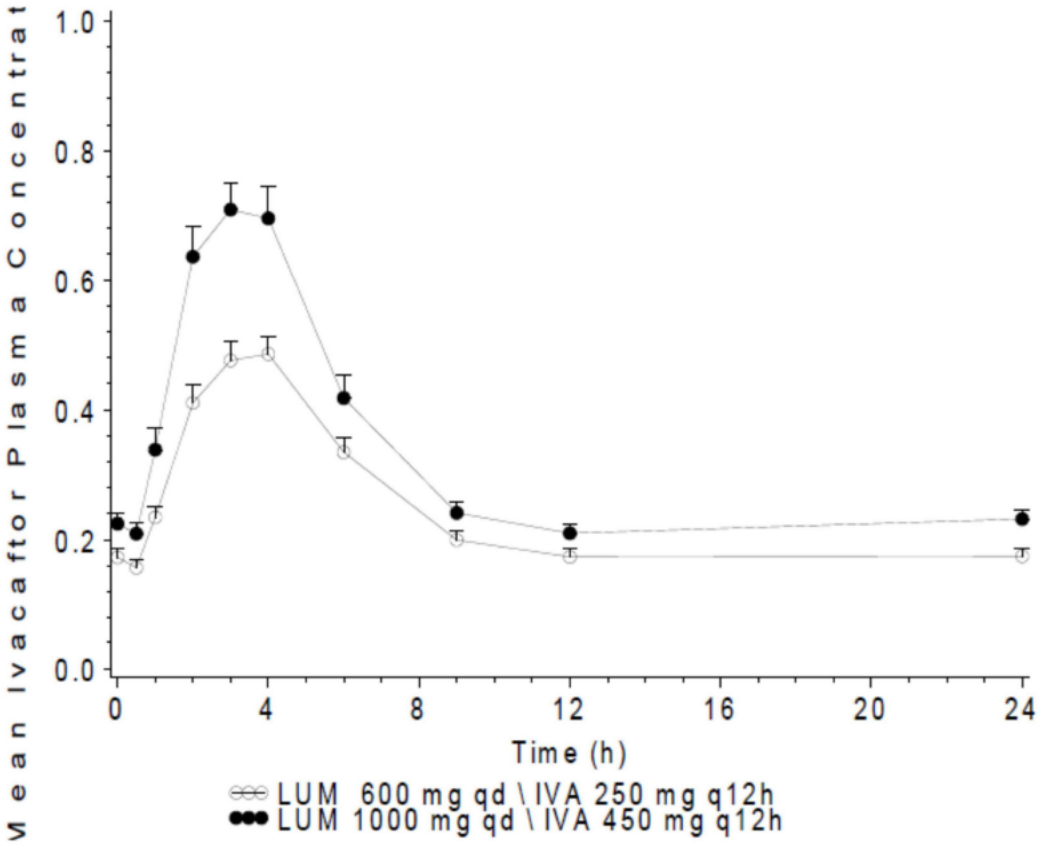
A)



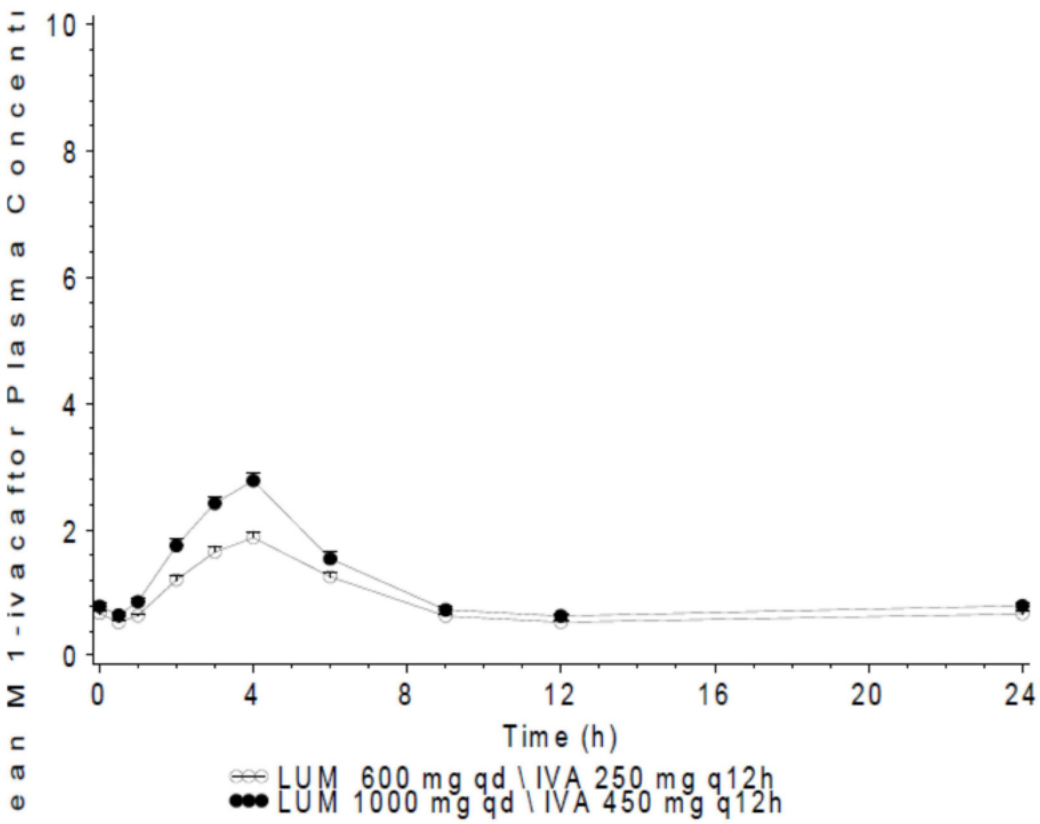
B)


ean M28-lumacaftor Plasma Concen
10
8
6
4
2
0
0
4
8
12
16
20
24
Time (h)
LUM 600 mg qd \ IVA 250 mg q12h
LUM 1000 mg qd \ IVA 450 mg q12h

C)


Mean Ivacaftor Plasma Concentrat
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
Time (h)
LUM 600 mg qd \ IVA 250 mg q12h
LUM 1000 mg qd \ IVA 450 mg q12h

D)


ean M1-ivacaftor Plasma Concentr
10
8
6
4
2
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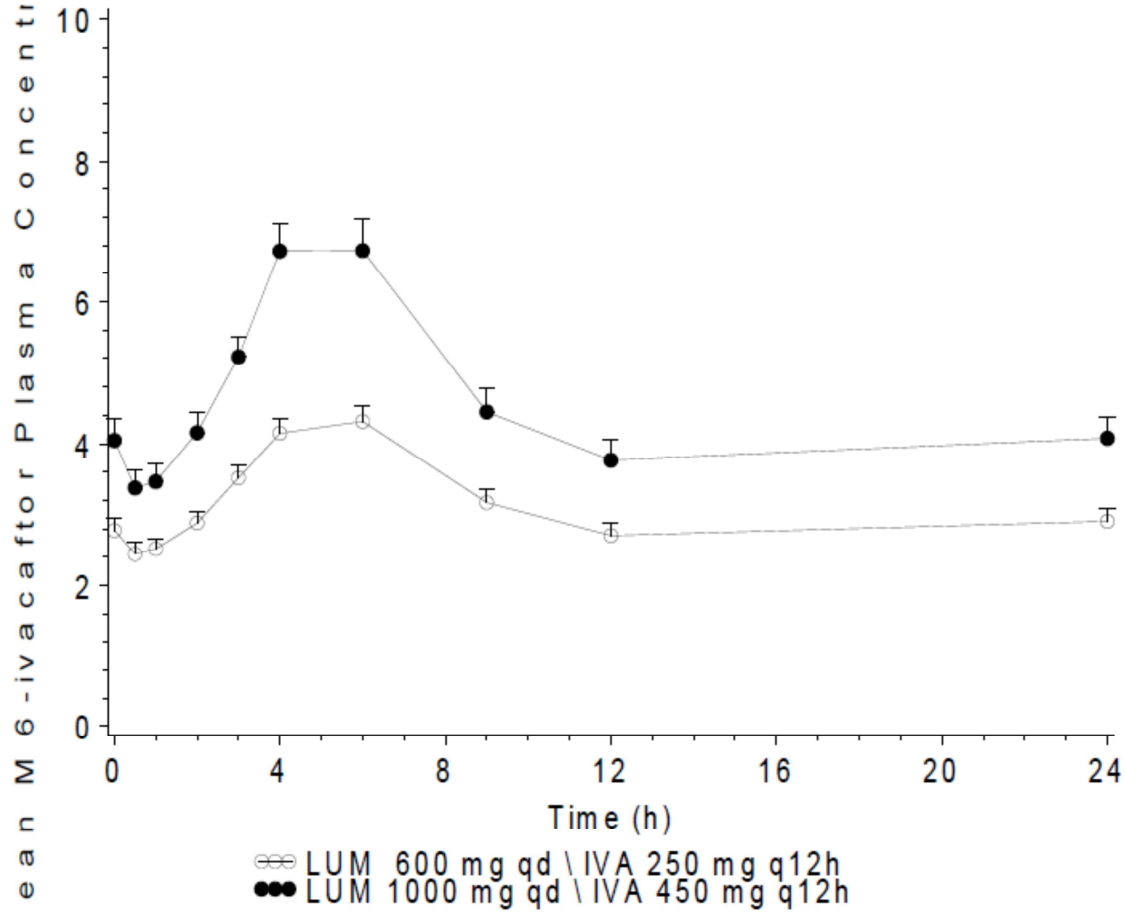
0
4
8
12
16
20
24
Time (h)
LUM 600 mg qd \ IVA 250 mg q12h
LUM 1000 mg qd \ IVA 450 mg q12h

E)



Source: Figure 11-5 through Figure 11-9 in sponsor's study report

Table 4: Sponsor's Results for Lumacaftor and M28 (Lumacaftor Metabolite) Pharmacokinetic Parameters (Mean and SD)

	Treatment	
Analyte Parameter	**Therapeutic Dose Regimen Day 7 [N = 50]**	**Supratherapeutic Dose Regimen Day 14 [N = 36]**
Lumacaftor		
AUC_τ (µg·h/mL)	525 (157)	566 (154)
C_{max} (µg/mL)	35.9 (9.69)	41.1 (10.9)
t_{max} (h)[a]	4.00 (0.52, 6.00)	4.00 (2.00, 4.00)
M28-lumacaftor		
AUC_τ (µg·h/mL)	43.9 (11.2)[b]	60.5 (14.8)
C_{max} (µg/mL)	2.02 (0.522)	2.77 (0.751)
t_{max} (h)[a]	11.92 (0.52, 23.92)	11.92 (0.00, 24.00)

Note: Supratherapeutic dose regimen: LUM 1000 mg qd/IVA 450 mg q12h; Therapeutic dose regimen: LUM 600 mg qd/IVA 250 mg q12h.

[a] Median (minimum, maximum) values are presented for t_{max}.

[b] n = 49; one AUC_τ value was not estimated due to insufficient data in the dosing interval.

Source: Table 11-3 in sponsor's study report

Table 5: Sponsor's Results for Ivacaftor, M1 and M6 (Ivacaftor Metabolites) Pharmacokinetic Parameters (Mean and SD)

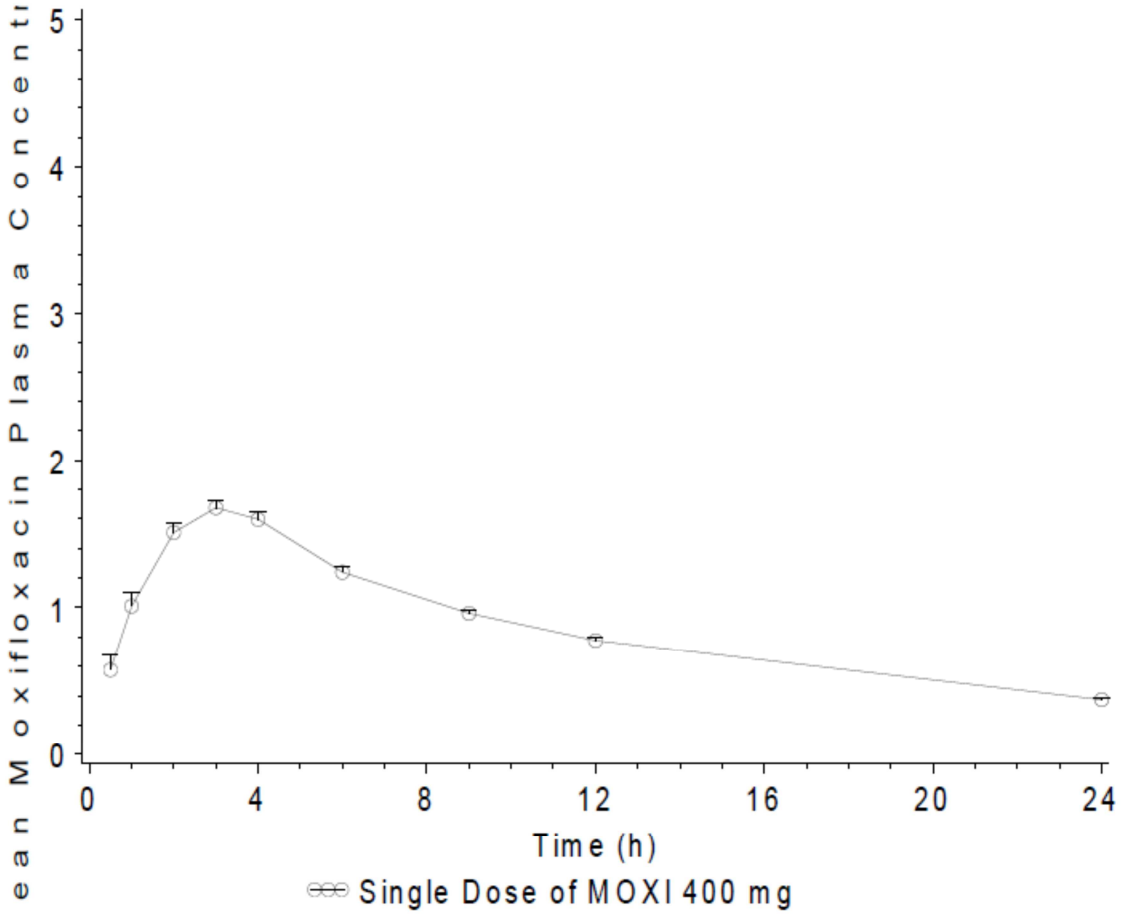
Analyte Parameter	Treatment: Therapeutic Dose Regimen Day 7 [N = 50]	Treatment: Supratherapeutic Dose Regimen Day 14 [N = 36]
Ivacaftor		
AUC_τ (µg·h/mL)	3.58 (1.35)	4.83 (1.77)
C_{max} (µg/mL)	0.573 (0.197)	0.797 (0.286)
t_{max} (h)[a]	3.52 (2.00, 6.00)	3.00 (1.05, 4.00)
M1-ivacaftor		
AUC_τ (µg·h/mL)	12.3 (3.90)	16.2 (4.54)
C_{max} (µg/mL)	2.02 (0.559)	2.88 (0.714)
t_{max} (h)[a]	4.00 (2.00, 6.00)	4.00 (2.00, 4.00)
M6-ivacaftor		
AUC_τ (µg·h/mL)	40.5 (14.1)	60.1 (22.9)
C_{max} (µg/mL)	4.61 (1.44)	7.16 (2.57)
t_{max} (h)[a]	6.00 (3.00, 9.00)	4.02 (4.00, 6.10)

Note: Supratherapeutic dose regimen: LUM 1000 mg qd/IVA 450 mg q12h; Therapeutic dose regimen: LUM 600 mg qd/IVA 250 mg q12h.

[a] Median (minimum, maximum) values are presented for t_{max}.

Source: Table 11-4 in sponsor's study report

Figure 2: Sponsor's Mean Plasma Concentration-Time Profiles for Moxifloxacin after Administration of a Single Dose of Moxifloxacin 400 mg.



Source: Figure 11-10 in sponsor's study report

Table 6: Sponsor's Results for Moxifloxacin Pharmacokinetic Parameters (Mean and SD) after Administration of a Single Dose of Moxifloxacin 400 mg

Parameter	N = 55
$AUC_{0\text{-}24h}$ (µg·h/mL)	20.3 (3.37)
C_{max} (µg/mL)	1.94 (0.418)
t_{max} (h)[a]	2.03 (0.50, 4.00)

[a] Median (minimum, maximum) values are presented for t_{max}.

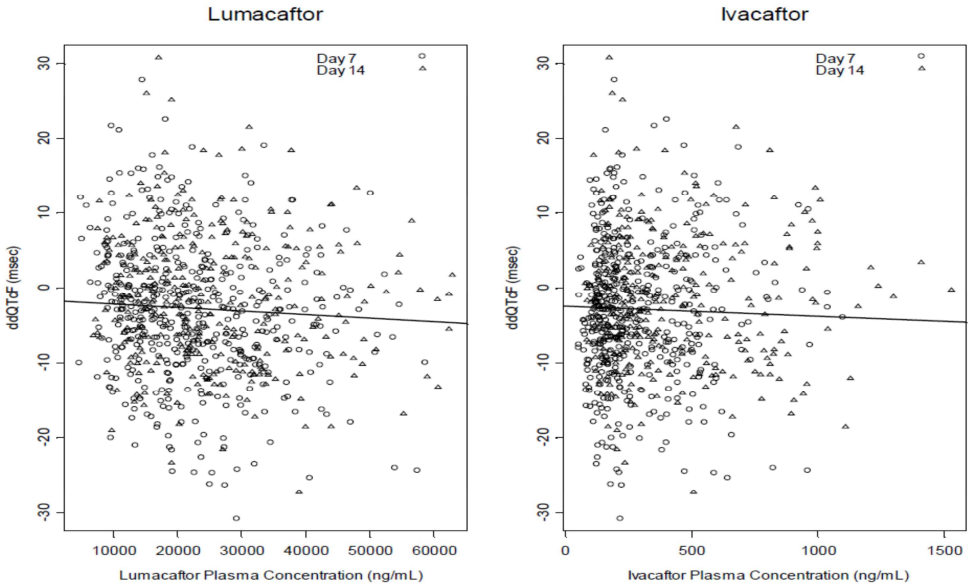
Source: Table 11-5 in sponsor's study report

4.2.8.4.2 Exposure-Response Analysis

Sponsor's scatter-plot of ΔΔQTcF vs. lumacaftor and ivacaftor plasma concentrations are shown in Figure 3. No correlations were observed between the ΔΔQTcF and lumacaftor/ivacaftor concentrations. Linear mixed-effects models with intercept and slope parameters were applied to assess the relationships between ΔΔQTcF and

lumacaftor/ivacaftor concentrations. Sex, age, and dosing day (Day 7 versus Day 14) were evaluated as covariates on the intercept during the model development process. None of these were significant based on the model selection criteria. Both slopes (for ΔΔQTcF vs. lumacaftor and ΔΔQTcF vs. ivacaftor concentrations) were less than zero in the lumacaftor and ivacaftor QTc models. The 95% CI of the slopes in both QTc models included zero; thus, no statistically significant concentration-dependent response for QTcF changes was detected.

Figure 3: Sponsor's Concentration-ΔΔQTcF Scatterplot for Lumacaftor and Ivacaftor Plasma Concentrations



Source: Figure 11-13 in sponsor's study report

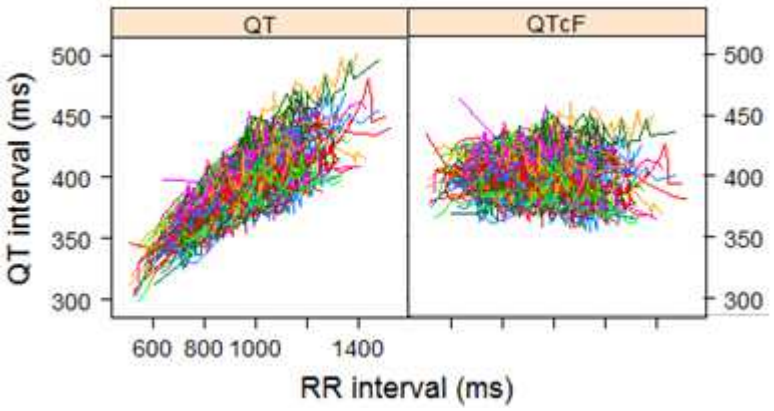
Reviewer's Comments: A plot of ΔΔQTcF vs. plasma concentrations of lumacaftor, ivacaftor and associated metabolites is presented in Figure 3. *A slight trend for increase in QTcF prolongation is observed with increasing M28 (lumacaftor metabolite) concentration. This increase is not clinically meaningful within the concentration range seen in patients.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor provided only QTcF correction intervals. This reviewer chose to present QTcF for the primary statistical analysis. The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, time, and treatment-time interaction as fixed effects and baseline values as a covariate. The analysis results are listed in Table 7 and Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between 600 mg lumacaftor qd/250 mg ivacaftor q12h and placebo on Day 7 and between 1000 mg lumacaftor qd/450 mg ivacaftor q12h and placebo are 1.5 ms and 5.3 ms; respectively.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for 600 mg Lumacaftor QD/ 250 mg Ivacaftor Q12h and Moxifloxacin 400 mg on Day 7 (Part B)

		Treatment Group			
	Placebo	600 mg Lumacaftor QD + 250 mg Ivacaftor Q12H			
	ΔQTcF	ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-3.7	47	-7.2	-3.5	(-5.9, -1.2)
1	-2.5	47	-6.9	-4.4	(-7.1, -1.7)
2	-3.3	48	-5.8	-2.5	(-5.1, 0.1)
3	-2.3	49	-8.0	-5.7	(-8.4, -3.1)
4	-4.6	49	-8.8	-4.2	(-7.0, -1.4)
6	-3.4	49	-6.1	-2.7	(-5.2, -0.2)
9	-4.9	48	-10.4	-5.5	(-8.3, -2.6)
12	-2.2	48	-4.3	-2.1	(-5.6, 1.5)
23.5	-2.7	49	-3.9	-1.2	(-3.9, 1.5)

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for 1000 mg Lumacaftor QD/450 mg Ivacaftor Q12H and Moxifloxacin 400 mg on Day 14 (Part B)

		Treatment Group								
	Placebo	1000mg Lumacaftor QD + 450mg Ivacaftor Q12H				Moxifloxacin 400 mg				
	ΔQTcF	ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	90% CI
0.5	-3.4	35	-5.5	-2.1	(-4.7, 0.6)	55	-2.9	0.6	(-1.7, 2.8)	(-2.5, 3.6)
1	-2.0	35	-3.9	-1.9	(-5.1, 1.2)	55	0.8	2.8	(0.0, 5.5)	(-1.0, 6.5)
2	-1.4	35	-3.6	-2.2	(-5.4, 1.1)	55	5.1	6.5	(3.7, 9.3)	(2.7, 10.4)
3	-1.9	35	-4.9	-3.0	(-6.1, 0.2)	55	7.5	9.4	(6.7, 12.1)	(5.7, 13.1)
4	-3.1	35	-4.3	-1.2	(-4.6, 2.3)	54	5.4	8.5	(5.5, 11.5)	(4.4, 12.6)
6	-3.8	35	-5.4	-1.6	(-4.6, 1.5)	54	2.9	6.7	(4.1, 9.3)	(3.1, 10.3)
9	-2.3	35	-6.6	-4.2	(-7.4, -1.1)	53	1.4	3.8	(1.0, 6.5)	(0.0, 7.5)
12	-4.1	34	-3.0	1.1	(-3.1, 5.3)	55	-0.6	3.6	(-0.0, 7.2)	(-1.3, 8.5)
23.5	-3.2	35	-6.0	-2.7	(-6.0, 0.5)	54	3.5	6.8	(3.9, 9.7)	(2.8, 10.7)

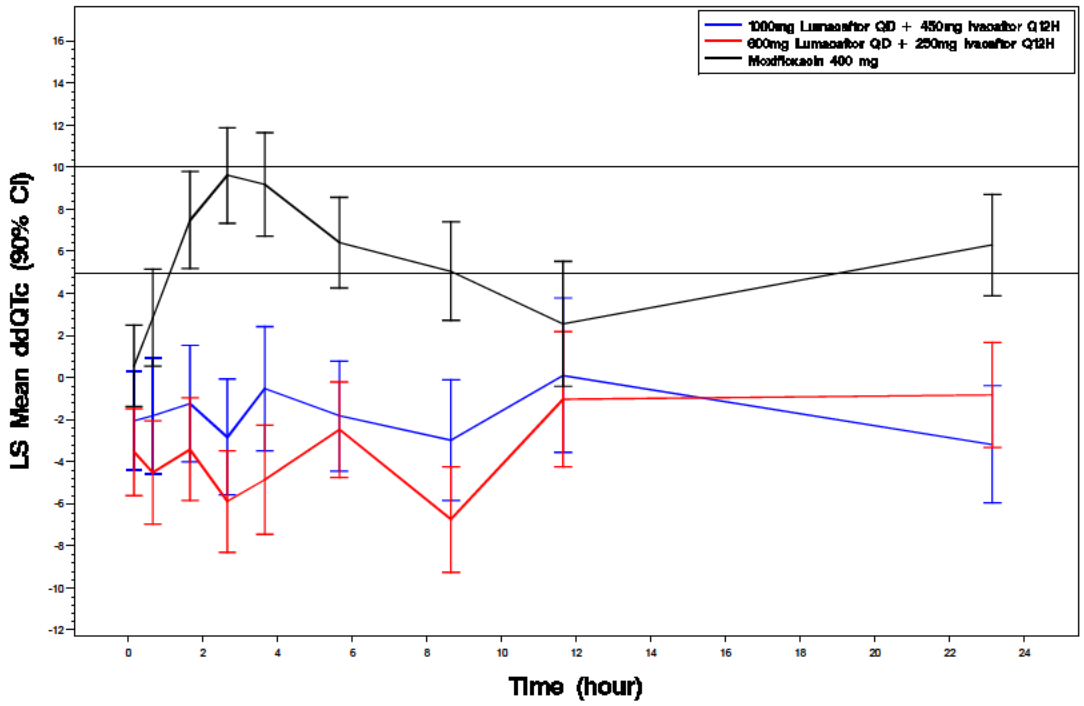
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 6.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 5.7 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 5: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. Two subjects's QTcF were above 480 ms in moxifloxacin group.

Table 9: Categorical Analysis for QTcF

TREATA(Treatment Group)	QTCF		
	450 ms<Value<=480 ms	Value<=450 ms	Total
1000mg Lumacaftor QD + 450mg Ivacaftor Q12H	0	24	24
600mg Lumacaftor QD + 250mg Ivacaftor Q12H	0	25	25
Moxifloxacin 400 mg	2	53	55
Placebo	0	58	58
Total	2	160	162

Table 10 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 30 ms.

Table 10: Categorical Analysis of ΔQTcF

TREATA(Treatment Group)	QTCF_CFB	
	Value<=30 ms	Total
1000mg Lumacaftor QD + 450mg Ivacaftor Q12H	23	23
600mg Lumacaftor QD + 250mg Ivacaftor Q12H	23	23
Moxifloxacin 400 mg	55	55
Placebo	56	56
Total	157	157
Frequency Missing = 5		

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment, time, and treatment-time interaction as fixed effects and baseline values as a covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between 600 mg lumacaftor qd /250 mg ivacaftor q12h and placebo and between 1000 mg lumacaftor qd /450 mg ivacaftor q12h and placebo are -0.1 bpm and 2.0 bpm; respectively. Table 12 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in treatment group.

Table 11: Analysis Results of ΔHR and ΔΔHR for 600 mg Lumacaftor QD / 250 mg Ivacaftor Q12H, 1000 mg Lumacaftor QD / 450mg Ivacaftor Q12H and Moxifloxacin 400 mg

		Treatment Group											
	Placebo	1000mg Lumacaftor QD + 450mg Ivacaftor Q12H				600mg Lumacaftor QD + 250mg Ivacaftor Q12H				Moxifloxacin 400 mg			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-1.9	35	-5.5	-3.7	(-5.9, -1.4)	47	-8.2	-6.4	(-8.4, -4.4)	55	-2.2	-0.4	(-2.2, 1.5)
1	-1.1	35	-3.5	-2.4	(-4.9, -0.0)	47	-7.6	-6.5	(-8.7, -4.4)	55	-2.0	-0.9	(-2.9, 1.0)
2	-1.5	35	-5.4	-3.9	(-6.0, -1.9)	48	-7.3	-5.8	(-7.6, -4.0)	55	-1.3	0.2	(-1.5, 1.9)
3	-0.0	35	-4.8	-4.8	(-7.0, -2.6)	49	-7.8	-7.8	(-9.8, -5.9)	55	1.5	1.5	(-0.3, 3.3)
4	-0.3	35	-5.2	-4.9	(-7.1, -2.6)	49	-7.4	-7.1	(-9.1, -5.2)	54	0.4	0.7	(-1.1, 2.6)
6	0.9	35	-5.6	-6.5	(-8.8, -4.2)	49	-5.2	-6.0	(-8.0, -4.1)	54	0.8	-0.1	(-1.9, 1.8)
9	1.3	35	-3.6	-4.9	(-7.5, -2.3)	48	-5.7	-7.0	(-9.3, -4.7)	53	3.0	1.6	(-0.5, 3.7)
12	-0.3	34	-1.6	-1.2	(-4.5, 2.0)	48	-3.3	-3.0	(-5.8, -0.1)	55	1.1	1.4	(-1.2, 4.1)
23.5	0.6	35	-1.9	-2.5	(-4.7, -0.3)	49	-5.1	-5.8	(-7.7, -3.8)	54	2.7	2.1	(0.2, 3.9)

Table 12: Categorical Analysis for HR

TREATA(Treatment Group)	HR		
	HR <= 100 bpm	HR >100 bpm	Total
1000mg Lumacaftor QD + 450mg Ivacaftor Q12H	24	0	24
600mg Lumacaftor QD + 250mg Ivacaftor Q12H	25	0	25
Moxifloxacin 400 mg	55	0	55
Placebo	56	2	58
Total	160	2	162

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment, time, and treatment-time interaction as fixed effects and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between 600 mg lumacaftor qd/ 250 mg ivacaftor q12h and placebo and between 1000 mg lumacaftor qd/450 mg ivacaftor q12h and placebo are 3.1 ms and 2.5 ms; respectively. Table 14 presents the categorical analysis of PR. No subject who experienced PR interval greater than 200 ms is in treatment group.

Table 13: Analysis Results of ΔPR and ΔΔPR for 600 mg Lumacaftor QD / 250 mg Ivacaftor Q12H, 1000 mg Lumacaftor QD / 450mg Ivacaftor Q12H and Moxifloxacin 400 mg

		Treatment Group											
		1000mg Lumacaftor QD + 450mg Ivacaftor Q12H				600mg Lumacaftor QD + 250mg Ivacaftor Q12H				Moxifloxacin 400 mg			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	1.2	35	0.1	-1.1	(-3.9, 1.8)	47	0.5	-0.7	(-3.2, 1.8)	55	2.3	1.1	(-1.2, 3.5)
1	1.2	35	-1.3	-2.5	(-5.5, 0.6)	47	0.2	-0.9	(-3.6, 1.8)	55	3.9	2.8	(0.3, 5.3)
2	0.5	35	-1.1	-1.6	(-4.6, 1.4)	48	1.0	0.5	(-2.2, 3.1)	55	2.5	2.0	(-0.5, 4.5)
3	1.4	35	0.9	-0.5	(-3.5, 2.5)	49	0.3	-1.0	(-3.7, 1.6)	55	3.0	1.7	(-0.8, 4.1)
4	2.2	35	-0.5	-2.7	(-5.6, 0.1)	49	1.8	-0.5	(-3.0, 2.0)	54	2.3	0.1	(-2.3, 2.5)
6	0.7	35	-1.5	-2.2	(-5.1, 0.7)	49	-0.1	-0.8	(-3.3, 1.7)	54	-2.1	-2.8	(-5.2, -0.5)
9	0.0	35	-2.6	-2.6	(-5.7, 0.5)	48	-1.2	-1.2	(-4.0, 1.5)	53	-0.2	-0.2	(-2.7, 2.3)
12	2.4	34	0.2	-2.2	(-5.1, 0.6)	48	1.5	-0.9	(-3.4, 1.5)	55	1.4	-1.0	(-3.3, 1.3)
23.5	2.1	35	-2.4	-4.4	(-7.4, -1.5)	49	-1.6	-3.7	(-6.3, -1.0)	54	3.9	1.8	(-0.7, 4.4)

Table 14: Categorical Analysis for PR

TREATA(Treatment Group)	PR		
	PR <= 200 ms	PR >200 ms	Total
1000mg Lumacaftor QD + 450mg Ivacaftor Q12H	24	0	24
600mg Lumacaftor QD + 250mg Ivacaftor Q12H	25	0	25
Moxifloxacin 400 mg	55	0	55
Placebo	56	2	58
Total	160	2	162

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment, time, and treatment-time interaction as fixed effects and baseline values as a covariate. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between 600 mg lumacaftor qd/ 250 mg ivacaftor q12h and placebo and between 1000 mg lumacaftor qd/450 mg ivacaftor q12h and placebo are 1.4 ms and 2.1 ms; respectively. Table 16 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms is in treatment group.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for 600 mg Lumacaftor QD/ 250 mg Ivacaftor Q12H, 1000 mg Lumacaftor QD/ 450mg Ivacaftor Q12H and Moxifloxacin 400 mg

		Treatment Group											
		1000 mg Lumacaftor QD + 450mg Ivacaftor Q12H				600 mg Lumacaftor QD + 250mg Ivacaftor Q12H				Moxifloxacin 400 mg			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	1.3	35	0.6	-0.7	(-1.9, 0.5)	47	0.3	-1.0	(-2.1, 0.0)	55	0.1	-1.2	(-2.2, -0.3)
1	1.1	35	0.9	-0.2	(-1.5, 1.1)	47	0.5	-0.6	(-1.8, 0.5)	55	0.0	-1.1	(-2.2, 0.0)
2	1.2	35	1.2	-0.0	(-1.3, 1.2)	48	0.5	-0.8	(-1.9, 0.4)	55	0.6	-0.6	(-1.7, 0.5)
3	0.6	35	1.0	0.4	(-0.9, 1.6)	49	0.9	0.3	(-0.8, 1.4)	55	0.3	-0.3	(-1.3, 0.8)
4	0.7	35	0.9	0.3	(-0.9, 1.4)	49	-0.3	-1.0	(-2.0, 0.0)	54	-0.1	-0.8	(-1.7, 0.2)
6	0.6	35	1.6	0.9	(-0.2, 2.1)	49	0.7	0.1	(-0.9, 1.1)	54	-0.9	-1.5	(-2.5, -0.6)
9	0.2	35	0.4	0.2	(-1.0, 1.4)	48	-0.0	-0.2	(-1.3, 0.9)	53	-0.9	-1.1	(-2.1, -0.1)
12	-0.7	34	0.1	0.8	(-0.5, 2.1)	48	-0.9	-0.2	(-1.3, 0.9)	55	-0.9	-0.2	(-1.2, 0.9)
23.5	0.8	35	-1.0	-1.7	(-3.0, -0.5)	49	-0.5	-1.2	(-2.4, -0.1)	54	-0.2	-0.9	(-2.0, 0.2)

Table 16: Categorical Analysis for QRS

Table of TREATA by QRS			
TREATA(Treatment Group)	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
1000mg Lumacaftor QD + 450mg Ivacaftor Q12H	24	0	24
600mg Lumacaftor QD + 250mg Ivacaftor Q12H	25	0	25
Moxifloxacin 400 mg	54	1	55
Placebo	57	1	58
Total	160	2	162

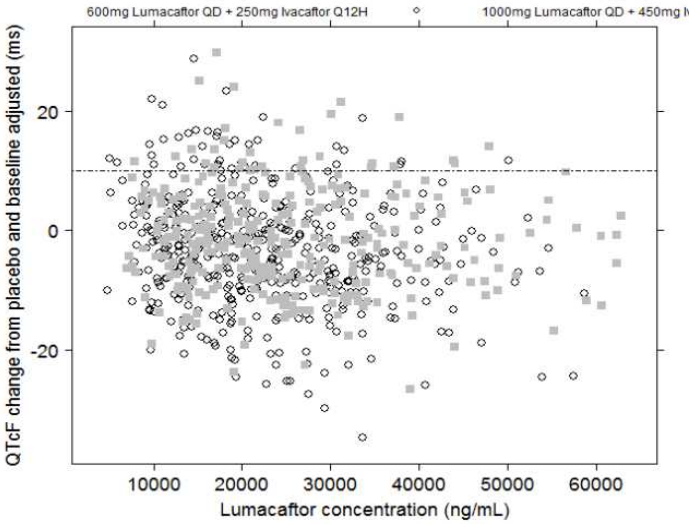
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profiles for lumacaftor, ivacaftor and the associated metabolites (M28 for lumacaftor, and M1 and M6 for ivacaftor) are illustrated in Figure 1.

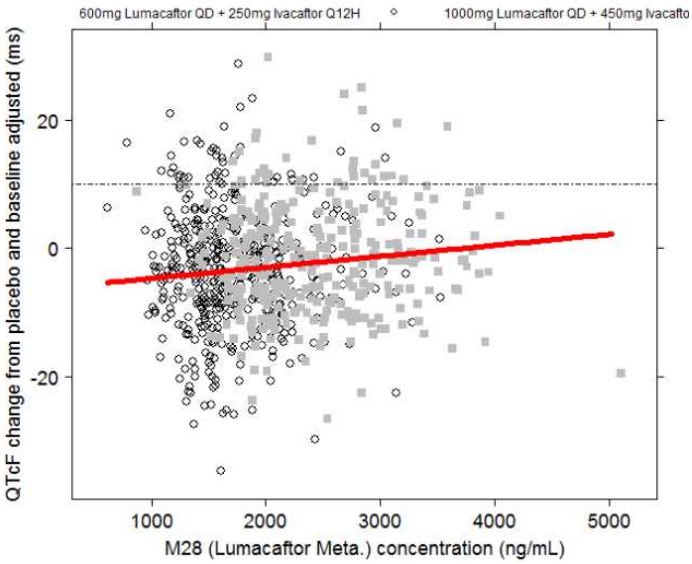
The relationships between ΔΔQTcF and plasma concentrations of lumacaftor, ivacaftor and the associated metabolites (M28 for lumacaftor, and M1 and M6 for ivacaftor) are visualized in Figure 6 with no evident exposure-response relationship for all these moieties except M28 (lumacaftor metabolite, which demonstrates a modest increase in QTcF with increase in M28 concentration). These exposure-response relationships were investigated by linear mixed-effects modeling. Amongst three different models, a linear model with intercept was used for further analysis since this model was found to fit the data best.

Figure 6: Concentration-ΔΔQTcF Relationship for Plasma Concentrations of A) Lumacaftor, B) M28 (Lumacaftor metabolite), C) Ivacaftor, D) M1 (Ivacaftor metabolite), and E) M6 (Ivacaftor metabolite)

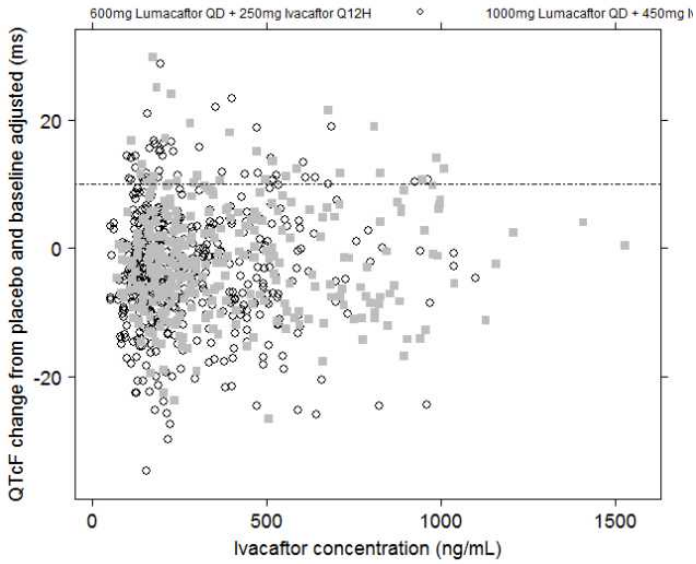
A) **Lumacaftor**



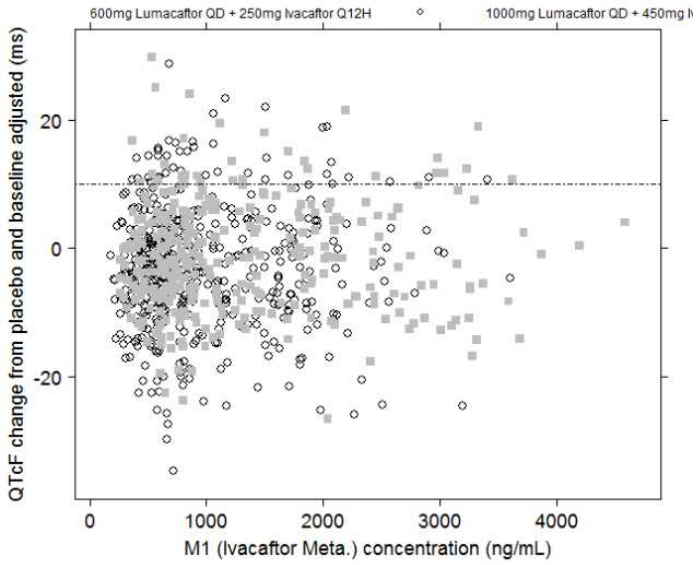
B) **M28 (Lumacaftor metabolite)**



C) **Ivacaftor**



D) **M1 (Ivacaftor metabolite)**



E) **M6 (Ivacaftor metabolite)**

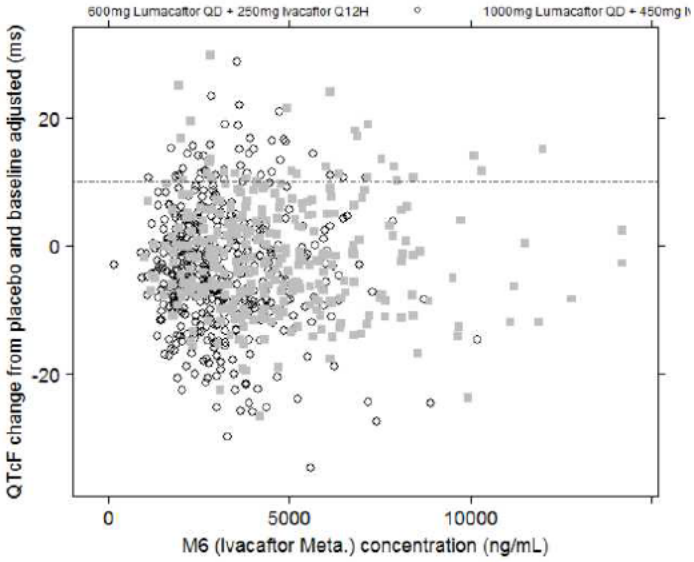


Table 17 summarizes the results of the M28 concentration-ΔΔQTcF analyses. The slope for the M28 concentration-ΔΔQTcF relationship is statistically positive; however, it is relatively flat. The goodness-of-fit plot in Figure 7 shows the observed median-quantile M28 concentrations and associated mean (90% CI) ΔΔQTcF together with the mean (90% CI) predicted ΔΔQTcF. The mean (90% CI) predicted ΔΔQTcF at the mean peak M28 concentrations for therapeutic and supratherapeutic lumacaftor/ ivacaftor combination doses are below 0 as shown in Figure 8 and thus are not clinically relevant.

Table 17: Exposure-Response Analysis of M28 (Lumacaftor Metabolite) Associated with ΔΔQTcF

Parameter	Estimate	P-value
ΔΔQTcF = Intercept + slope* M28 Concentration		
Intercept (ms)	-6.37 (-9.6; -3.13)	0.0018
Slope (ms per ng/mL)	0.00172 (0.000431; 0.003)	0.0307
Residual Variability (ms)	7.5	

Figure 7: Observed Median-Quantile M28 (Lumacaftor Metabolite) Concentration and Associated Mean (90% CI) ΔΔQTcF (colored dots) together with the Mean (90% CI) Predicted ΔΔQTcF (black line with shaded grey area)

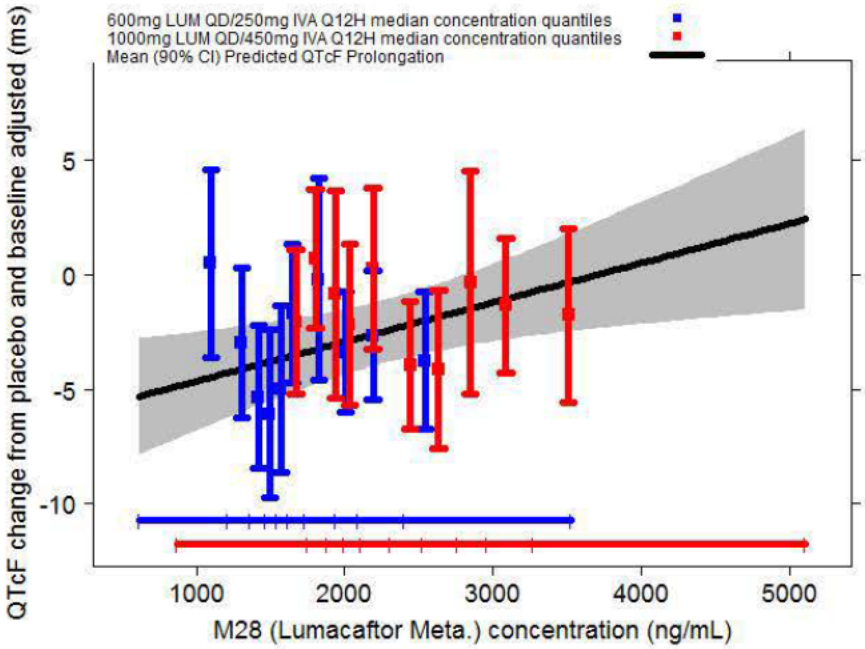
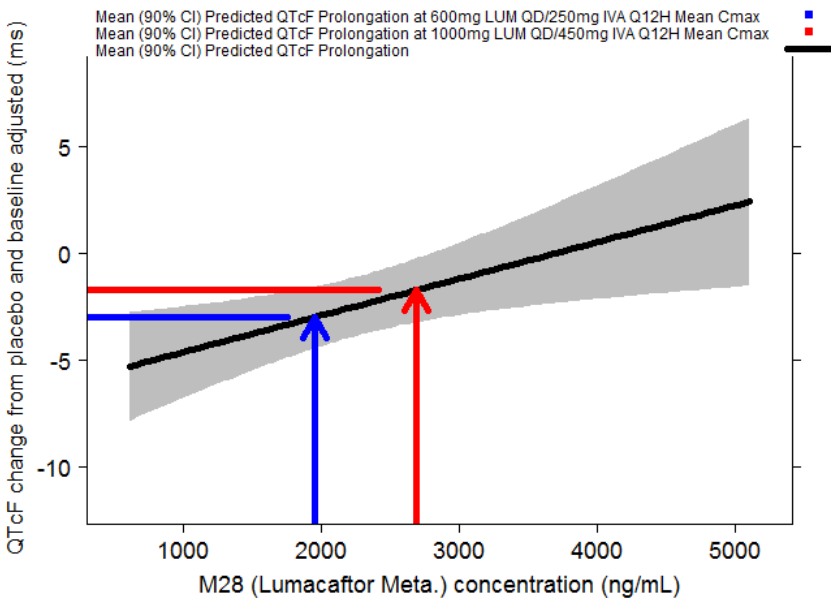


Figure 8: Mean (90% CI) Predicted ΔΔQTcF at Mean C_{max} for M28 (Lumacaftor Metabolite)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically significant effects were seen on PR or QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Lumacaftor Clinical Pharmacology

Therapeutic Dose	600 mg of lumacaftor qd/250 mg of ivacaftor q12h and 400 mg of lumacaftor q12h/250 mg of ivacaftor q12h in subjects who are homozygous for the *F508del-CFTR* mutation (Phase 3 program; Study 103 and Study 104).
Maximum Tolerated Dose	All doses evaluated in clinical studies were well tolerated. No maximum tolerated dose was established in humans.
Principal Adverse Events	Subjects With CF Study 102 evaluated lumacaftor monotherapy and lumacaftor and ivacaftor combination therapy in subjects with CF who are homozygous and heterozygous for the *F508del-CFTR* mutation (largest sample size and longest duration evaluated to date). In this study, 97 subjects received lumacaftor monotherapy for 4 weeks followed by lumacaftor and ivacaftor combination therapy for 4 weeks. The most common AEs in Study 102 are summarized below. • **Subjects receiving lumacaftor monotherapy:** cough, CF pulmonary exacerbation, productive cough, respiration abnormal (chest tightness), shortness of breath, nausea, headache, hemoptysis, diarrhea, upper respiratory tract infection, rash, fever, flatulence, and C-reactive protein increased. • **Subjects receiving lumacaftor and ivacaftor combination therapy:** cough, CF pulmonary exacerbation, headache, upper respiratory tract infection, nasal congestion, productive cough, and hemoptysis. AEs in subjects with CF (subjects who are homozygous for the *F508del-CFTR* mutation) from other studies have been similar to those listed above. Healthy Subjects In healthy subjects who received 1 dose or repeated doses of lumacaftor monotherapy or lumacaftor and ivacaftor combination therapy, the most common adverse events occurring in at least 3 subjects on treatment included headache, skin rash, diarrhea, dizziness, nasal congestion, increased liver enzymes, and nausea.

Maximum Dose Tested	Single Dose	Healthy Subjects 600 mg evaluated in Study 007 (**lumacaftor monotherapy**) Subjects With CF 200 mg evaluated in Study 002 (**lumacaftor monotherapy**)
	Multiple Dose	Healthy Subjects 400 mg qd evaluated in Study 006 (**lumacaftor monotherapy** and **lumacaftor and ivacaftor combination therapy**) Subjects With CF 400 mg q12h evaluated in Study 102 (**lumacaftor monotherapy** and **lumacaftor and ivacaftor combination therapy**)
Exposures Achieved at Maximum Tested Dose	Single Dose	Healthy Subjects 600 mg evaluated in Study 007 (fed condition) **Lumacaftor monotherapy**: • Mean (SD) C_{max}:30700 (9050) ng/mL • Mean (SD) $AUC_{0-\infty}$ 839000 (303000) ng·h/mL
	Multiple Dose	Healthy Subjects 400 mg qd evaluated in Study 006 (fed condition) **Lumacaftor monotherapy**: • Mean (SD) C_{max}: 27900 (8900) ng/mL • Mean (SD) AUC_{0-24h}: 435000 (139000) ng·h/mL **Lumacaftor and ivacaftor combination therapy**: • Mean (SD) C_{max}: 25000 (8660) ng/mL • Mean (SD) AUC_{0-24h}: 387000 (142000) ng·h/mL Subjects With CF 400 mg q12h evaluated in Study 102 (fed condition) **Lumacaftor monotherapy:** • Mean (SD) C_{max}: 23700 (6190) ng/mL • Mean (SD) AUC_{0-24h}: 336000 (95200) ng·h/mL **Lumacaftor and ivacaftor combination therapy:** • Mean (SD) C_{max}: 24200 (6990) ng/mL • Mean (SD) AUC_{0-24h}: 372000 (134800) ng·h/mL

Range of Linear PK	Healthy Subjects • Single Dose: 50 to 600 mg evaluated in Study 001 and Study 007 (both evaluated **lumacaftor monotherapy**) • Multiple Dose: 50 to 400 mg evaluated in Study 001, Study 005, and Study 006 (**lumacaftor monotherapy** data used for cross-study assessment of PK linearity) Subjects With CF Multiple Dose: 25 to 400 mg evaluated in Study 101 and Study 102 (**lumacaftor monotherapy** data used for cross-study assessment of PK linearity)	
Accumulation at Steady State	Healthy Subjects Based on $AUC_{0\text{-}24h}$, the accumulation ratio following once a day dosing ranged from 1.9 to 2.2 over 50 to 200 mg in Study 001 (**lumacaftor monotherapy**), consistent with the half-life of lumacaftor. Subjects With CF Based on $AUC_{0\text{-}24h}$, the accumulation ratio following once a day dosing ranged from 1.7 to 2.0 over 25 to 200mg in Study 101 (**lumacaftor monotherapy**), consistent with the half-life of lumacaftor.	
Metabolites	Healthy Subjects Inactive metabolite M28, M28-lumacaftor, circulates at 25% of the parent AUC following a single dose of 200 mg of lumacaftor in Study 004 (**lumacaftor monotherapy**). Subjects With CF • M28-lumacaftor versus parent drug plasma AUC ratio decreased from 33% at a 25 mg/day dose to 15% at a 200 mg/day dose after 28 days of lumacaftor monotherapy in Study 101 (**lumacaftor monotherapy**). • M28-lumacaftor presented at 7 to 10% of parent plasma AUC at clinical doses (600 mg qd and 400 mg q12h in Study 102 (**lumacaftor monotherapy** and **lumacaftor and ivacaftor combination therapy**).	
Absorption	Absolute and Relative Bioavailability	Healthy Subjects: Absolute Bioavailability Absolute bioavailability has not been determined. Healthy Subjects: Relative Bioavailability Part B of Study 007 (**lumacaftor and ivacaftor combination therapy**) evaluated the relative bioavailability of the fixed-dose combination tablet (lumacaftor and ivacaftor in the same tablet) used in the Phase 3 studies (Study 103 and Study 104) compared to lumacaftor and ivacaftor formulated as separate tablets. • Overall, the lumacaftor C_{max} and $AUC_{0\text{-}\infty}$ of the fixed-dose combination were comparable when lumacaftor and ivacaftor were administered in combination as separate tablets. • The lumacaftor geometric mean ratio (90% CI) of the fixed-dose combination versus the separate tablet was 0.93 (0.87, 1.00) and 1.00 (0.96, 1.04) for C_{max} and $AUC_{0\text{-}\infty}$, respectively.
	t_{max}	Healthy Subjects: Median t_{max}: 3 to 6 hours in Study 001, Study 003, and Study 007 (all evaluated **lumacaftor monotherapy**) Subjects With CF Median t_{max}: 3 to 4 hours in Study 101 (**lumacaftor monotherapy**)

Distribution	V/F	30 to 40 L in Study 001 (**lumacaftor monotherapy**)
	% bound	Nonclinical Studies The plasma protein binding of lumacaftor and M28-lumacaftor was high, greater than 98% in all species examined. Mean protein binding values ranged from • 97.02% to 99.91% in mouse plasma, • 98.65% to 100.00% in rat plasma, • 98.84% to 99.93% in rabbit plasma, • 98.85% to 99.85% in dog plasma, and • 99.97% to 100% in human plasma.
Elimination	Route	Healthy Subjects **Study 004 (Lumacaftor monotherapy):** • Mean fecal recovery was 90% (on average) with individual recovery ranging from 81% to 93%. Lumacaftor accounted for 42% of the radioactive dose in feces. • Mean urinary recovery was 8.6% with individual recovery ranging from 6.9% to 13%. Unchanged lumacaftor was minimally observed in urine (0.10% to 0.25% of the dose). • • Lumacaftor was mostly eliminated as parent, but partly metabolized by oxidation (presumably CYP3A4/5 based on in vitro profiling) and glucuronidation
	$t_{½\lambda z}$ (based on terminal slope)	Healthy Subjects Approximately 26 hours in Study 001 (**lumacaftor monotherapy**) Subjects With CF Mean ranged from 19 to 27 hours in Study 101 (**lumacaftor monotherapy**)
	CL/F	Healthy Subjects Approximately 1 L/hour in Study 001 (**lumacaftor monotherapy**)

Intrinsic Factors	Age	Available PK data in **healthy subjects and subjects with CF** to date are from adults (18 years and older). PK data in adolescents (12 through 17 years of age): • PK data in adolescent subjects with CF are being collected during the Phase 3 clinical studies (Study 103 and Study 104). • The effect of age and weight on the PK of lumacaftor will be evaluated based on data collected in subjects with CF 12 years and older in Study 103 and Study 104. PK data in children (6 through 11 years of age): • The effect of age and weight on the PK of lumacaftor will also be evaluated based on data collected in subjects with CF in a planned PK study in children 6 through 11 years of age
	Sex	Healthy Subjects Comparison between males versus females in Study 001 and Study 005 suggests that sex does not play a significant role in lumacaftor PK.
	Race	Subjects With CF Based on the 2011 CF Foundation's Patient Registry, approximately 94% of patients with CF in the registry are Caucasian. All patients with CF from Study 101, and the majority of patients with CF from Study 102 (approximately 99%) were Caucasian. Limited information is available for the assessment of race.
	Hepatic and Renal Impairment	Healthy Subjects There is currently no information on the PK in subjects with hepatic or renal impairment. Based on the human ADME study (Study 004), the elimination in the feces was the predominant route of elimination for lumacaftor and its metabolites, with minimal renal excretion. Thus, renal clearance is likely to play a minimal role in the elimination of lumacaftor. The hepatic impairment study for lumacaftor in combination with ivacaftor is ongoing (Study 010).
	Disease Status	While the terminal $t_{1/2}$ and accumulation findings are consistent with the data observed in healthy subjects, the median steady-state AUCs in Study 101 in subjects with CF were approximately 2-fold lower than that of Study 005 in healthy subjects when comparing the same dose (200 mg qd).

Extrinsic Factors	Drug Interactions	In vitro studies indicated that lumacaftor is a substrate of CYP3A4/5, a potential inhibitor of CYP2C8 and CYP2C9, and a moderate inducer of CYP3A4. In lumacaftor/ivacaftor DDI studies (Study 005 and Study 006), lumacaftor markedly reduced ivacaftor (CYP3A4 substrate) $AUC_{0\text{-}12h}$ and C_{max} by approximately 80% and 70%, respectively. Preliminary PK results from Study 009 (Cohort 1) indicated that lumacaftor exposure ($AUC_{0\text{-}12h}$) in combination with ivacaftor decreased by approximately 14% when coadministered with ciprofloxacin (probe: moderate inhibitor of CYP3A). Ivacaftor exposure ($AUC_{0\text{-}12h}$) in combination with lumacaftor increased by approximately 28% when coadministered with ciprofloxacin. Based on comparable lumacaftor exposures during lumacaftor monotherapy and lumacaftor and ivacaftor combination therapy in Study 005, Study 006, and Study 102, ivacaftor appeared to have minimal effect on lumacaftor.
	Food Effects	With a capsule formulation (Study 003), high-fat breakfast modestly increased the exposure to lumacaftor compared to the fasting condition (1.33- and 1.17-fold increase in C_{max} and $AUC_{0\text{-}\infty}$, respectively).
Expected High Clinical Exposure Scenario	Lumacaftor is partly eliminated via CYP3A metabolism. The inhibitory effect of a strong CYP3A inhibitor may represent a high clinical exposure scenario. An ongoing DDI study (Study 009) is evaluating interactions with lumacaftor and ivacaftor combination therapy when coadministered with itraconazole (probe: strong CYP3A inhibitor). Preliminary PK results from the first part of Study 009 evaluating lumacaftor and ivacaftor combination therapy coadministered with a moderate CYP3A inhibitor (ciprofloxacin) indicated that lumacaftor exposure ($AUC_{0\text{-}12h}$) in combination with ivacaftor did not increase in the presence of a moderate CYP3A inhibitor. Thus, a strong CYP3A inhibitor is not expected to cause a large increase in the exposure of lumacaftor. Since lumacaftor is eliminated by hepatic routes (metabolism and secretion) hepatic impairment may also represent a high clinical exposure scenario. Exposures in subjects with moderate hepatic impairment have not been evaluated, but are currently being evaluating in an ongoing study, Study 010.	

ADME: absorption, distribution, metabolism, excretion; AEs: adverse events; AUC: area under the concentration versus time curve; $AUC_{0\text{-}\infty}$: area under the concentration versus time curve from the time of dosing extrapolated to infinity; $AUC_{0\text{-}12h}$: area under the concentration versus time curve from the time of dosing to 12 hours; $AUC_{0\text{-}24h}$: area under the concentration versus time curve from the time of dosing to 24 hours; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CI: clearance index; CL/F : apparent clearance, or oral clearance, as appropriate; CYP: cytochrome P450; C_{max}: maximum observed concentration; PK: pharmacokinetic; qd: once daily; q12h: every 12 hours; DDI: drug-drug interaction; M28-lumacaftor: M28, metabolite of lumacaftor; SD: standard deviation; t_{max}: time of maximum concentration; $t_{½λz}$: half-life, time required for a 50%decrease in the concentration of the drug (based on terminal slope); and V/F volume of distribution

Ivacaftor Clinical Pharmacology

Therapeutic Dose	250 mg of ivacaftor q12h will be administered with either 600 mg of lumacaftor qd or 400 mg of lumacaftor q12h in subjects who are homozygous for the *F508del-CFTR* mutation (Phase 3 program; Study 103 and Study 104).	
Maximum Tolerated Dose	All doses studied in clinical studies were well tolerated. No maximum tolerated dose was established in humans.	
Principal Adverse Events	Subjects With CF **Ivacaftor Monotherapy:** The most common AE's (occurring in ≥ 8% of subjects with CF who have a *G551D* mutation in the *CFTR* gene) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea and dizziness. **Lumacaftor and Ivacaftor Combination Therapy:** Please see principal adverse events in Table 1under subjects taking lumacaftor taken with ivacaftor.	
Maximum Dose Tested	Single Dose	**Ivacaftor Monotherapy (Healthy Subjects):** 800 mg in Study VX05-770-001
	Multiple Dose	**Ivacaftor Monotherapy (Healthy Subjects):** 450 mg q12h for 4.5 days in Study VX09-770-008 (fed condition) **Lumacaftor and Ivacaftor Combination Therapy (Subjects With CF):** 250 mg q12h for 28 days in Study VX08-770-102 (fed condition)
Exposures Achieved at Maximum Tested Dose	Single Dose	**Ivacaftor Monotherapy (Healthy Subjects):** 800 mg in Study VX05-770-001 • Mean (SD) C_{max}:2335 (473) ng/mL • Mean (SD) $AUC_{0-\infty}$: 43496 (9473) ng·h/mL
	Multiple Dose	**Ivacaftor Monotherapy (Healthy Subjects):** 450 mg q12h for 4.5 days in Study VX09-770-008 (fed condition) • Mean (SD) C_{max}: 5450 (2560) ng/mL • Mean (SD) AUC_{0-12h}: 51600 (28000) ng·h/mL **Lumacaftor and Ivacaftor Combination Therapy (Subjects With CF):** 250 mg of ivacaftor q12h in combination with 600 mg of ivacaftor qd of lumacaftor for 28 days in Study VX08-770-102 (fed condition) • Mean (SD) C_{max}: 619 (391) ng/mL • Mean (SD) AUC_{12h}: 3800 (2490) ng·h/mL

Range of Linear PK	**Ivacaftor Monotherapy:** Healthy Subjects • Single Dose: 25 to 800 mg in Study 770-001 • Multiple Doses: 125 to 250 mg in Study 770-001 Subjects With CF Multiple Doses: 25 to 250 mg in Study 770-101	
Accumulation at Steady State	**Ivacaftor Monotherapy (Healthy Subjects):** After every 12 hour dosing, steady-state plasma concentrations of ivacaftor were reached by days 3 to 5, with an accumulation ratio ranging from 2.2 to 2.9 (Study 770-001). **Lumacaftor and Ivacaftor Combination Therapy (Healthy Subjects):** The accumulation ratio is less than 1 when ivacaftor is given in combination with lumacaftor as exposure on Day 1 is higher than that at steady state due to the induction effect of lumacaftor (Study 005 and Study 006).	
Metabolites	**Ivacaftor Monotherapy (Healthy Subjects; Study VX06-770-003):** • Metabolite profiling in urine and feces indicated extensive metabolism of ivacaftor in humans following oral dose administration. • VRT-837018 (M1, hydroxy metabolite; M1-ivacaftor) and VRT-842917 (M6, acid metabolite; M6-ivacaftor) are the 2 major metabolites in humans, which accounted for approximately 65% of dose excreted following a single dose of 133 mg 14C-ivacaftor in healthy male subjects. • M1-ivacaftor has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6-ivacaftor has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.	
Absorption	Absolute and Relative Bioavailability	**Ivacaftor Monotherapy:** The exposure of ivacaftor increased approximately 2- to 4-fold when given with food containing fat.
	t_{max}	**Ivacaftor Monotherapy:** The median (range) tmax is approximately 4.0 (3.0; 6.0) hours in the fed state. **Lumacaftor and Ivacaftor Combination Therapy (Subjects With CF):** In Study 102, the median t_{max} is approximately 3.0 to 4.0 hours in the fed state.
Distribution	V/F	**Ivacaftor Monotherapy:** After oral administration of 150 mg q12h for 7 days in Study X (fed condition), the mean (± SD) for apparent volume of distribution was 353 (122) L.
	% bound	**Ivacaftor Monotherapy:** Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

Elimination	Route	**Ivacaftor Monotherapy (Healthy Subjects):** In Study VX06-770-003, following a single oral dose of 133 mg 14C-ivacaftor solution, 71.6% of dose administered was excreted in feces (mainly as metabolites). 5.48% of dose administered was excreted in urine (mainly as metabolites).
	Terminal t½	**Ivacaftor Monotherapy:** The apparent terminal half-life was approximately 12 hours following a single dose.
	CL/F	**Ivacaftor Monotherapy :** The mean apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and subjects with CF. The CL/F (SD) for the 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.
Intrinsic Factors	Age	**Ivacaftor Monotherapy:** Ivacaftor monotherapy is approved for the treatment of CF) in patients age 6 years of age and older. The same dose as adult is used for children 6 years and older.
	Sex	**Ivacaftor Monotherapy** The effect of gender on ivacaftor pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of ivacaftor. No dose adjustments are necessary based on gender.
	Race	Since CYP3A is the main metabolism pathway for ivacaftor, it is expected that race would not be a significant covariate for PK variations of ivacaftor.
	Hepatic and renal impairment	**Ivacaftor Monotherapy** Studies in patients with moderately impaired hepatic function indicated 2- fold increase in ivacaftor AUC_{∞}. **Ivacaftor in combination with lumacaftor:** There is currently no information on the PK of ivacaftor in combination with lumacaftor in subjects with hepatic or renal impairment. The hepatic impairment study for lumacaftor in combination with ivacaftor is ongoing.
	Disease Status	The PK of ivacaftor is similar between healthy adult subjects and subjects with CF.

Extrinsic Factors	Drug interactions	**Ivacaftor Monotherapy** Please see the Ivacaftor Investigator's Brochure. **Lumacaftor and Ivacaftor Combination Therapy:** In lumacaftor/ivacaftor DDI studies (Study 005 and Study 006), lumacaftor markedly reduced ivacaftor (CYP3A4 substrate) AUC_{0-12h} and C_{max} by approximately 80% and 70%, respectively. Lumacaftor exposure appeared to slightly decrease in the combination with ivacaftor. Preliminary PK results from Study 009 (Cohort 1) indicated that ivacaftor exposure (AUC_{0-12h}) in combination with lumacaftor increased by approximately 28% when co-administered with ciprofloxacin. The drug interaction studies for lumacaftor in combination with ivacaftor with rifampin and itraconazole are ongoing (Study 009, Cohort 2 and Cohort 3).
	Food Effects	**Ivacaftor Monotherapy** The exposure of ivacaftor increased approximately 2- to 4-fold when given with food containing fat.
Expected High Clinical Exposure Scenario	Ivacaftor is extensively metabolized with CYP3A being the major metabolic pathway. The inhibitory effect of a strong CYP3A inhibitor may represent the expected high clinical exposure scenario. Study VX08-770-006 (ketoconazole DDI study with ivacaftor monotherapy) showed a significant increase in ivacaftor exposure with geometric mean ratio (ivacaftor monotherapy with:without ketoconazole) of 2.65 for C_{max} and 8.45 for $AUC_{0-\infty}$. When lumacaftor is given in combination with ivacaftor, the effect of a strong CYP3A inhibitor is expected to be attenuated due to the CYP3A induction effect of lumacaftor. Preliminary PK results from Study 009 with a moderate CYP3A inhibitor (ciprofloxacin) indicated that ivacaftor exposure (AUC_{0-12h}) in combination with lumacaftor increases by approximately 28% in the presence of a moderate CYP3A inhibitor. Based on the comparison of ivacaftor exposure levels to historical data, there appeared to still be a large net decrease in ivacaftor exposures in combination with lumacaftor and ciprofloxacin, suggesting a net induction effect in the presence of a moderate CYP3A inhibitor. Thus, a strong CYP3A inhibitor is not expected to cause a large increase in the exposure of ivacaftor when given in combination with lumacaftor. Since ivacaftor is eliminated by hepatic route and has previously shown a significant effect in a hepatic impairment study (ivacaftor alone), hepatic impairment may also represent a high clinical exposure scenario when ivacaftor is given in combination with lumacaftor. Ivacaftor exposures in moderate hepatic impairment subjects have not been evaluated in combination with lumacaftor but are currently being studied.	

AEs: adverse events; AUC: area under the concentration versus time curve; $AUC_{0-\infty}$: area under the concentration versus time curve from the time of dosing extrapolated to infinity; AUC_{0-12h}: area under the concentration versus time curve from the time of dosing to 12 hours; CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator; CL/F : apparent clearance, or oral clearance, as appropriate; CYP: cytochrome P450; C_{max}: maximum observed concentration; PK: pharmacokinetic; qd: once daily; q12h: every 12 hours; DDI: drug-drug interaction; M1-ivacaftor: M1, metabolite of ivacaftor; M6-ivacaftor: M6, metabolite of ivacaftor; SD: standard deviation; t_{max}: time of maximum concentration; $t_{½,z}$: half-life, time required for a 50%decrease in the concentration of the drug (based on terminal slope); and V/F volume of distribution

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

/s/

MOH JEE NG
02/12/2015

QIANYU DANG
02/12/2015

DHANANJAY D MARATHE
02/12/2015

JIANG LIU
02/12/2015

MICHAEL Y LI
02/13/2015

NORMAN L STOCKBRIDGE
02/13/2015

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) PHARMACOLOGY/TOXICOLOGY CONSULT REVIEW

Date:
February 2, 2015

From:
Andrew Goodwin, Nonclinical Reviewer, DPARP

Through:
Timothy Robison, Nonclinical Team Leader, DPARP

To:
Edwin Jao, Quality Reviewer, ONDQA
Craig Bertha, Quality Team Leader, ONDQA

Re:
Nonclinical consult to the chemistry, manufacturing, and controls (CMC) review team for NDA 206038 (lumacaftor/ivacaftor combination for cystic fibrosis, Vertex Pharmaceuticals)

Background
Ivacaftor (VX-770), a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, received FDA approval as a monotherapy for certain cystic fibrosis (CF) patients in 2012. Lumacaftor (VX-809) is a proposed CFTR (b) (4) being developed as a fixed dose combination with ivacaftor; there is no lumacaftor monoproduct registration program. The lumacaftor-ivacaftor combination product received breakthrough designation for the treatment of CF in patients with two copies of the ΔF508 mutation in 2012. A rolling NDA submission was initiated in July 2014, the completed NDA 206038 submission was received on November 5, 2014, and the filing was accepted with Priority Review and a PDUFA goal date of July 5, 2015.

Consult Request
In email correspondence dated October 7-9, 2014 and December 14-16, 2014, Dr. Jao requested nonclinical input on the issues described below. This memo provides the requested nonclinical evaluation and recommendations related to the acceptability of the sponsor's approach and any additional information that may be required.

1. "There are several compounds that were found to possess **structural alerts** by *in-silico* methods (Derek and Leadscope). The applicant proposed to control them as regular impurities based on the negative Ames test results of "several structural analogs" (no structures and test results are submitted)." The structures of these compounds (b) (4) are shown below.

(b) (4)

2. "The applicant also proposed to control several compounds as regular impurities that were found **non-structure alert**, while a structurally very similar compound was found as a **structural alert**, but Ames negative." The structures of these compounds (b) (4) are shown below

(b) (4)

3. Regarding the specification for the (b) (4): "While the proposed acceptance criterion for this (b) (4) is (b) (4) ppm, all batch data (14 batches) from the commercial production site is below (b) (4) ppm, except one smaller batch for clinical study which contains (b) (4) ppm. Therefore there is plenty of room for tightening if you have safety concerns."

4. Two additional compounds which are visually structural alerts by in-house standards (b) (4) but the applicant claims that they are not by their in-silico study.

(b) (4)

5. Confirm the sponsor's assertion that [redacted] are qualified at the levels listed in the following table (excerpted from NDA 206038 3.2.S.4.5):

Table 1 Toxicology Qualification Summary

Impurity	Acceptance Criteria	Qualified Level	Actual Daily Exposure at the Specification Limit
[redacted]	NMT [redacted]% w/w	[redacted] mg/day	[redacted] mg/day
	NMT [redacted]% w/w	[redacted] mg/day	[redacted] mg/day

Safety Assessment

1. [redacted]

In the CMC document "Control of Materials" (3.2.S.2.3), [redacted] were described as being structural alerts for mutagenicity, based on Derek Nexus 3.1.1 and Leadscope Enterprise 3.1.1-10 analysis. However, these statements are contradicted in the detailed in silico analysis report (VX-809-TX-031) submitted in the nonclinical module of the NDA (4.2.3.7). This report shows negative or inactive results for each of the three structures across the Derek Nexus (4.0.5) and Leadscope Enterprise (3.2.3-1, Model Applier 1.7.0; *Salmonella* and *E. coli*) platforms. Further, the sponsor's CMC document referenced additional justification for two of these compounds in the Toxicology Written Summary (2.6.6); however, no such discussion is present in that document.

[redacted] were submitted for a CDER Computational Toxicology consult review on October 28, 2014. Dr. Mark Powley provided an expert report on November 13, 2014 based on analysis with three (Q)SAR software platforms: Derek Nexus 4.0.5, Leadscope Model Applier 1.8.3-1, and CASE Ultra 1.4.6.6. All three of the structures were considered negative for mutagenic potential based on the software prediction and Dr. Powley's expert assessment.

From the nonclinical perspective, the sponsor's proposal to control [redacted] as regular impurities is considered to be acceptable.

2. [redacted]

[redacted] were submitted for a CDER Computational Toxicology consult review on October 28, 2014. Dr. Mark Powley provided an expert report on November 13, 2014 based on analysis of these structures as well as the parent lumacaftor (VX-809) structure with three (Q)SAR software platforms: Derek Nexus 4.0.5, Leadscope Model Applier 1.8.3-1, and CASE Ultra 1.4.6.6.

All four impurity structures, as well as VX-809, returned a positive software prediction for *Salmonella* mutagenicity. This prediction in the CASE Ultra analysis was based on the presence of (b) (4) in each of the five structures, as shown below for VX-809.

(b) (4)

VX-809 has been determined to be negative for genotoxicity in an in vitro bacterial reverse mutation assay, in vitro Chinese Hamster Ovary cell chromosomal aberration assay, and in vivo mouse micronucleus assay (see nonclinical review by Dr. Timothy Robison dated January 3, 2008). Therefore, the presence of this alerting moiety in the four impurities is of no nonclinical concern. (b) (4) also generated an equivocal prediction in the Leadscope analysis based on the presence of a (b) (4) moiety. However, Dr. Powley's expert assessment judged this finding to be of questionable relevance due to the presence of additional known reactive groups in the mutagenic structures in the training set. Overall, the expert prediction was negative for genotoxic potential for (b) (4)

From the nonclinical perspective, the sponsor's proposal to control (b) (4) as regular impurities is considered to be acceptable.

3. (b) (4)

There is no specified limit for (b) (4) in the (b) (4) *Guideline* document pertaining to (b) (4) The sponsor asserts a permissible daily exposure (PDE) of (b) (4) mg and proposes an acceptable limit of (b) (4) ppm, corresponding to a maximum daily exposure of (b) (4) ug at the proposed (b) (4) mg daily dose of lumacaftor.

During development, the sponsor was informed on August 13, 2012 that levels of (b) (4) above (b) (4) ug per day (equivalent to that in a (b) (4) mg dose of ivacaftor) would require qualification based on a NOAEL in a suitable 3-month toxicology study in one species in order to support phase 3 development and an NDA. A teleconference was subsequently held on September 12, 2012 between Dr. Robison and the sponsor. (b) (4) Dr. Robison indicated a requirement for a two-fold safety margin on a mg/m^2 basis between the clinical dose and the NOAEL dose, as calculated for both children and adults. The NOAEL in that study was (b) (4) mg/kg/day, as confirmed by Division of Antivirals Products reviewer Dr. Mark Powley (refer to the nonclinical review by Dr. Robison filed to IND 79521 on November 2, 2012.)

In the NDA 206038 submission, the sponsor provided a supplemental validation study (AR-14302) with an improved lower limit of quantification of (b) (4) ppm (vs. (b) (4) ppm previously). This study determined the level of (b) (4) in the test article lot employed in study VX-222-TX-005 to be (b) (4) ppm. At the NOAEL of 1000 mg/kg/day, this level corresponds to a daily (b) (4) exposure of (b) (4) mg/kg/day or (b) (4) mg/m^2/day.

The proposed (b) (4) limit of (b) (4) ug/day in the lumacaftor-ivacaftor drug product corresponds to (b) (4) mg/m^2/day for a 60 kg adult and (b) (4) mg/m^2/day for a 20 kg child. Therefore, the referenced dog study provides (b) (4)-fold and (b) (4)-fold safety margin on a body surface area basis for adults and children, respectively. The sponsor's proposed specification for (b) (4) is considered acceptable from the nonclinical perspective.

4. (b) (4)

The sponsor's in silico study report (VX-809-TX-031) made overall negative calls for predicted genotoxicity for (b) (4), two impurities present in the VX-809 starting material with structural alerts for mutagenicity. Based on the Chemist's concern regarding visual structural alerts, a CDER computational toxicology consult was requested on December 23, 2014 and results were received from Dr. Mark Powley on January 8, 2014.

(b) (4) returned negative predictions with the DEREK and Leadscope methods in both the sponsor's study as well as the consult report from Dr. Powley. The application of the two (Q)SAR models, both yielding negative predictions, by the sponsor would generally be considered sufficient to eliminate concern about an impurity with a structural alert. However it is noted that the CDER Computational Toxicology group also applies the Case Ultra model, which returned a positive prediction for both *Salmonella* and *E. coli* mutagenicity. In a follow-up email dated January 8, 2015, Dr. Powley suggested that the discrepancy might owe to the fact that only Case Ultra includes (b) (4)

(b) (4) was considered to be negative for *Salmonella* mutagenicity but positive for potential *E. coli* mutagenicity in both the sponsor's in silico report as well as the consult report from Dr. Powley. As with (b) (4) the addition of the Case Ultra model increased the positive signal for this (b) (4) in the training set being mutagenic in *E. coli*. The sponsor discounted the positive Leadscope prediction based on the negative genotoxicity testing results for a number of structures containing (b) (4) without other alerting features. In Dr. Powley's email dated January 8, 2014, he noted that the sponsor's argument was not unreasonable and that many of the mutagenic (b) (4) in the Case Ultra training set also contained additional alerting features. However, he noted that the (b) (4) alone could reasonably be expected to be mutagenic and called into question the robustness of the purported negative data for other compounds quoted by the sponsor.

The overall consult recommendation from Dr. Powley was that, while (b) (4) do not represent the strongest of positive predictions, neither should they be considered negative for genotoxic potential in the absence of additional data.

Chemistry reviewer Dr. Edwin Jao provided additional information regarding the potential exposure to [redacted] at the proposed clinical dose level in an email dated January 8, 2014. Each of these compounds is an impurity in the starting material which is controlled through the [redacted] resulting in a maximum concentration in the VX-809 drug substance of [redacted] ppm. Based on the proposed 800 mg daily dose of VX-809 in the drug product, the daily exposure would be [redacted] ug.

In summary, [redacted] are considered to be potentially genotoxic impurities. However, the expected exposure to these compounds is below the [redacted] ug per day threshold for a chronic product and therefore there is no safety concern from the nonclinical perspective.

5. [redacted]

The sponsor has proposed that two organic impurities, [redacted] are qualified based on levels of these compounds present in the VX-809 material used in the 3-month VX-809 dog study (VX-809-TX-008). No details are provided and the reviewer is unclear as to how the sponsor arrived at their "qualified levels" of [redacted] and [redacted] mg for the two compounds.

The table below provides the reviewer's calculation of the human dose of these two impurities that would be supported by study VX-809-TX-008. This study has been previously reviewed by Dr. Timothy Robison (September 30, 2010) who identified [redacted] mg/kg/day as the NOAEL. Applying a 2-fold safety margin on a mg/m^2 basis, qualified levels of [redacted] and [redacted] mg per day were calculated for [redacted], respectively. These values are greater than the potential clinical exposure based on the sponsor's specifications and the 800 mg daily dose level for VX-809 (lumacaftor).

Impurity	% in Tox Batch[a]	Exposure at Dog NOAEL[b]	Max Supported Human Dose[c]	Proposed Specification	Clinical Exposure[d]
[redacted]	[redacted]%	[redacted] mg/kg/day	[redacted] mg/day	NMT [redacted]%	[redacted] mg/day
	[redacted]%	[redacted] mg/kg/day	[redacted] mg/day	NMT [redacted]%	[redacted] mg/day

NMT: Not More Than
[a] From VX-809 certificate of analysis in VX-809-TX-008 study report
[b] [redacted] mg/kg/day * impurity level = listed exposure at dog NOAEL
[c] Calculated with a 2-fold safety margin on a mg/m^2 basis
[d] Calculated based on the proposed specification and 800 mg daily dose of VX-809

In summary, the sponsor's proposed specifications for [redacted] (NMT [redacted]%) and [redacted] (NMT [redacted]%) are acceptable from the nonclinical perspective.

Appendices
Computational toxicology consultation reports from Dr. Mark Powley dated November 13, 2014 and January 8, 2015

To: Andrew Goodwin
cc: Timothy Robison
From: CDER/OTS/OCP/DARS: The Chemical Informatics Group
Re: NDA 206038
Date: November 13, 2014

Lumacaftor and seven impurities have been evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: *Derek Nexus* 4.0.5 (*DX*), *Leadscope Model Applier* 1.8.3-1 (*LMA*), and *CASE Ultra* 1.4.6.6 (*CU*). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify a positive study call.

The (Q)SAR assessment of mutagenic potential for the impurities is consistent with recommendations described in the ICH M7 guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion. The API, **Lumacaftor**, is included in the report for comparison purposes.

Based on the assessment, the impurities evaluated appear to lack mutagenic potential.

Chemical 1: Lumacaftor

(b) (4)

Lumacaftor is known to be negative for bacterial mutagenicity (i.e., both *Salmonella* and *E. coli* mutagenicity). (b) (4)

(b) (4)

(b) (4)

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To: **Andrew Goodwin**
cc: **Timothy Robison**
From: **CDER/OTS/OCP/DARS: The Chemical Informatics Group**
Re: **NDA 206038**
Date: **January 8, 2015**

Two impurities have been evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: *Derek Nexus* 4.1.0 (*DX*), *Leadscope Model Applier* 1.8.3-1 (*LMA*), and *CASE Ultra* 1.4.6.6 (*CU*). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify a positive study call.

The (Q)SAR assessment of mutagenic potential for the impurities is consistent with recommendations described in the ICH M7 guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.

Overall, both (b) (4) are both predicted to be positive for bacterial mutagenicity.

(b) (4)

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/s/

ANDREW C GOODWIN
02/02/2015

TIMOTHY W ROBISON
02/02/2015
I concur

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206038 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Orkambi Established/Proper Name: lumacaftor/ivacaftor Dosage Form: oral tablet Strengths: 200mg/125mg, (b) (4)		
Applicant: Vertex Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: November 05, 2014 Date of Receipt: November 05, 2014 Date clock started after UN:		
PDUFA Goal Date: July 05, 2015	Action Goal Date (if different):	
Filing Date: January 04, 2015	Date of Filing Meeting: December 03, 2014	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): cystic fibrosis patients 12yr and older who are homozygous for F508del		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 74633, 79521	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☒	☐		ivacaftor alone also has orphan designation
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☒	☐	☐	same product (ivacaftor) is now being used in combination with lumacaftor
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		eCTD backbone serves as an index
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☐	☒		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☒		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and*	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT-IRT 12/10/2014
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 12, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 03, 2014

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Leila P. Hann	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Anthony Durmowicz		Y
Division Director/Deputy	Badrul Chowdhury/Lydia Gilbert-McClain		Y/Y
Office Director/Deputy	Curt Rosebraugh/Mary Parks		N/Y
Clinical	Reviewer:	Robert Lim	Y
	TL:	Anthony Durmowicz	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jianmeng Chen	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Lan Zeng	Y
	TL:	David Petullo/Greg Levin	Y/Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew Goodwin	N
	TL:	Timothy Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Edwin Jao/Arthur Shaw	N/Y
	TL:	Craig Bertha	Y
Biopharmaceutics	Reviewer	John Duan	Y
	TL:		
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Lissa Owens	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**: Review completed 12/11/2014	☐ Not Applicable ☒ YES ☒ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): February 03, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60

☒	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 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
12/31/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 206038

Application Type: New NDA

Name of Drug/Dosage Form: Orkambi (lumacaftor - ivacaftor) oral tablet

Applicant: Vertex Pharmaceuticals, Inc.

Receipt Date: November 05, 2014

Goal Date: July 05, 2015

1. Regulatory History and Applicant's Main Proposals

NDA 206038 is a combination of lumacaftor and ivacaftor. This is an NME NDA which has Breakthrough Designation, Orphan Designation, and is on a rolling review. This will be a priority application.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *the pharmacologic class has not been established*

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

N/A

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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