

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208215Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208215/Original 1

SUPPL # N/A

HFD # 530

Trade Name: DESCOVY®

Generic Name: emtricitabine and tenofovir alafenamide (F/TAF)
200/25 mg fixed-dose combination tablet

Applicant Name: Gilead Sciences, Inc.

Approval Date, If Known: April 7, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☐ NO ☒

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

The development program for the emtricitabine and tenofovir alafenamide (F/TAF) fixed dose combination tablets (Descovy) is based upon the fact that identical dosages of these antivirals are combined in Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide [E/C/F/TAF]). Two pivotal relative bioavailability (BA) studies comparing the exposures of emtricitabine and tenofovir alafenamide between the fixed dose combination of Descovy (F/TAF) and Genvoya® (E/C/F/TAF) form the basis of for approval of the NDA 208215. Genvoya® was approved on November 5, 2015. If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

The current application seeks approval of a fixed-dose-combination for F/TAF, containing a drug substance (TAF), single active moiety of which has not previously been approved by the FDA under section 505(b) of the FDCA. Because the F/TAF product is currently under review in NDA 208215 and the E/C/F/TAF product in NDA 207561 (approved on November, 2015) both contain the drug substance TAF, the applicant requested 5 years under "umbrella exclusivity" policy. The "umbrella exclusivity" will apply to the F/TAF product during any remaining portion of, and to the same extent as, the E/C/F/TAF product's NCE exclusivity.

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

YES ☐ NO ☒

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

No

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA#	21500	EMTRIVA (emtricitabine) 200 mg Capsule
NDA#	21896	EMTRIVA (emtricitabine) 10 mg/mL Oral Solution
NDA#	21752	TRUVADA (emtricitabine/tenofovir disoproxil fumarate) 200mg/300 mg Tablet
NDA #	203100	STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Fixed-Dose Combination 150 mg/150 mg/200 mg/300mg Tablets
NDA #	207561	GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) Fixed-Dose Combination 150 mg/150 mg/200 mg/10mg Tablet

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should

only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☐ NO ☒

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

The applicant submitted Phase 2 clinical trial data but it is not necessary to support the approval of this application.

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

support approval of the application?

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐

NO ☐

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

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

Investigation #1

YES ☐

NO ☐

Investigation #2

YES ☐

NO ☐

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

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

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

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

Investigation #1

!

!

IND #

YES ☐

! NO ☐

! Explain:

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

=====

Name of person completing form: Myung-Joo Patricia Hong, M.S.
Title: Senior Regulatory Project Manager
Date: March 28, 2016

Name of Office/Division Director signing form: Jeffrey Murray, M.D., MPH
Title: Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products

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

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

/s/

MYUNG JOO P HONG
03/25/2016

JEFFREY S MURRAY
04/04/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208215 Original Submission #1	NDA Supplement #: N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: DESCovy® Established/Proper Name: emtricitabine and tenofovir alafenamide (F/TAF) Dosage Form: 200/25 mg fixed-dose combination tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): N/A
RPM: Myung-Joo Patricia Hong, M.S.		Division: Division of Antiviral Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	For ALL 505(b)(2) applications, two months prior to EVERY action: - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	
❖ Actions		
- Proposed action - User Fee Goal Date is <u>April 7, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 4
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval - April 4, 2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included (3/25/16)
Original applicant-proposed labeling	☒ Included (4/7/15)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included (3/25/16)
Original applicant-proposed labeling	☒ Included (4/7/15)
Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included (3/22/16)
- Proprietary Name - Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	- Grant Letter - 5/19/15 - Review - 5/15/15
Labeling reviews <i>(indicate dates of reviews)</i>	- RPM: PLR Format Review - 4/23/15 - DMEPA: 12/10/15 & 3/25/16 - DMPP/PLT (DRISK): 3/15/16 - OPDP: 3/15/16 - SEALD: ☒ None - CSS: ☒ None - Product Quality: PI, Immediate Container Label & Access Carton/Container Label – Included in Integrated Product Quality Assessment Review (page 82 - 91) - 12/18/15 & 2/23/16 - Other: ☒ None
Administrative / Regulatory Documents	
- RPM Filing Review⁴/Memo of Filing Meeting <i>(indicate date of each review)</i> - All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review - 5/29/15 ☒ Not a (b)(2)
NDA only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included

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

Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (indicate date) - If yes, OC clearance for approval (indicate date of clearance communication)	☐ Yes ☒ No ☐ Not an AP action
- Pediatrics (approvals only) - Date reviewed by PeRC <u>February 10, 2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)	4/9/15, 6/2/15, 6/23/15, 7/23/15, 8/28/15, 11/4/15, 12/1/15, 12/15/15, 12/17/15, 12/24/15, 1/13/16, 1/19/16, 1/20/16, 2/2/16, 2/3/16, 2/11/16, 2/12/16, 2/29/16, 3/9/16, 3/18/16, 3/24/16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (indicate date of mtg)	☒ N/A or no mtg
Pre-NDA/BLA meeting (indicate date of mtg)	December 15, 2014 - Minutes included
EOP2 meeting (indicate date of mtg)	October 17, 2013 - EOP 2 Meeting scheduled under IND 111851; however, Gilead cancelled after receiving FDA's preliminary comments sent 10/15/2013 - Preliminary comments included
Mid-cycle Communication (indicate date of mtg)	October 1, 2015 - Minutes included
Late-cycle Meeting (indicate date of mtg)	January 11, 2016 – Minutes included
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)	None

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	• Approval – April 4, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	• Approval - February 25, 2016 • Addendum - April 4, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	2
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	• Filing Review - 5/19/15 • Approval - 12/7/15
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	• Memorandum explaining why no Financial Disclosure Information was included - 3/1/16 • The approval is based on BA/BE studies.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	• Filing Review - 5/20/15 • Approval - 12/2/15
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	• Approval – 12/18/15

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	Please see CDTL review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	• Filing Review - 6/6/15 • Approval - 12/7/15 • Addendum - 3/30/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	• Memorandum - 6/12/15 • BA/BE Sites Inspection Review Summaries - 9/10/15 & 1/5/16
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	• Filing Review – 6/2/15 • Approval - 12/2/15 (Dr. Powley) & 12/3/15 (Dr. Wrzesinski)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	• Filing Review - 6/16/15 • Pending Approval - 12/18/15 • Approval - 2/23/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Granted - Included in Integrated Product Quality Assessment Review (page 81) - 12/18/15 & 2/23/16
☐ Review & FONSI <i>(indicate date of review)</i>	N/A
☒ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Included in Integrated Product Quality Assessment Review (page 81) - 12/18/15 & 2/23/16

❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable
Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

MYUNG JOO P HONG
04/04/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Division Antiviral Products
10903 New Hampshire Ave
Silver Spring, Md. 20993
February 25, 2016

From: William B. Tauber, M. D.
Medical Officer DAVP

To: NDA 208215

Subject: Financial Disclosure Regarding Studies: GS-US-311-1088,
GS-US-311-1472, GS-US-311-1473, GS-US-311-1386, GS-
US-311-0101, GS-US-120-0118 and GS-US-299-0102

PURPOSE AND SCOPE OF MEMO

This memorandum is intended to document declarations made by Gilead Sciences Inc. regarding financial interests and possible conflicts of interest regarding Investigators who participated in the studies listed above. This Memorandum will be added to the Clinical Review of NDA 208215.

Financial Disclosure Statement: In Module 1.3.4 of the original submission dated 07 April 2015 under the Heading of Lists of Investigators who are Gilead Employees. Gilead Sciences identifies [REDACTED] (b) (6), MD as a Gilead Employee after he left the position of principal investigator participating in Study GS-US-292-0102 in NDA 207561. He is no longer an investigator for this study or any other Gilead-sponsored clinical study. In addition, on Form OMB No. 0910-0396, Patricia Carlos, Manager of Regulatory Affairs for Gilead Sciences, Inc. certifies that no financial arrangements were established with listed clinical investigators participating in Studies [REDACTED] or GS-US-311-1473 whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)(3). These [REDACTED] supported the determination of PK bioequivalence of exposures between F/TAF (Descovy) and F/TAF in the 4 fixed-drug combination (FDC) Genvoya.

This submission contains no financial disclosures statements for Studies GS-US-311-1088, GS-US-311-1386, GS-US-311-0101, GS-US-311-0101, and GS-US-120-0118. These 5 studies were generally open-label, conducted in healthy volunteers, consisted of single doses usually repeated or short courses of differing doses of study drugs, concomitant drug-drug interaction measurements with TAF and or FTC in combination with other antiretrovirals to examine the PK bioequivalence

of F/TAF with its components TAF and FTC; the effects of food on PK, DDI interactions with FTC and or TAF with EFV, DRV/COBI, COBI by itself, DDI interactions with protease inhibitors including atazanavir, darunavir, lopinavir all boosted with ritonavir as well as unboosted dolutegravir, and lastly an analysis of TFV-DP concentrations in PBMCs in subjects receiving FTC/TAF or FTC/TDF in combination with 3rd agents boosted and unboosted. All of these five studies are characterized by objective laboratory measurements, sparse dosing of study drugs, healthy volunteer participants, are open label and except for the PBMC, no clear comparison between efficacies or outcomes. It is presumed that PK and DDI studies of this type are relatively immune to investigator bias. The decision by the Applicant to omit the financial disclosure statements from these 5 studies is therefore not assessed to represent a concern regarding the validity of the results obtained.

Study GS-US-299-0102

In addition to the 7 studies listed above, Gilead Sciences submitted clinical study GS-US-299-0102, a Phase 2, double blinded, active controlled study of 150 HIV-1 infected, treatment naïve subjects randomized 2:1 to either Darunavir/Cobicistat/FTC (emtricitabine)/TAF (10mg) or Darunavir +COBI+ Truvada (TVD).

When TAF is given with a CYP3A4 inhibitor “boosted” darunavir the resulting TAF exposures do not demonstrate boosting. The theoretical explanation for this phenomenon is the Pgp efflux pump activity unique to darunavir. Although not specifically stated, Study GS-US-299-0102 appears to have been submitted to provide evidence of non-inferiority of TAF 10mg compared to TDF 300mg despite the lower exposure levels of TAF observed when it is combined with “boosted” darunavir. This may be intended to support Gilead’s contention that the serum exposure is less important than the PBMC concentrations. PBMC concentrations have been demonstrated to be 4 times higher with TAF 10mg than with TDF 300mg.

Financial Disclosure Findings Study GS-US-299-0102

Study GS-US-299-0102 was potentially subject to investigator bias. This study was conducted by two populations of investigators/study sites. One group of investigators/study sites met criteria prompting filing a Financial Disclosure Statement. The other group of investigators/sites did not meet these criteria. In the Study Synopsis the Applicant indicates a total of 38 participating study centers, 37 in the U.S. and one in Puerto Rico. In Section 1.3.4 Financial Certification and Disclosure, the applicant certifies a portion of these sites, with their Principal and Sub-investigators as having no financial interest or arrangements as described in 21 CFR 54.4(a)(3). The Applicant identifies other sites as having Principal and or sub-investigators as meeting the criteria for Financial Disclosure of either significant payments > \$25,000 or Equity Interest of > \$ 50,000. In this reviewer’s assessment of the submitted material, 18 sites met these criteria and will be subsequently designated Financial Disclosure Positive (FD+). The remaining 20 sites did not meet criteria prompting a Financial Disclosure Statement and will subsequently designated Financial Disclosure Negative (FD-). For the purposes of this analysis, a site was designated as FD+ if either the Principal Investigator or subinvestigator in the absence of a identified PI met the criteria for Financial Disclosure specified above.

The 18 FD+ sites represent 47% of the total number of sites in GS-US-299-0102. Of the treatment arms, 49/103 (48%) of the D/C/F/TAF subjects and 20/50 (40%) of the DRV + COBI + TVD

subjects were studied in FD+ sites. The remaining 20 FD- sites were 53% of the total and enrolled 54/103 (52%) of the D/C/F/TAF subjects and 30/50 (60%) of the DRV + COBI + TVD subjects.

Study GS-US-299-0102 Efficacy

The primary efficacy endpoints for GS-US-299-0102 was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA-defined snapshot algorithm. The rates of virologic success through Week 48 were also assessed using the FDA-defined snapshot algorithm. The Applicant calculated the difference in percentages as 3.3% with a 95% CI of -11.4 to 18.1% for the prespecified efficacy endpoint at 24 weeks. The lower bound of this CI was greater than the -12% prespecified level of -12% which lead Gilead to declare non-inferiority of the TAF containing product compared to the Truvada containing product. At 48 weeks, the difference in percentages was -6.2% with a 95% CI of -19.9% to 7.4% and non-inferiority was not met.

Table 1 Applicant Values for HIV-1 < 50 copies/mL at 24 and 48 weeks

	Virologic Success TAF N=103	Virologic Success TDF N=50
Sampled at 24 weeks	77/103 (75%)	37/50 (74%)
Sampled at 48 weeks	78/103 (77%)	42/50 (84%)

When 24 and 48 weeks efficacy data of the FD+ sites are compared with FD- sites the following is noted. The percentages of TAF recipients were balanced between FD + and FD- centers. The percentages of TDF recipients were numerically higher among the FD- populations. There were 8 discontinuations for non-safety reasons in the TAF group prior to the 24 week sampling. These discontinuations were equal between FD+ and FD- centers. There were an additional 2 discontinuations in the TAF group prior to the 48 week sampling. There were 2 non-safety TDF discontinuations by 24 weeks and 1 additional at 48 weeks all in the FD- groups.

At 24 weeks the percentages of virologic successes for both TAF and TDF arms were similar between FD+ and FD- populations. At 48 weeks, there is improvement in the numbers of virologic success in both populations but to a much greater extent in the TDF arm of FD+ sites. There was a surge in virologic successes among FD+ population TDF recipients between the 24 and the 48 week sampling ultimately achieving 100% success. There is no current explanation for these observations. The difference in the TDF efficacy data of the FD+ and FD- populations may be due to differences in study conduct. It is noted that the FD+ TDF population did not experience any discontinuations.

Table 2 Reviewer Derived Values for HIV-1 < 50 copies/mL at 24 and 48 weeks

	Subjects at Sites where Financial Disclosure Required		Subjects at Sites where Financial Disclosure Not Required		Totals	
	TAF	TDF	TAF	TDF	TAF	TDF
BASELINE	49/103 (48%)	20/50 (40%)	54/103 (52%)	30/50 (60%)	103	50
VL < 50 copies/mL at 24 weeks	36/49 (74%)	15/20 (75%)	41/54 (76%)	22/30 (73%)	77/103(75%)	37/50 (74%)
VL < 50 copies/mL at 48 weeks	37/49 (76%)	20/20 (100%)	40/54 (74%)	23/30 (77%)	77/103 (75%)	43/50 (86%)

Study GS-US-299-0102 Safety

There were no deaths observed during the conduct of this trial. Overall, there were 7 subjects who experienced an SAE or discontinuation for an adverse event or both. Of the 7 subjects, 2 (1TAF, 1TDF) were identified in FD+ subjects and 5 (4 TAF, 1 TDF) were observed in FD- subjects. There were 118 AEs that were assessed as related to study drugs. There were 62 subjects who experienced these related AEs; 36 were participating at a FD+ site and 26 were participating at a FD- site.

There were 11 subjects who experienced Grade 3 AEs. Of these 11, 4 subjects (2TAF, 2 TDF) were in the FD+ group and 7 subjects (5 TAF, 2 TDF) were in the FD- group. The AEs were assessed as related in one FD+ subject and one FD- subject. Thirteen subjects had related Grade 2 AEs, 6 were from FD+ sites and 7 were from FD- sites.

There 222 Grade 2 AEs experienced by 82 subjects. Of these 82 subjects, 45 were in the FD+ group and 37 were in the FD- group. Of these 82 subjects, 55 were TAF recipients and 27 were TDF recipients.

Discussion:

For Studies GS-US-311-1088, (b) (4) GS-US-311-1473, GS-US-311-1386, GS-US-311-0101, and GS-US-120-0118 the low likelihood of bias due to the objective nature of the data collected combined with statements made by the Sponsor make systematic bias due to financial interests of the investigators unlikely.

GS-US-299-0102 as a double-blind, comparative, active control study would in general be more of a risk for systematic bias. The Financial Disclosure statements in this study indicate that a large proportion of the investigators participating in this trial met the standard criteria for disclosure of potential financial interest conflicts. Applying the rule that all subjects participating at sites in which the Principal Investigator or subinvestigator (if a Principal Investigator is not identified) meet criteria for Financial Disclosure should be regarded as potentially subject to bias, the following relevant data are noted:

- This study was Phase 2 with 150 subjects randomized 2:1 between study regimens
- 47% of sites met criteria for Financial Disclosure and are designated FD+

- 53% of sites did not meet criteria for Financial Disclosure and are designated FD-
- 48% of D/C/F/TAF recipients and 40% of DRV+ COBI+ Truvada (TDF) were studied at FD+ sites.
- At 24 weeks of treatment, primary efficacy endpoint (HIV-1 RNA < 50 copies/mL) was achieved by a similar percentage of participants for both study agents TAF and TDF in both FD+ and FD- subjects.
- The combined data between both FD+ and FD- was subjected to statistical analysis and the lower confidence interval of -11.4 met prespecified boundaries of -12% and TAF containing regimen was declared non-inferior.
- At 48 weeks of treatment, the percentages achieving the secondary efficacy endpoint (HIV-1 RNA < 50 copies/mL) were similar for the TAF regimen in both FD+ and FD- sites but were different for FD+ TDF sites compared to FD- sites. The FD+ sites had 5 subjects who had not met the primary efficacy endpoint who met the secondary endpoint for efficacy of TDF. The comparable FD-1 site had one subject who met the secondary endpoint but not the primary.
- The combined secondary endpoint data of both the FD+ and FD- groups was affected by the changes in TDF data to the extent that the lower confidence interval was now -19.9%.
- The safety data between the FD+ and FD- sites while generally similar did indicate fewer SAEs and Grade 3 AEs but numerically more related AEs and Grade 2 AEs among subjects from FD+ sites compared to FD- sites.
- When combined, the percentages of TAF and TDF Grade 2 AEs were proportional to the 2:1 enrollment.

Conclusions:

For the first 7 studies discussed in this memorandum, the objective nature of the data collected augmented by statements made by the Sponsor permit the conclusion that systematic bias related to financial interests of investigators is very unlikely.

The possibility of systematic bias is higher in Study GS-US-299-0102. Nearly 50% of the principal investigators responsible for nearly 50% of enrolled subjects met criteria for Financial Disclosure. There are suggestions that there were some differences in the research environment of FD+ compared to FD- populations. The FD+ sites may have been more supportive of their enrolled subjects than FD- sites. There were fewer lost to follow-up subjects in FD+ sites and there was a remarkable surge in virologic success in FD+ sites between 24 and 48 weeks. The surges of 5 subjects were in the comparator arm which would argue against unblinding and bias in favor of the Applicant preferred regimen. The safety data is mostly balanced but it is noted that there are numerically fewer serious or severe AEs in FD+ subjects. There are also numerically more related designations and Grade 2 AEs in FD+.

In summary, there are no convincing data supporting the contention of systematic bias due to financial interests of investigators discovered during the review of Study GS-US-299-0102. The large percentage of investigators meeting the criteria of Financial Disclosure is clearly undesirable due to the perception of possible bias. In future submissions, Applicants with prior history of high percentages of investigators meeting Financial Disclosure criteria should be required to provide additional analyses comparing efficacy and safety data generated by FD+ and FD- study sites.

Recommendations: Accept the data from all 8 studies as without any identified evidence of systematic bias due to the financial interests of the investigators or their study sites.

Date February 25, 2016
William B. Tauber, M.D.
CDER/OAP/DAVP

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

/s/

WILLIAM B TAUBER
02/29/2016

RUSSELL D FLEISCHER
03/01/2016

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

8 Pages have been withheld in Full
immediately following this page
These pages are included in this
review.

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

/s/

MYUNG JOO P HONG
03/01/2016

JEFFREY S MURRAY
03/01/2016

From: [Hong, Myung-Joo P.](#)
To: ["erik.berglund@gilead.com"](mailto:erik.berglund@gilead.com)
Subject: NDA 208215.Labeling Proposal
Date: Thursday, March 24, 2016 4:28:00 PM
Attachments: [3.24.16.PI to Gilead.docx](#)

Hello Erik, please find attached our labeling proposal with minor changes. Please submit your response by 3/28/16.

(b) (4)

I have one question. Upon approval of the NDA (Original 1), do you plan a Press Release for the approval and are you intend to provide and discussion about 25 mg?

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
☎ 301-796-0807
☎ 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

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

/s/

MYUNG JOO P HONG
03/24/2016

From: [Hong, Myung-Joo P.](#)
To: ["Erik Berglund"](#)
Cc: ["Regulatory Archives"](#); ["paul.tomkins@gilead.com"](mailto:paul.tomkins@gilead.com)
Subject: NDA 208215.Labeling Proposal and PREA PMR Revision
Date: Friday, March 18, 2016 4:35:00 PM
Attachments: [3.18.16.PI to Gilead.docx](#)

Hi Erik, we had some discussion about the age change for deferred PMR (regarding "age range 6 yrs to less than 18 yrs" in switching study). Since the label is appropriately labeled for use in ages 12 to less than 18 years for this indication, the age range between 6 years to less than 18 years for the switching study will cause some confusion. We decided to change the age range to **"6 years to less than 12 years."** But the study protocol goes up to 18 yrs, we want all of the data not just the data for 6-12, when you submit the final study report. The revised PREA PMR is:

"Conduct your deferred pediatric study in HIV-1 infected, virologically suppressed patients **6 years to less than 12 years** switching from other nucleoside reverse transcriptase inhibitors (NRTIs) to assess the pharmacokinetics, safety, tolerability and antiviral activity of age-appropriate DESCovy tablets in combination with an approved third antiretroviral drug. Study participants should be monitored for 48 to 96 weeks to assess safety and durability of antiviral response."

Protocol Submission:	July, 2014 (completed)
Study Completion:	December, 2017
Final Report Submission:	June, 2018

Please find attached our labeling proposal. Please submit your label proposal by 3/22/16.

Would you also submit the final container label (200mg/25 mg) with updated information if you need to update "NDC 61958-XXXX-X ?" The draft container labels submitted on 1/11/16 were acceptable.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
☎ 301-796-0807
☎ 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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

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

/s/

MYUNG JOO P HONG
03/18/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 29, 2016

To: Patricia Carlos	From: Patricia Hong
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 208215

Document to be mailed: ☐ YES ☒ NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1500. Thank you.



ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 29, 2016

NDA: 208215/Original Submission

TO: Patricia Carlos, Manager, Regulatory Affairs

FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

SUBJECT: Advice/Information Request

Please refer to your Original NDA submitted on April 7, 2015. We have the following comments from the review team.

Labeling

DAVP is recommending FTC/TAF (200/25 mg) to be co-administered with the protease inhibitors (PIs) (darunavir [DRV], lopinavir [LPV], and atazanavir [ATV]) when combined with a CYP3A4 inhibitor (cobicistat [COBI] or ritonavir [RTV]). This dosage strength is expected to produce plasma TAF exposures that are similar to or greater than TAF exposures from EVF/COBI/FTC/TAF, the reference product used to approve FTC/TAF. DAVP is concerned with the numerical decrease in virologic success at Week 48 observed in Study GS-US-299-0102 (recognizing the limitations of this trial) which can potentially be attributed to reduced TAF exposures. This conservative approach aims to ensure maximal efficacy of FTC/TAF PI-based HIV regimens (b) (1) (A)

[REDACTED]

1. FTC/TAF (200/25 mg) when combined with DRV/RTV or DRV/COBI will produce similar plasma TAF exposures to that observed from EVG/COBI/FTC/TAF. (b) (1) (A)
[REDACTED]
2. FTC/TAF (200/25 mg) when combined with LPV/RTV or LPV/COBI will produce plasma TAF exposures slightly higher than that observed from EVG/COBI/FTC/TAF. The expected increase in TAF exposures and the expected corresponding increase in TFV exposures are not expected to compromise the safety of the regimens. Note that LPV/RTV or LPV/COBI can be taken under fasted conditions which can lead to further decreases in TAF exposures and produce TAF exposures that are comparable to that from

EVG/COBI/FTC/TAF due to the differential food effect on FTC/TAF compared to EVG/COBI/FTC/TAF.

3. DAVP acknowledges that ATV/RTV or ATV/COBI produces plasma TAF exposures that exceed those observed when combined with DRV or LPV plus CYP3A inhibitor and are lower than those observed with EVG/COBI/FTC/TAF. TAF exposures resulting from ATV/CYP3A inhibitor plus FTC/TAF (200/25 mg) are not expected to compromise the safety of this regimen. Also, recommending one FTC/TAF dosage strength to be administered with all antiretroviral agents will provide a less confusing dosing recommendation for health care providers.
4. We acknowledge the data you submitted regarding comparative intracellular levels of TFV diphosphate (TFV-DP). As TFV-DP concentrations in peripheral blood mononuclear cells may not be representative of TFV-DP concentrations in other relevant tissues, our conservative approach is to target plasma TAF concentrations that are similar to or exceed TAF concentrations associated with EVG/COBI/FTC/TAF.

DAVP believes that this approach, although conservative, is the best available path that will not compromise the efficacy of PI+CYP3A inhibitor + FTC/TAF regimens without significantly increasing safety risks. It should be noted that we hope this recommendation can be changed if the ongoing clinical efficacy and safety trial with DRV/COBI/FTC/TAF produces favorable efficacy results.

Our label proposal is attached below. Please submit a revised label by March 4, 2016.

We are providing this above information via electronic mail for your convenience. Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

30 Pages of Draft Labeling have been Withheld
in Full as b4 (CCI/TS) immediately following this
page



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 12 , 2016

To: Patricia Carlos	From: Patricia Hong
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 208215

Document to be mailed: ☐ YES ☒ NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1500. Thank you.



ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 12, 2016

NDA: 208215/Original Submission

TO: Patricia Carlos, Manager, Regulatory Affairs

FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

SPONSOR: Gilead Sciences, Inc.

SUBJECT: PMR Comments

Please refer to your original NDA submitted on April 7, 2015. The DAVP is proposing the following postmarketing requirements (PMRs). Please provide your response to this request by **February 22, 2016**.

PREA PMR

1. Conduct your deferred pediatric study in HIV-1 infected patients 4 weeks to less than 6 years to assess the pharmacokinetics, safety and tolerability, and antiviral activity of an age-appropriate formulation of emtricitabine and tenofovir alafenamide given in combination as DESCovy fixed dose combination product. Study participants should be monitored for 24 to 48 weeks to assess safety and durability of antiviral response.

Protocol Submission:

Trial Completion:

Final Report Submission:

(b) (4)

2. Conduct your deferred pediatric study in HIV-1 infected patients 6 years to less than 18 years to assess the pharmacokinetics, safety, tolerability and antiviral activity of age-appropriate DESCovy tablets in combination with an approved third antiretroviral drug. Study participants should be monitored for 48 to 96 weeks to assess safety and durability of antiviral response.

Protocol Submission:

Trial Completion:

Final Report Submission:

(b) (4)

Please confirm the proposed timelines for commitments 1 and 2, taken from your Agreed iPSP. In general, we expect study reports to be completed and submitted about 6 months after the final subject visits. If the dates proposed above are not appropriate, please provide the justification and propose new dates.

We recommend revision of the eligibility criteria for the proposed study in pediatric patients 4 weeks to less than 6 years of age. Consider increasing the age limit for enrolling treatment naïve patients up to 2 years of age (i.e., 4 weeks to 2 years). This will broaden the available patient population and will provide better characterization of DESCOVY use in pediatric patients with potentially high viral load.

We are providing this above information via electronic mail for your convenience. Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MYUNG JOO P HONG
02/12/2016

From: [Hong, Myung-Joo P.](#)
To: ["patricia.carlos@gilead.com"](mailto:patricia.carlos@gilead.com)
Subject: NDA 208215.Additional Question about (b) (4)
Date: Thursday, February 11, 2016 4:50:04 PM

Hi Patricia, I am following up on an email correspondence I sent below regarding the (b) (4) in the prescribing information section of labeling. We have not received Gilead's response for this request under NDA 208215. However, we have received a response for this question under NDA 208351 (ODEFSEY). We would like to add the following comment to clarify and get more understanding of Gilead's thinking:

- The Division would like to understand how Gilead decides which products to label (b) (4) or if Gilead recommends this statement for all products.

Please provide your response by February 19, 2016.

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA | CDER | OAP | DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

From: Hong, Myung-Joo P.
Sent: Wednesday, January 20, 2016 3:38 PM
To: patricia.carlos@gilead.com
Subject: NDA 208215.Question about (b) (4) applicable to 3 NDAs (208215, 208351 and (b) (4))

Hello Patricia, we have the following information request:

(b) (4)

208215.”

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA | CDER | OAP | DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
02/11/2016

PeRC Meeting Minutes
February 10, 2016

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Linda Lewis
Ikram Elayan
Thomas Smith
Daiva Shetty
Meshaun Payne
Dianne Murphy
Gerri Baer
Rosemary Addy (Dysport and KamRab reviews only)
Wiley Chambers (Did not review Afluria)
Julia Pinto
Maura O'Leary
Lili Mulugeta
Freda Cooner
Peter Starke
Gil Burckart
Raquel Tapia
Greg Reaman
Dionna Green
Lisa Faulcon (KamRab review only)
Adrienne Hornatko-Munoz (KamRab, Afluria and Flucelvax reviews only)
Barbara Buch
Rachel Witten
Michelle Roth-Kline
George Greeley

Agenda

(b) (4)

11:30	NDA 208215	Descovy (emtricitabine/tenofovir alafenamide) FDC tablets Partial Waiver/Deferral/Plan/Assessment (w/Agreed iPSP)	DAVP	Myung-Joo (Patricia) Hong	For use in combination with antiretrovirals for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
11:40	IND 125589	GS-9883/F/TAF FDC Tablets iPSP Partial Waiver/Assessment	DAVP	Suzanne Strayhorn	Treatment of HIV

(b) (4)

**Descovy (emtricitabine/tenofovir alafenamide) FDC tablets Partial
Waiver/Deferral/Plan/Assessment (w/Agreed iPSP)**

- Proposed Indication: For use in combination with antiretrovirals for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older with antiretroviral treatment history or who are virologically suppressed to replace their

- current antiretroviral treatment regimen
- The product triggers PREA as a new active ingredient and has a PDUFA Goal date of April 7, 2016.
 - The Division noted that this fixed dose combination product application is based on bioavailability and bioequivalence data only. There were no clinical trials included in this application.
 - The iPSP includes plans for studies down to 4 weeks of age. The division agrees with this plan because this combination product (2 NRTI's) is part of the preferred backbone of therapy for HIV patients down to 1 month of age.
 - *PeRC Recommendations:*
 - The PeRC agreed to the Division's plan for partial waiver in patients less than 4 weeks of age as studies are impossible and highly impractical and to a deferral in patients 4 weeks to less than 12 years old.
 - The PeRC agreed to the assessment in patients 12-18 years of age.

GS-9883/Emtricitabine/Tenofovir Alafenamide FDC Tablets iPSP Partial Waiver/Deferral

- Proposed Indication: Treatment of HIV
- The Division clarified that this fixed dose combination product includes INSTI (GS-9883) plus 2 NRTIs (emtricitabine and tenofovir alafenamide). This regimen is likely to be used in patients down to 1 month of age because INSTI treatment may be an alternative to PI and may, ultimately be safer than treatment with PI. Therefore, the division is requiring that the sponsor develop a formulation that could be used down to 1 month of age because use of a single FDC would be of potential benefit.
- The plan includes patients who are treatment naïve up to 6 months of age. The division disagrees with this approach because this population is increasingly difficult to enroll. Therefore the division is recommending that treatment naïve patients up to 2 years of age may be enrolled as well as patients who are not treatment naïve but are virologically suppressed.
- The division will require the sponsor to attempt to develop a formulation; however, currently it is premature to establish the type of formulation because it is still not clear what to dose of the individual components will be down to 1 months of age for TAF and for GS-9883.
- *PeRC Recommendations:*
 - The PeRC agreed with the sponsor's plan to request a partial waiver in pediatric patients 0 to less than 4 weeks as studies are impossible or highly impracticable and to the deferral in patients 1 month to 17 years.
 - The PeRC agreed to the Divisions comments provided in the iPSP

(b) (4)

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

/s/

MESHAUN L PAYNE
02/26/2016

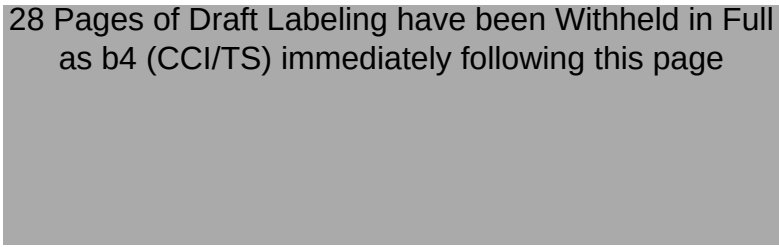
From: [Hong, Myung-Joo P.](#)
To: ["Patricia Carlos"](#)
Subject: NDA 208215 Labeling Proposal
Date: Wednesday, February 03, 2016 3:42:46 PM
Attachments: [2.3.16.PI to Gilead.docx](#)

Dear Patricia, please find attached our labeling proposal. Please submit your response to our proposal by 2/9/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
☎ 301-796-0807
☎ 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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



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

/s/

MYUNG JOO P HONG
02/03/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 2, 2016

To: Patricia Carlos	From: Patricia Hong
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 208215

Document to be mailed: ☐ YES ☒ NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1500. Thank you.



ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 2, 2016

NDA: 208215/Original Submission

TO: Patricia Carlos, Manager, Regulatory Affairs

FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

SUBJECT: Advice/Information Request

Please refer to your Original NDA submitted on April 7, 2015. We have the following comments from the review team.

Labeling

1. We acknowledge the advice communicated to the Sponsor on 6/23/15. Upon further consideration and internal discussion, we do not agree with your proposals for Sections 6 and 14. We recommend avoiding reference to another drug's prescribing information (PI) for the communication of essential safety and efficacy information for the following reasons:

- To meet the requirements at 21CFR 201.56(a)(1), we recommend that a summary of essential safety and efficacy information for use of a drug (e.g., DESCOVY) be contained directly in its PI (e.g., the DESCOVY PI).

-  (b) (4)

Please see the current Division recommendations for meeting this requirement in FDA comments contained in Sections 6 and 14 of the DESCOVY labeling (correspondence dated 12/17/2015).

2. We acknowledge that your proposed labeling is in the requested format and structure of the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064); however, during our review of your submitted labeling, we found that you have not provided adequate information to support the labeling content for subsection 8.1, specifically the human

safety data. Thus, your proposed PLLR labeling changes cannot be agreed upon until this information request is fulfilled. No partial PLLR conversions may be made. Please submit the following information:

- a. a review and summary of the available published literature regarding emtricitabine use in pregnant and lactating women
- b. a review and summary of relevant cases reported in your pharmacovigilance database
- c. an interim report of an ongoing pregnancy registry, in this case, the Antiretroviral Pregnancy Registry
- d. revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Please refer to the “Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format” available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Our label proposal is attached below. Please submit a revised label and the PLLR information requested above to the NDA within one week of receiving this correspondence.

We are providing this above information via electronic mail for your convenience. Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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

/s/

MYUNG JOO P HONG
02/02/2016

From: [Hong, Myung-Joo P.](#)
To: patricia.carlos@gilead.com
Subject: NDA 208215.Question about (b) (4) applicable to 3 NDAs (208215, 208351 and (b) (4))
Date: Wednesday, January 20, 2016 3:38:04 PM

Hello Patricia, we have the following information request:

- Please describe the reason(s) for including (b) (4) in the Prescribing Info for the products currently under review in NDAs (b) (4) 208351 and 208215."

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA | CDER | OAP | DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
01/20/2016

From: [Hong, Myung-Joo P.](#)
To: patricia.carlos@gilead.com
Subject: NDA 208215.Information Request
Date: Tuesday, January 19, 2016 12:20:46 PM

Dear Patricia, we have the following information request:

- Please provide all relevant background information from primary data sources (e.g., final clinical PK study reports, individual case reports) to support the following statement which has been added under the Section 8.2. "Lactation" (under data subsection) in the Descovy label.

[REDACTED] (b) (4)

(b) (4) [REDACTED] If this data has been already submitted to the Agency please provide us a reference number for the submitted data.

*Warm Regards,
Pat*

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
☎ 301-796-0807
☎ 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
01/19/2016

From: [Hong, Myung-Joo P.](#)
To: patricia.carlos@gilead.com
Subject: NDA 208215.Information Request
Date: Wednesday, January 13, 2016 10:54:40 AM

Hello Patricia, can you provide a brief description of each subject who discontinued from Study 102 for investigator discretion, withdrew consent, lost to follow-up or non-compliance? Please submit your response by January 15, 2015 (4 PM).

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
☎ 301-796-0807
☎ 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208215

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Patricia Carols
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carols:

Please refer to your New Drug Application (NDA) dated and received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/tenofovir alafenamide Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by December 8, 2015 (COB, PST) in order to continue our evaluation of your NDA.

Based on the batch release data and stability behavior of the emtricitabine and tenofovir alafenamide tablets, we recommend the following changes to the drug product specification for both strengths:

- a) Reduce the acceptance criterion for (b) (4) NMT (b) (4) % (b) (4) to NMT (b) (4) % (b) (4)
- b) Reduce the acceptance criterion for Total TAF-Related Impurities from NMT (b) (4) to NMT (b) (4). The acceptance criterion at release could remain at NMT (b) (4) if preferred.

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

**Stephen
Miller -S**

Digitally signed by Stephen Miller -S
DN: cn=US, ou=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Stephen Miller -S,
0.9.2342.19200300.100.1.1=13000870
13
Date: 2015.12.01 12:55:29 -05'00'

Stephen Miller, Ph.D.
On Behalf of
Balajee Shanmugam, Ph.D.
Branch Chief, Branch III (Acting)
Division of New Drug Products 1
Office of Pharmaceutical Quality

Kord Bacheh Changi, Maryam

From: Kord Bacheh Changi, Maryam
Sent: Tuesday, December 15, 2015 12:46 PM
To: 'patricia.carols@gilead.com'
Subject: RE: Information Request NDA 208215

Importance: High

Good afternoon,

We are reviewing the CMC portion of NDA 208215 and We have the following Information Request:

“We concur with their justification of the acceptance criterion for TAF-related degradants. Please resubmit the DP specification and related documents to show the reduction of the acceptance criterion for (b) (4) to NMT (b) (4)%. Please indicate the timeframe for submitting this revised documentation.”

Please submit the response as an amendment to your application. Please also submit a copy to me via email by January 15, 2016.

Please kindly confirm the receipt of this email.

Best,

Maryam Changi, PharmD,
RBPM, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
Phone: (240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov





NDA 208215

LABELING PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated April 6, 2015, received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for DESCOVY (emtricitabine and tenofovir alafenamide) (b) (1) (A) 200/25 mg fixed-dose combination tablets.

On November 6, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by January 11, 2016. The resubmitted labeling will be used for further labeling discussions.

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

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

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

We have the following comments from the review team. These comments refer to our recommended labeling changes for carton and container labeling.

Container Label and Access Container Label and Carton Labeling

1. As presented, the labels and labeling for both strengths use the same colored gray box around the strength statement. Please revise the colored box for one of the strengths to a dissimilar color other than gray to help differentiate the labels and labeling to prevent strength selection errors. Additionally, ensure the colors used for your Descovy product line are distinguishable from the colors used in your Truvada product line.
2. Replace "TRADENAME" with the conditionally acceptable proprietary name, Descovy.
3. Revise the active ingredients to read as follows, "emtricitabine and tenofovir alafenamide."

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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

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

/s/

MYUNG JOO P HONG
12/17/2015

5 Pages of a Late Cycle Meeting Background Package dated January 11, 2016 has been removed, a duplicate of this review can be found in the Late Cycle Meeting Section of this review section.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: November 4, 2015

To: Patricia Carlos	From: Patricia Hong
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 208215

Document to be mailed: ☐ YES ☒ NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1500. Thank you.



ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: November 4, 2015

NDA: 208215/Original Submission

TO: Patricia Carlos, Manager, Regulatory Affairs

FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

SUBJECT: Advice/Information Request

Please refer to your April 7, 2015 submission submitted to NDA 208215. We have the following requests from the review team.

Clinical Pharmacology

1. Food effect
 - a. The food effect on TAF is greater for F/TAF relative to E/C/F/TAF. Please discuss whether this could be due to formulation differences or other factors.
2. Study 311-1089
 - a. When will the CSR be submitted?
 - b. When will you have sufficient TFV-DP long term stability data to cover the samples from this study?
 - c. Assess baseline (i.e., day 1) TFV and/or TFV-DP concentrations. TFV-DP has a half-life of ~1 week and we want to ensure that the difference in week 4 TFV-DP concentrations between the F/TAF and F/TDF groups are not due to an imbalance in TFV-DP concentrations at baseline.
 - d. Interim PK report
 - i. Submit the sample analysis reports. We recommend incurred sample reanalysis to assess reproducibility.
 - ii. Submit the TAF and TFV-DP concentration-time and PK parameter datasets.
 - iii. If the above are not available, when do you anticipate they can be submitted?

Please submit your response by **November 12, 2015**.

We are providing this above information via electronic mail for your convenience. Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MYUNG JOO P HONG
11/04/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208215

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DESCOVY (emtricitabine, tenofovir alafenamide), (b) (4) 200/25 mg fixed-dose combination tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 1, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Russ Fleischer, PA-C, MPH
Acting Clinical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 1, 2015, 11 – 11:30 AM

Application Number: 208215

Product Name: DESCOVY (emtricitabine, tenofovir alafenamide), (b) (4)
200/25 mg fixed-dose combination tablets

Indication: Treatment of HIV infection in adults and pediatric patients 12 years of age and older

Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Russ Fleischer, PA-C, MPH, Acting Clinical Team Leader

Meeting Recorder: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

FDA Participants:

Office of Antiviral Products

Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Russ Fleischer, PA-C, MPH, Acting Clinical Team Leader, Division of Antiviral Products
William Tauber, M.D., Clinical Reviewer, Division of Antiviral Products
Adam Sherwat, M.D., Clinical Team Leader, Division of Antiviral Products
Jules O'Rear, Ph.D., Clinical Virology Team Leader, Division of Antiviral Products
Lisa Naeger, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
Claudia Wrzesinski, Ph.D., Nonclinical Reviewer, Division of Antiviral Products
Elizabeth Thompson, M.S., Chief, Project Management Staff
Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager, Division of Antiviral Products
Alicia Moruf, PharmD., MPH, Regulatory Project Manager, Division of Antiviral Products

Office of Clinical Pharmacology

John Lazor, Pharm.D., Director, Division of Clinical Pharmacology IV
Islam Younis, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV
Jason Xu, Pharmacy Student

Office of Pharmaceutical Quality

Stephen Miller, Ph.D., Product Quality CMC-Lead

Office of Biostatistics

Greg Soon, Ph.D., Statistical Team Leader, Division of Biostatistics IV

Office of Surveillance and Epidemiology

Monica Calderon, PharmD., BCPS, DMEPA Reviewer

Eastern Research Group Participants

Marc Goldstein, Independent Assessor

Gilead Sciences' Participants:

Andrew Cheng, M.D., Ph.D., Senior Vice President, Development Operations

Dana Pizzuti, M.D., Vice President, Regulatory Affairs

Brian Kearney, PharmD., Vice President, Clinical Pharmacology

Martin Rhee, M.D., Director, Clinical Research

Bob Scott, Ph.D., Senior Director, Process Development

Julia Zack, Senior Clinical Pharmacologist, Clinical Pharmacology

Patricia Carlos, Manager, Regulatory Affairs

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

As stated earlier, the purpose of this meeting is not to discuss the issues identified in detail but in the spirit of transparency to provide a status update on the review of your application. The application is still under review and no regulatory decisions have been determined.

The following comments in **standard** font were sent to Gilead on September 29, 2015 via electronic correspondence; and the additional meeting discussions are in *italic* font. During the teleconference, clinical team leader reiterated the comments below.

Clinical

- a. Two issues regarding the dosing of F/TAF with boosted protease inhibitors have been observed and are under additional review:

- In Study 120-0118, when F/TAF was administered with atazanavir, lopinavir or darunavir, increases in TAF exposures were substantially lower with ritonavir boosting compared to cobicistat boosting of TAF in Study 311-0101. In our view, these differences should be noted in Section 7 of the Prescribing Information (Drug Interactions).

No discussion occurred.

- In Study 299-0102, virologic success for treatment naïve subjects was approximately 75% for both study arms of which one consisted of cobicistat boosted darunavir, emtricitabine and TAF at the 10mg dosage. In comparison, when elvitegravir is substituted for darunavir and all other elements are identical, the virologic success rate for a similar population is 93% for E/C/F/TAF. This suggests reduced efficacy possibly due to lower TAF exposure when F/TAF is combined with darunavir/cobicistat. In our view, the finding of reduced efficacy observed in Study 299-0102 is very concerning.

Gilead will provide the data to explain why the apparent imbalance between the lower virologic success of the darunavir based regime compared to the elvitegravir based regime does not represent reduced efficacy.

- b. An additional issue regards the administration of F/TAF in the fasted state. Our assessment is TAF exposure with F/TAF administered in the fasted state is much lower compared to E/C/F/TAF administered in the fasted state. In contrast with the proposed label where F/TAF is recommended to be given with or without food, we strongly recommend that F/TAF be administered with food.

No discussion occurred.

3.0 INFORMATION REQUESTS

Clinical Pharmacology

- a. Exposure-response data may help to understand the effect of lower TAF exposures from administration of D/C/F/TAF 10 mg compared to E/C/F/TAF 10 mg. Please provide box plots for exposures ($C_{\max}$, AUC, and $C_{\min}$) of all analytes measured in Study 299-0102 stratified by week 48 virologic outcome.

Gilead requested if they can submit model predicted exposures metrics (C_{max} , AUC, and C_{min}) for TAF only. The Division agreed with Gilead's proposal and requested to submit observed data for all other components.

- b. In Study 311-1089, intracellular TFV-DP data for F/TAF plus a third agent compared to the same data for F/TDF plus the identical third agent (including boosted proteases) consistently showed higher concentrations in the F/TAF arm. However, method validation data for the TFV-DP bioanalytical method was not provided. Please submit a bioanalytical methods report for quantification of TFV-DP to accompany the Study 311-1089 PBMC PK report.
- c. The effect of food on TAF exposure is much larger for F/TAF (75%) compared to E/C/F/TAF (18%) and the relative BA studies comparing the products were conducted in the fed state. Compared to E/C/F/TAF, significantly lower exposures of TAF are expected after administration of F/TAF in the fasted state.

Please fill in the table with TAF AUC values below so that exposures of TAF can be compared between relevant studies. In addition, please plot the data in box plot form.

Study #	Study Description	Arm	Mean (90% CI) steady-state TAF AUC
311-1386	Effect of food on TAF administered as F/TAF	fed	
		fasted	
299-0102	Phase 2 D/C/F/TAF	fed	
292-0110 (NDA 207561)	Effect of food on TAF administered as E/C/F/TAF	fed	
		fasted	
292-0104 and 292-0111 (NDA 207561)	E/C/F/TAF Pivotal Studies	fed	

Gilead agreed to provide the requested information listed above in a timely manner.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology do not believe a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks.

5.0 ADVISORY COMMITTEE MEETING

- No Advisory Committee Meeting is scheduled for this application.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- DAVP reminded Gilead that the Late Cycle Meeting (LCM) is scheduled for January 11, 2016. The purpose of the LCM is to share information and discuss any review issues identified to date, as well as objectives for the remainder of the review cycle. The Division will send the meeting backgrounder package for the LCM by secure e-mail by December 30, 2015.

The Division informed Gilead that the meeting minutes will be issued within 30 days.

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

/s/

RUSSELL D FLEISCHER
10/08/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208215

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated and received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine, tenofovir alafenamide (F/TAF) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by September 10, 2015 in order to continue our evaluation of your NDA.

- Based on our review of the provided dissolution data, we recommend that you set the dissolution acceptance criterion for both 200/25 mg (b)(4) strengths of the Descovy® (FTC/TAF) FDC tablets at Q (b)(4)% in 30 minutes. Therefore, we request that you submit a revised Drug Product Specifications table and stability protocol reflecting this change in dissolution acceptance criterion (i.e., Q = (b)(4)% at 30 minutes).

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager at (240) 402-2725.

Sincerely,

Stephen Miller - S

Digitally signed by Stephen Miller - S
DN: cn=U.S. Government, ou=FDA,
ou=FDA, ou=People, cn=Stephen Miller - S,
0.9.2342.19200300.100.1.1=1300087013,
Date: 2015.08.28 10:52:11 -0400

Stephen Miller, Ph.D.
On Behalf of
Balajee Shanmugam, Ph.D.
Branch Chief, Branch III (Acting)
Division of New Drug Products 1
Office of Pharmaceutical Quality



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

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2/Pre-Phase 3

Meeting Date and Time: October 17, 2013; 2:30-4:00 PM
Meeting Location: WO Building 22; Conference Room 1315

Application Number: 111851
Product Name: Emtricitabine/tenofovir alafenamide (F/TAF)
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative):

Robert Temple, M.D., Deputy Director, Center for Drug Evaluation and Research (CDER)
John Jenkins, M.D., Director, Office of New Drugs (OND)
Edward Cox, M.D., MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, M.S., Associate Director of Regulatory Affairs, OAP
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Kendall Marcus, M.D., Deputy Director for Safety, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Narayana Battula, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Su-Young Choi, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Shirley Seo, Ph.D., Clinical Pharmacology Team Lead, DCP IV
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghanous, Ph.D., DABT, Pharmacology/Toxicology Team Lead, DAVP
Stephen Miller, Ph.D., CMC Lead, DNDQA II, Branch V
Fuqiang Liu, Ph.D., CMC Reviewer, DNDQA II, Branch V
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoixing Soon, Ph.D., Biometrics Team Lead, DV IV
Antoine El Hage, Ph.D., Reviewer, Office of Scientific Investigation (OSI)
Elizabeth Thompson, M.S., Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Regulatory Project Manager, DAVP
Danyal Chaudhry, M.S., Project Manager, Office of Surveillance and Epidemiology
Krishnakali Ghosh, Ph.D., Office of Drug Manufacturing and Product Quality (OMPQ)/ New Drug Manufacturing Assessment Branch (NDMAB)/ Generic Drug Manufacturing Assessment Branch (GMAB)

SPONSOR ATTENDEES

Andrew Cheng, MD, PhD Senior Vice-President, Development Operations
Martin Rhee, MD Director, Clinical Research
Brian Kearney, PharmD Senior Director, Clinical Pharmacology
Michael Wulfsohn, MD, PhD Vice President, Biometrics
Christian Callebaut, PhD Senior Scientist, Clinical Virology
Scott McCallister, MD Senior Director, Clinical Research
Christophe Beraud, PhD Director, Regulatory Affairs
Naomi Kautz, MSc Senior Manager, Regulatory Affairs
David Pizzuti, MD, Vice President, Regulatory Affairs

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for October 17, 2013, 2:30-4:00 PM between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

On May 12, 2011, Gilead submitted IND 111851, emtricitabine/tenofovir alafenamide (F/TAF) fixed-dose combination tablet (FDC) for the treatment of HIV-1 infection in combination with other antiretrovirals. Gilead Sciences requested a Type B, Pre-Phase 3 meeting on August 1, 2013, to discuss the proposed registration plan for F/TAF FDC and the meeting was granted on August 9, 2013.

TAF single agent is currently being investigated under IND 63737. TAF is a pro-drug of tenofovir diphosphate, which provides lower systemic tenofovir exposure. In addition to the

F/TAF FDC IND, Gilead is also studying TAF in a four-drug fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) under IND 111007.

The proposed indication for F/TAF FDC is for the treatment of HIV-1 infection in adults and pediatric subjects 12 years of age and older in combination with other antiretroviral agents. Gilead proposes to support this indication by bridging F/TAF to the E/C/F/TAF Phase 3 clinical data in addition to data from Study GS-US-311-1089, a Phase 3, 96-week study of F/TAF in combination with other agents in HIV-1 infected subjects who are virologically-suppressed on F/TDF-containing regimens. The proposed Phase 3 study protocol for GS-US-311-1089 will be submitted to the Agency in fourth quarter 2013.

The specific objectives of the meeting include:

- Discuss the biopharmaceutics bridging strategy for F/TAF FDC tablet to E/C/F/TAF FDC
- Discuss the adequacy of bridged E/C/F/TAF FDC Phase 3 studies in treatment-naïve (GS-US-292-0104, GS-US-292-0111), treatment-experienced (GS-US-292-0117, GS-US-292-0119 and GS-US-292-0109), renally impaired (GS-US-292-0112) and adolescent (GS-US-292-0106) subjects, plus the proposed 48-week Phase 3 study of the F/TAF FDC tablet in combination with PI/r in HIV-1 infected subjects who are virologically suppressed on FTC/TDF-containing regimens (Study GS-US-311-1089) to support registration of F/TAF for the proposed indication
- Discuss the proposed safety database for the F/TAF FDC tablet program and its adequacy to support registration of the F/TAF FDC tablet for the proposed indication

On October 2, 2013, Gilead requested to add question number 4 below and on October 9, 2013, they requested the face-to-face meeting be changed to a teleconference. These requests were officially submitted to the IND on October 11, 2013.

DISCUSSION

1. Does the Agency agree with the clinical pharmacology data supporting F/TAF FDC tablet, [REDACTED]

(b) (4)

The utility of the BE study for the proposed indication (in combination with other ARVs) is unclear. At this time, we do not have sufficient data to support [REDACTED]

(b) (4)

(b) (4)

2. Does the Agency agree that the studies conducted primarily with the E/C/F/TAF STR supports an indication of the F/TAF FDC tablet for use with other antiretroviral agents

for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older?

We do not agree. The indication you propose permits use of the F/TAF FDC tablet with any other ARV regimen. Studies conducted with E/C/F/TAF will support [REDACTED] (b) (4), having an effective exposure resulting from 25mg of the TAF component. [REDACTED] (b) (4)

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

- 3. Does the Agency agree that the proposed safety database is adequate to support the registration of the F/TAF FDC tablet?**

While we agree that the proposed safety database should provide adequate safety data applicable [REDACTED] (b) (4) [REDACTED] (b) (4)

[REDACTED] *We also note that apart from the two pivotal trials GS-US-292-0104 and 0111, all of the studies in the safety database are open label. Precautions should be taken to minimize safety signal ascertainment bias in favor of TAF.*

- 4. Towards support of the same indication presented in the F/TAF FDC tablet briefing document, would the Agency be willing to discuss the acceptability of submitting the initial F/TAF FDC tablet NDA with the BA/BE bridging Study GS-US-311-1088, the Drug interaction study GS-US-120-0118, cross reference to the E/C/F/TAF pivotal Phase 3 studies, along with 9 months of stability data for the F/TAF FDC tablet proposed commercial formulations?** [REDACTED]

We discussed this question internally and wish to provide the following preliminary comments. [REDACTED] (b) (4)

[REDACTED] (b) (1) (A)
[REDACTED] (b) (1) (A)

[REDACTED] *The drug interaction study GS-US-120-0118 which is expected to demonstrate TAF boosting with ritonavir is comparable to TAF boosting previously observed with cobicistat should precede the conduct of GS-US-311-1089.* [REDACTED] (b) (1) (A)

[REDACTED] (b) (4)

[REDACTED] *As recommended by ICH Q1A (R2) guidance, the NDA should include at least 12 months of long-term and 6 months of*

accelerated stability data for three registration batches of the drug product packaged in the container closure system proposed for marketing.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/

STACEY MIN
10/15/2013



NDA 208215

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Patricia Carols
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carols:

Please refer to your New Drug Application (NDA) dated and received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/tenofovir alafenamide Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by August 7, 2015 in order to continue our evaluation of your NDA.

One of the drug substances (TAF) has (b) (4) w/w load in the drug product and is considered a low dose product. Provide available data (e.g. stratified sampling of tablets with assay) to demonstrate that the proposed manufacturing process at commercial scale can consistently produce tablets with uniform dose.

We understand that the Access tablets differ from the US Presentation tablets only in terms of the color of the tablet coating. However, it appears from Figures 11 and 12 of NDA Section 3.2.P.5.2 (PDM-2026) that the dissolution of FTC and TDF (b) (4) the Access tablets [Lots CR1409B and CR1410B] (b) (4) US Presentation tablets [Lots CR1308B and CR1305B]; provide an explanation for the cause and significance of this observation.

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

Stephen
Miller -S

Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Stephen Miller -S,
0.9.2342.19200300.100.1.1=13000870
13
Date: 2015.07.23 11:34:06 -04'00'

Stephen Miller, Ph.D.
On Behalf of
Balajee Shanmugam, Ph.D.
Branch Chief, Branch III (Acting)
Division of New Drug Products 1
Office of Pharmaceutical Quality



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: June 23, 2015

To: Patricia Carlos	From: Patricia Hong
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 208215

Document to be mailed: ☐ YES ☒ NO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1500. Thank you.



ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: June 23, 2015

NDA: 208215/Original Submission

TO: Patricia Carlos, Manager, Regulatory Affairs

FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

SUBJECT: Advice/Information Request

Please refer to your April 7, 2015 submission submitted to NDA 208215. We are reviewing your proposed prescribing information (PI) and have the following labeling comments from the review team. These comments are for labeling changes in Sections 6 (Adverse Reactions) and 14 (Clinical Studies). The review of your proposed PI is on-going and we will have further edits to the PI as we review your application.

Labeling

According to 21 CFR 201.57(c)(15), the Clinical Studies section (Section 14) “must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively.” The drug in this case is the two drug fixed dose combination of emtricitabine and tenofovir alafenamide with the trade name of DESCovy which is currently under review. Furthermore, according to 21 CFR 201.56(d)(4), “omit clearly inapplicable sections, subsections, or specific information” from the PI. Safety and efficacy information regarding the use of elvitegravir and cobicistat is not applicable to the safety and efficacy of emtricitabine and tenofovir alafenamide with other antiretroviral agents in the treatment of HIV. (b) (4)

Therefore, information related to (b) (4) should be removed from the PI. Please refer to the (b) (4) label for example of similar labeling.

Specifically, please delete the proposed language in Section 14 which describe clinical studies conducted (b) (4) and edit as follows:

(b) (4)

(b) (4)

In addition to the changes to Section (b) (4), please make similar edits to Section (b) (4) and any other section of the labeling that refers to the safety and efficacy of GENVOYA and STRIBILD. Please submit a revised label to the NDA within 2 weeks of receiving this correspondence.

We are providing this above information via electronic mail for your convenience. Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MYUNG JOO P HONG
06/23/2015



NDA 208215

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated April 6, 2015, received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for DESCOVY (emtricitabine, tenofovir alafenamide) (b) (4) 200/25 mg fixed-dose combination tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 7, 2016.

This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 10, 2015.

In addition, the planned date for our internal mid-cycle review meeting is September 17, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues and additional labeling comments will be forthcoming in a separate correspondence.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies in children less than 4 weeks of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies in children 4 weeks to less than 18 years of age for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

DEBRA B BIRNKRANT
06/02/2015

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

DATE: June 12, 2015

TO: Division of Anti-Viral Products (DAVP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208215

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected (b) (4) and the inspectional outcome from the analytical site was classified as Voluntary Action Indicated (VAI). Although, the last inspection was classified as a VAI, based on the nature of the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

OSIS recently inspected Celerion, Inc. and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)
Clinical	Celerion, Inc.	2420 West Baseline Road Tempe, AZ 85283

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

/s/

SHILA S NKAH
06/12/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 208215

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

ATTENTION: Patricia Carlos
Manager, Regulatory Affairs

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated and received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emtricitabine, Tenofovir Alafenamide Tablets, (b) (4), 200 mg/25 mg.

We also refer to your correspondence dated and received April 8, 2015, requesting review of your proposed proprietary name, Descovy. We have completed our review of the proposed proprietary name Descovy, and have concluded it is conditionally acceptable.

If **any** of the proposed product characteristics as stated in your April 8, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Myung-Joo Hong, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

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

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

/s/

AZEEM D CHAUDHRY
05/19/2015

TODD D BRIDGES
05/19/2015



NDA 208215

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

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

Name of Drug Product: Emtricitabine, tenofovir alafenamide (F/TAF)
(b) (4) 200/25mg fixed-dose combination tablets

Date of Application: April 6, 2015

Date of Receipt: April 7, 2015

Our Reference Number: NDA 208215

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 6, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MYUNG JOO P HONG
04/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111851

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/tenofovir alafenamide (F/TAF) fixed-dose combination tablet.

We also refer to the teleconference between representatives of your firm and the FDA on December 15, 2014. The purpose of the pre-NDA meeting was to discuss the Phase 1 bioequivalence data in conjunction with the E/C/F/TAF Phase 3 clinical data prior to the filing of the F/TAF NDA.

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

If you have any questions, call Stacey Min, Senior Regulatory Project Manager at (301) 796-4253 or the main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 15, 2014; 4:00 – 4:30 PM, EST
Meeting Location: Teleconference

Application Number: IND 111851
Product Name: Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet
Indication: Treatment of HIV-1 infection in adults and children 12 years of age and older
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda Lewis, M.D., Medical Team Lead
Meeting Recorder: Stacey Min, Pharm.D., Senior Regulatory Project Manager

FDA ATTENDEES

Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Mario Sampson, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Leslie Chinn, Ph.D., Acting Clinical Pharmacology Team Lead, DCP IV
Kelly Kitchens, Ph.D., Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)
Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Elizabeth Thompson, M.S., Chief, Project Management Staff, DAVP
Stephen Miller, Ph.D., CMC Lead, ONDQA II, Branch V
Felicia Duffy, RN, BSN, MEd, Risk Management Analyst, Division of Risk Management

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Andrew Cheng, M.D., Ph.D., Senior Vice President, Development Operations
Brian Kearney, Pharm.D., Vice President, Clinical Pharmacology
Martin Rhee, M.D., Director, Clinical Research

Christophe Beraud, Ph.D., Director, Regulatory Affairs
Julia Zack, Pharm.D., Director, Clinical Pharmacology
Patricia Carlos, B.Sc. Manager, Regulatory Affairs

1.0 BACKGROUND

On November 28, 2011, Gilead submitted IND 63737, tenofovir alafenamide (TAF), an oral prodrug of tenofovir (TFV) that utilizes a different metabolic pathway, resulting in higher intracellular levels of active phosphorylated metabolite tenofovir-diphosphate and lower levels of circulating TFV compared to tenofovir disoproxil fumarate (TDF). It is hypothesized that these features may lead to less risk of nephrotoxicity and less decrease in bone mineral density. On May 12, 2011, Gilead submitted IND 111851 for emtricitabine/TAF (F/TAF) fixed-dose combination tablet (FDC) for the treatment of HIV-1 infection. F/TAF (b) (4)
(b) (4) F/TAF 200/25 mg (b) (4).

Gilead plans to register F/TAF based on (b) (4)
(b) (4) Study GS-US-311-1473) (b) (4)
(b) (4) IND 111007, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) FDC which has safety and efficacy data.

The purpose of this meeting was to discuss the adequacy of the Phase 1 bioequivalence data with the Phase 3 data from E/C/F/TAF for the NDA submission planned in April 2015.

Gilead submitted the pre-NDA meeting request on September 19, 2014 and the FDA provided preliminary responses on December 11, 2014. Gilead provided additional follow-up comments in preparation for the teleconference on December 12, 2014 on Questions 2, 4a, 5 and additional comment #2 from the FDA. Gilead's questions are provided in **bold** font followed by the FDA's preliminary response in regular font and meeting discussion in *italicized* font.

2.0 DISCUSSION

2.1 F/TAF Submission Strategy Questions

Question 1: Does the Agency agree that the studies described above support the proposed indication for the F/TAF FDC tablets?

FDA Response to Question 1:

The results of the pivotal BE studies appear to support bridging of the proposed F/TAF FDC products to the reference E/C/F/TAF FDC products. However, a complete review of the BE studies is required to verify the adequacy of BE studies, and therefore, to support the proposed indication. The BE Studies will be officially evaluated during the NDA review. Also refer to the Clinical Pharmacology additional comments.

From the clinical standpoint, the safety and efficacy of the data from the E/C/F/TAF registration package should be adequate.

Discussion: *No further discussion.*

Question 2: Does the Agency agree with the proposal not to submit a Safety Update for the F/TAF NDA?

FDA Response to Question 2:

We recommend a limited Safety Update containing deaths and drug-related SAEs and discontinuations observed in TAF containing clinical trials be provided at the time of the F/TAF NDA.

Gilead's Response to Question 2:

As the registration strategy of F/TAF is to bridge via bioequivalence (BE) to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) for which clinical efficacy and safety data are generated, Gilead considers that the safety update for E/C/F/TAF is also appropriate as the safety update for the F/TAF NDA. Gilead proposes that the E/C/F/TAF safety update be cross-referenced as part of the F/TAF NDA submission. The E/C/F/TAF safety update is planned to be submitted in Feb 2015 and its scope is summarized below.

For the 6 ongoing studies that contributed to the primary safety database for the E/C/F/TAF FDC original NDA submission (Table 1), cumulative and interval safety data, i.e. SAEs (including deaths), AEs that led to discontinuation of study drug, and pregnancies, including new and/or updated narratives, will be provided. For all other ongoing studies and new studies initiated after the data cut date for the original NDA submission (Table 2), new and/or updated narratives for SAEs (including deaths) and pregnancies will be provided.

Table 1. Ongoing Studies Providing Primary Clinical Safety Information for the E/C/F/TAF FDC

Study	Study Design	Treatment Group (N ^a)	Data Cut Dates	
			Original NDA	Safety Update
HIV-Infected, ART-Naïve Adult Subjects				
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study	E/C/F/TAF (N = 435) STB (N = 432)	26 Aug 2014	01 Dec 2014
GS-US-292-0111	Phase 3, randomized, double-blind, multicenter, active-controlled study	E/C/F/TAF (N = 431) STB (N = 435)	19 Sep 2014	01 Dec 2014
GS-US-292-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study Open-label extension phase of E/C/F/TAF, including virologically suppressed subjects from Study GS-US-299-0102	<u>Randomized phase:</u> E/C/F/TAF (N = 112) STB (N = 58) <u>Open-label extension phase:</u> Continue E/C/F/TAF (N = 105) Switch to E/C/F/TAF (N = 161)	07 Mar 2014	01 Dec 2014
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-292-0109	Phase 3, randomized, open-label study of switching from a TDF-containing combination regimen to E/C/F/TAF FDC	Switch to E/C/F/TAF (N = 959) Continue TVD+3rd agent (N = 477)	28 Aug 2014	01 Dec 2014
HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment				
GS-US-292-0112	Phase 3, open-label, multicenter, multiple cohort study	E/C/F/TAF (N = 248)	09 Sep 2014	04 Dec 2014

HIV-Infected, ART-Naïve Adolescent Subjects				
GS-US-292-0106	Phase 2/3, open-label, multicenter, 2-part, single-group study	E/C/F/TAF (N = 48)	22 Aug 2014	12 Dec 2014

ART = antiretroviral therapy; COBI = cobicistat; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; FTC = emtricitabine; STB = Stribild; TDF = tenofovir disoproxil fumarate; TVD = Truvada

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

b Most subjects in the randomized phase of Study GS-US-292-0102 received study drug for ≥ 60 weeks when unblinding occurred; most subjects in the open-label extension had completed ≥ 24 weeks of treatment.

Table 2. Ongoing Studies Providing Supportive Clinical Safety Information for the E/C/F/TAF FDC

Study	Study Design	Data Cut Dates	
		Original NDA	Safety Update
GS-US-292-0117	Phase 3, 2-part study of TAF vs. placebo added to a failing regimen followed by treatment with E/C/F/TAF + atazanavir (ATV)	24 Aug 2014	01 Dec 2014
GS-US-292-0119	Phase 3, open-label study of switching from optimized stable ARV regimens containing darunavir (DRV) to E/C/F/TAF FDC + DRV	24 Aug 2014	01 Dec 2014
GS-US-292-1249	Phase 3b, open-label study	24 Aug 2014	01 Dec 2014
GS-US-236-0128	Phase 3b, randomized, double-blind study of E/C/F/TDF vs. ritonavir-boosted atazanavir (ATV/r) plus Truvada (TVD). After 48 weeks, during open label extension phase, subjects continued E/C/F/TDF or were randomized to either E/C/F/TAF or ATV/r + TVD (3:1 ratio)	24 Aug 2014	01 Dec 2014
GS-US-337-1624	Phase 1 study to evaluate PK DDI potential between LDV/SOF FDC and E/C/F/TAF FDC	No subjects at time of original NDA	12 Dec 2014

ART = antiretroviral therapy; COBI = cobicistat; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; FTC = emtricitabine; STB = Stribild; TDF = tenofovir disoproxil fumarate; TVD = Truvada

Discussion:

The Division reviewed Gilead's proposal on the safety update submission and stated that it was not adequate to provide a safety update on data collected 4-5 months prior to submission of the NDA. The Division stated that the sponsor should plan to submit a 120 day safety update for this NDA that includes limited safety data with a cut off in April 2015.

Question3: Does the Agency have any comments on the draft TPL?

FDA Response to Question 3:

In general, the draft TPL appears to be acceptable but labeling issues will be addressed during the NDA review. Please make note of the recommendations published in the Pregnancy and Lactation Labeling Rule as they apply to new product labels.

Discussion: No further discussion.

2.2 NDA Format and General Content Questions

Question 4:

a) Does the Agency have any comments on the proposed draft NDA table of contents?

FDA Response to Question 4a:

The proposed draft NDA table of contents is generally acceptable. We are uncertain why you propose to provide the study report for GS-US-299-0102 (Module 5.3.5.1) to this NDA. This

study is a Phase 2, double blinded study of the safety and efficacy of darunavir/cobicistat/emtricitabine/TAF compared to cobicistat boosted darunavir plus emtricitabine/TDF FDC. Please confirm that this study report has not been previously submitted to the Agency and describe the regulatory purpose of its inclusion in this NDA.

ESUB Response: From a technical standpoint (not content related) yes, the proposed NDA table of contents is acceptable however, please see general comments below:-

- Do not create additional nodes in the eCTD structure beyond what is in the specifications (e.g. m1.2.1 – m1.2.3). FDA FORM 3674 and the rest of the documents can reside under m1.2 cover letter section as separate document from the cover letter but with clear leaf titles, indicating the content of the document.
- Please provide section m5.2 (tabular listing)
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

Gilead's Response to Question 4a:

Gilead confirms that the clinical study report of GS-US-299-0102 has not been submitted to the Agency.

Gilead proposes to include this clinical study report in the F/TAF NDA as it provides relevant clinical data on the use of F/TAF with antiretroviral agents other than EVG.

Discussion:

The Division acknowledged and agreed with Gilead's justification for submitting the results of Study GS-US-299-0102 to the NDA.

b) Does the Agency agree with the proposal to cross-reference previously submitted nonclinical and clinical study reports to their respective NDAs?

FDA Response to Question 4b:

We concur with your proposal not to resubmit clinical study reports previously submitted to other NDAs but rather to cross-reference these clinical study reports.

We agree with your proposal to cross-reference non-clinical study reports which have been previously submitted to the agency.

ESUB Response: Yes. Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted

information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. nda, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

Discussion: *No further discussion.*

Question 5:

Does the Agency agree with the proposal for submission and cross reference of financial disclosure information?

FDA Response to Question 5:

This proposal is acceptable. Please confirm which studies you consider covered clinical studies for this application.

Gilead's Response to Question 5:

Gilead proposes the cross reference of financial disclosure information for the following E/C/F/TAF covered studies:

Study Number	Study Title
GS-US-292-0102	A Phase 2, Randomized, Double-Blinded Study of the Safety and

	Efficacy of Elvitegravir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults
GS-US-292-0104	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naïve Adults
GS-US-292-0106	A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naïve Adolescents
GS-US-292-0109	A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects
GS-US-292-0111	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naïve Adults
GS-US-292-0112	A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

Additional covered clinical studies for which new financial disclosure information will be submitted are as follows:

Study Number	Study Title
GS-US-299-0102	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults
(b) (4)	
GS-US-311-1473	A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-

Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets

Discussion:

The response is adequate and the Division does not have any additional comments on the financial disclosure submission.

Question 6:

Does the Agency agree with the proposal to cross reference the E/C/F/TAF nonclinical summaries in the F/TAF FDC NDA?

FDA Response to Question 6:

Yes, we agree.

Discussion: *No further discussion.*

2.3 Additional Comments

General:

1. FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with DRUG following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the BLA application in the appropriate module so it can be reviewed accordingly.

Discussion: *No further discussion.*

Clinical Pharmacology:

2. Please include TFV PK results for (b) (4) GS-US-311-1473. While you have shown data for FTC and TAF, it is also important to assess TFV.

Gilead's Response to Additional Comment #2:

Studies (b) (4) GS-US-311-1473 were conducted in accordance with the FDA "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations", U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003" where exposure of parent drug TAF is the basis for assessing bioequivalence of F/TAF in comparison to E/C/F/TAF.

These studies were conducted following input and review of the Agency as reflected in the, correspondence accompanying study synopses submitted on 23 May 2014 and in the study protocols provided for Agency review on 16 June 2014; specifically, "...*Bioequivalence assessment in these studies will characterize the rate and extent of TAF and FTC absorption by evaluating their plasma exposures by AUClast, AUCinf and Cmax. Tenofovir (TFV), the major metabolite of TAF accounting for >10% of total exposure, will not assessed in accordance with the FDA guidance...*".

On 26 June 2014 the Agency provided a written response to Gilead's 23 May and 16 June 2014 submission stating that "*The overall design of both bioequivalence studies, as presented in the respective protocols is acceptable. However, although bioequivalence will be assessed based on FTC and TAF,*" (b) (4)

Following incorporation of the Agency's recommendation, these studies have been completed with TAF and FTC BE evaluation plus descriptive PK for EVG and COBI. TFV concentrations were not assessed in these studies as TFV plasma exposures are not linked to the efficacy or the safety of TAF.

Appropriateness of these studies is supported by the characterization of TAF and TFV in the E/C/F/TAF development program, including PK/PD assessment of the contribution the metabolite TFV to efficacy and safety. Briefly, whereas TAF exposure demonstrated a dose-response relationship with antiviral activity, TFV exposure did not correlate with either antiviral activity or safety.

Discussion:

The Division acknowledges that Gilead's response is sufficient. The original request was made in the event that tenofovir levels were measured during the trials.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please refer to the October 1, 2014 letter granting this meeting and the December 11, 2014 preliminary comments outlining the contents of a complete application under "the Program".

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Since there were no additional discussions on the content of this application, your NDA is expected to be complete at the time of submission and there were no agreements for late submission of application components.

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

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

PREA REQUIREMENTS

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

We acknowledge receipt of your Agreed PSP dated July 16, 2014. Please plan to submit the Agreed PSP to the NDA, along with the corresponding requests for waiver and/or deferral of pediatric studies.

PRESCRIBING INFORMATION

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

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

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

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide official minutes of the meeting	FDA	January 14, 2015
Gilead will submit the additional information that was emailed to Stacey Min, Senior Regulatory Project Manager on December 12, 2014 to the IND	Sponsor	Submitted by the Sponsor on December 16, 2014

5.0 ATTACHMENTS AND HANDOUTS

Gilead's handout providing follow-up comments for Questions 2, 4a, 5 and additional comment #2 is attached.

7 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DEBRA B BIRNKRANT
12/23/2014



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

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2/Pre-Phase 3

Meeting Date and Time: October 17, 2013; 2:30-4:00 PM
Meeting Location: WO Building 22; Conference Room 1315

Application Number: 111851
Product Name: Emtricitabine/tenofovir alafenamide (F/TAF)
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative):

Robert Temple, M.D., Deputy Director, Center for Drug Evaluation and Research (CDER)
John Jenkins, M.D., Director, Office of New Drugs (OND)
Edward Cox, M.D., MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, M.S., Associate Director of Regulatory Affairs, OAP
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Kendall Marcus, M.D., Deputy Director for Safety, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Narayana Battula, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Su-Young Choi, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Shirley Seo, Ph.D., Clinical Pharmacology Team Lead, DCP IV
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghanous, Ph.D., DABT, Pharmacology/Toxicology Team Lead, DAVP
Stephen Miller, Ph.D., CMC Lead, DNDQA II, Branch V
Fuqiang Liu, Ph.D., CMC Reviewer, DNDQA II, Branch V
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoixing Soon, Ph.D., Biometrics Team Lead, DV IV
Antoine El Hage, Ph.D., Reviewer, Office of Scientific Investigation (OSI)
Elizabeth Thompson, M.S., Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Regulatory Project Manager, DAVP
Danyal Chaudhry, M.S., Project Manager, Office of Surveillance and Epidemiology
Krishnakali Ghosh, Ph.D., Office of Drug Manufacturing and Product Quality (OMPQ)/ New Drug Manufacturing Assessment Branch (NDMAB)/ Generic Drug Manufacturing Assessment Branch (GMAB)

SPONSOR ATTENDEES

Andrew Cheng, MD, PhD Senior Vice-President, Development Operations
Martin Rhee, MD Director, Clinical Research
Brian Kearney, PharmD Senior Director, Clinical Pharmacology
Michael Wulfsohn, MD, PhD Vice President, Biometrics
Christian Callebaut, PhD Senior Scientist, Clinical Virology
Scott McCallister, MD Senior Director, Clinical Research
Christophe Beraud, PhD Director, Regulatory Affairs
Naomi Kautz, MSc Senior Manager, Regulatory Affairs
David Pizzuti, MD, Vice President, Regulatory Affairs

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for October 17, 2013, 2:30-4:00 PM between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

On May 12, 2011, Gilead submitted IND 111851, emtricitabine/tenofovir alafenamide (F/TAF) fixed-dose combination tablet (FDC) for the treatment of HIV-1 infection in combination with other antiretrovirals. Gilead Sciences requested a Type B, Pre-Phase 3 meeting on August 1, 2013, to discuss the proposed registration plan for F/TAF FDC and the meeting was granted on August 9, 2013.

TAF single agent is currently being investigated under IND 63737. TAF is a pro-drug of tenofovir diphosphate, which provides lower systemic tenofovir exposure. In addition to the

F/TAF FDC IND, Gilead is also studying TAF in a four-drug fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) under IND 111007.

The proposed indication for F/TAF FDC is for the treatment of HIV-1 infection in adults and pediatric subjects 12 years of age and older in combination with other antiretroviral agents. Gilead proposes to support this indication by bridging F/TAF to the E/C/F/TAF Phase 3 clinical data in addition to data from Study GS-US-311-1089, a Phase 3, 96-week study of F/TAF in combination with other agents in HIV-1 infected subjects who are virologically-suppressed on F/TDF-containing regimens. The proposed Phase 3 study protocol for GS-US-311-1089 will be submitted to the Agency in fourth quarter 2013.

The specific objectives of the meeting include:

- Discuss the biopharmaceutics bridging strategy for F/TAF FDC tablet to E/C/F/TAF FDC
- Discuss the adequacy of bridged E/C/F/TAF FDC Phase 3 studies in treatment-naïve (GS-US-292-0104, GS-US-292-0111), treatment-experienced (GS-US-292-0117, GS-US-292-0119 and GS-US-292-0109), renally impaired (GS-US-292-0112) and adolescent (GS-US-292-0106) subjects, plus the proposed 48-week Phase 3 study of the F/TAF FDC tablet in combination with PI/r in HIV-1 infected subjects who are virologically suppressed on FTC/TDF-containing regimens (Study GS-US-311-1089) to support registration of F/TAF for the proposed indication
- Discuss the proposed safety database for the F/TAF FDC tablet program and its adequacy to support registration of the F/TAF FDC tablet for the proposed indication

On October 2, 2013, Gilead requested to add question number 4 below and on October 9, 2013, they requested the face-to-face meeting be changed to a teleconference. These requests were officially submitted to the IND on October 11, 2013.

DISCUSSION

1. Does the Agency agree with the clinical pharmacology data supporting F/TAF FDC tablet, (b) (1) (A)

The utility of the BE study for the proposed indication (in combination with other ARVs) is unclear. At this time, we do not have sufficient data to support (b) (4)

(b) (1) (A)

2. Does the Agency agree that the studies conducted primarily with the E/C/F/TAF STR supports an indication of the F/TAF FDC tablet for use with other antiretroviral agents

for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older?

We do not agree. The indication you propose permits use of the F/TAF FDC tablet with any other ARV regimen. Studies conducted with E/C/F/TAF will support [REDACTED] (b) (4), having an effective exposure resulting from 25mg of the TAF component. [REDACTED] (b) (1) (A)

[REDACTED] (b) (1) (A)

- 3. Does the Agency agree that the proposed safety database is adequate to support the registration of the F/TAF FDC tablet?**

While we agree that the proposed safety database should provide adequate safety data applicable [REDACTED] (b) (4), [REDACTED] (b) (1) (A)

We also note that apart from the two pivotal trials GS-US-292-0104 and 0111, all of the studies in the safety database are open label. Precautions should be taken to minimize safety signal ascertainment bias in favor of TAF.

- 4. Towards support of the same indication presented in the F/TAF FDC tablet briefing document, would the Agency be willing to discuss the acceptability of submitting the initial F/TAF FDC tablet NDA with the BA/BE bridging Study GS-US-311-1088, the Drug interaction study GS-US-120-0118, cross reference to the E/C/F/TAF pivotal Phase 3 studies, along with 9 months of stability data for the F/TAF FDC tablet proposed commercial formulations?** [REDACTED] (b) (1) (A)

We discussed this question internally and wish to provide the following preliminary comments. [REDACTED] (b) (1) (A)

[REDACTED] (b) (1) (A)

The drug interaction study GS-US-120-0118 which is expected to demonstrate TAF boosting with ritonavir is comparable to TAF boosting previously observed with cobicistat should precede the conduct of GS-US-311-1089. [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

As recommended by ICH Q1A (R2) guidance, the NDA should include at least 12 months of long-term and 6 months of

accelerated stability data for three registration batches of the drug product packaged in the container closure system proposed for marketing.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/

STACEY MIN
10/15/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208215

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DESCOVY (emtricitabine and tenofovir alafenamide), (b) (1) (A) 200/25 mg fixed-dose combination tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 11, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 11, 2016, 3-4 PM
Meeting Location: Teleconference

Application Number: NDA 208215
Product Name: DESCOVY
Indication: Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Sponsor/Applicant Name: Gilead Sciences, Inc.

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

As discussed during the Mid-Cycle Communication on October 1, 2015, the Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS).

LCM AGENDA

1. Introductory Comments - 2 minutes (Myung-Joo Patricia Hong, M.S./Islam Younis, Ph.D., Cross Discipline Team Lead)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues - 30 minutes

Our current assessment is to recommend an F/TAF (200 mg/25 mg) dosage regimen with darunavir/cobicistat (DRV/COBI) or darunavir/ritonavir (DRV/RTV). This recommendation is based on reduction in systemic TAF exposure, relative to TAF exposure from elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF), when co-administered with DRV/COBI or DRV/RTV and the results of the Phase 2 Study GS-US-299-102 where virologic success was numerically lower in the DRV/COBI/FTC/TAF treatment arm compared to DRV/COBI/FTC/TDF treatment arm. TAF exposure from F/TAF (200 mg/25 mg) when combined with DRV/COBI or RTV/COBI is expected to be similar to TAF exposure from EVG/COBI/FTC/TAF.

3. Information Requests - 2 minutes

The IR letter sent December 15, 2015 requested submission of finalized documents reflecting the agree-upon changes to the drug product control strategy by Jan 15, 2016.

4. Postmarketing Requirements/Postmarketing Commitments - 2 minutes

- As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in your Agreed iPSP for DESCovy.

5. Major Labeling Issues - 20 minutes

6. Review Plans - 2 minutes

- Continue with labeling review and discussions

7. Wrap-up and Action Items - 2 minutes

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

/s/

DEBRA B BIRNKRANT
12/24/2015



NDA 208215

LATE-CYCLE MEETING MINUTES

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DESCovy (emtricitabine and tenofovir alafenamide), (b) (1) (A) 200/25 mg fixed-dose combination tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 11, 2016.

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

If you have any questions, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Islam Younis, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology IV
Office of Clinical Pharmacology
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 11, 2016, 3 PM
Meeting Location: Teleconference

Application Number: NDA 208215
Product Name: DESCOVY
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Islam Younis, Ph.D.
Meeting Recorder: Myung-Joo Patricia Hong, M.S.

FDA ATTENDEES

OND/OAP/Division of Antiviral Products

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., MPH, Deputy Director, Division of Antiviral Products
Russ Fleischer, MPH, PA-C, Acting Clinical Team Leader, Division of Antiviral Products
Linda Lewis, M.D., Clinical Reviewer, Division of Antiviral Products
William Tauber, M.D., Clinical Reviewer, Division of Antiviral Products
Claudia Wrzesinski, Ph.D., Nonclinical Reviewer, Division of Antiviral Products
Jules O'Rear, Ph.D., Clinical Virology Team Leader, Division of Antiviral Products
Lisa Naeger, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
Beth Thompson, M.S., Chief Project Management Staff, Division of Antiviral Products
Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager, Division of Antiviral Products

OTS/Office of Clinical Pharmacology

Islam Younis, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV
Mario Sampson, PharmD., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV

Office of Pharmaceutical Quality

Stephen Miller, Ph.D., Product Quality Application Technical Leader
Frank Wackes, Ph.D., Facility Reviewer
Maryam Changi, PharmD., Product Quality BRPM

Office of Biostatistics

Thamban Valappil, Ph.D., Statistical Team Leader, Division of Biostatistics IV

Dan Rubin, Ph.D., Statistical Reviewer, Division of Biostatistics IV

Division of Medical Policy Programs

Sharon Mills, BSN, RN, CCRP, Senior Patient Labeling Reviewer

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)

APPLICANT ATTENDEES

Andrew Cheng, Senior Executive Vice President, Clinical Research and Development Operations
Dana Pizzuti, M.D., Vice President, Regulatory Affairs
Brian Kearney, PharmD., Vice President, Clinical Pharmacology
Martin Rhee, M.D., Director, Clinical Research
Julia Zack, Senior Clinical Pharmacologist, Clinical Pharmacology
Patricia Carlos, Manager, Regulatory Affairs
Christophe Beraud, Ph.D., Director, Regulatory Affairs
Erik Berglund, M.D., Ph.D., Associate Director, Regulatory Affairs
Doris Graupe, Manager, Regulatory Affairs, CMC
Bob Scott, Sr. Director, Process Development

1.0 BACKGROUND

NDA 208215 was submitted on April 7, 2015 for DESCOVY (emtricitabine and tenofovir alafenamide), 200/25 mg (b) (4) fixed-dose combination tablets.

Proposed indication(s): Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

PDUFA goal date: April 7, 2016

FDA issued a background package in preparation for this meeting on December 24, 2015.

2.0 DISCUSSION

1. Introductory Comments

The Division noted that the purpose of a Late-Cycle Meeting (LCM) is to share information and discuss any substantive review issues that have been identified to date and the plans for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the

application. The Division is sharing this material to promote a collaborative and successful discussion at the meeting.

The Division stated that during the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If Gilead submitted any new information in response to the issues identified in this background package prior to this LCM, the division may not be prepared to discuss that new information at this meeting.

Today's discussion will focus on the agenda proposed in our LCM background package.

Before discussing any review issues, OPQ updated the status of CMC reviews and informed the sponsor as follows:

- *Drug substance, drug product, biopharmaceutics, and process reviews are complete, and there are no outstanding issues with these reviews. The evaluation of inspection results from manufacturing, testing and packaging facilities has not yet been completed.*

The following information was noted in LCM background package. No discussion occurred for these topics:

- *No discipline review letters have been issued and no substantive review issues have been identified to date.*
- *No advisory committee meeting is planned.*
- *The Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS), at this time.*

2. Discussion of Minor Review Issues

Our current assessment is to recommend an F/TAF (200 mg/25 mg) dosage regimen with darunavir/cobicistat (DRV/COBI) or darunavir/ritonavir (DRV/RTV). This recommendation is based on reduction in systemic TAF exposure, relative to TAF exposure from elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF), when co-administered with DRV/COBI or DRV/RTV and the results of the Phase 2 Study GS-US-299-102 where virologic success was numerically lower in the DRV/COBI/FTC/TAF treatment arm compared to DRV/COBI/FTC/TDF treatment arm. TAF exposure from F/TAF (200 mg/25 mg) when combined with DRV/COBI or RTV/COBI is expected to be similar to TAF exposure from EVG/COBI/FTC/TAF.

Discussion: Gilead acknowledged the systemic TAF exposure is lower in DESCOPY combined with darunavir, relative to TAF exposure from GENVOYA. Gilead stated that the numerically lower virologic success in EVG/COBI/FTC/TAF observed in study GS-US-299-102 is mainly driven by dropouts. (b) (4)

(b) (4)

(b) (4) The drug-drug interaction study of DRV/RTV with F/TAF (200/25 mg) demonstrated higher exposure of TFV compared to those observed with GENVOYA. The Division requested Gilead to submit TFV exposure data when DRV/RTV is administered with F/TAF (200/25 mg). Gilead acknowledged the request and committed to provide the requested information within 24 hours. DAVP informed Gilead that they will take their point of view into consideration and will inform Gilead on DAVP position regarding the dose of TAF to be administered with DRV/RTV or DRV/COBI.

Post-Meeting Note: Gilead responded that “The co-administration of TAF with boosted DRV is associated with an approximately 3-fold increased TFV exposure as compared to unboosted F/TAF, this information is presented in NDA 208215 m2.7.2, Table 27 (p.82) and Table 34 (p 94) based on Study GS-US-311-0101 and GSUS-120-0118, respectively.

(b) (1) (A)

3. Information Requests

The information request letter sent on December 15, 2015 requested submission of finalized documents reflecting the agreed-upon changes to the drug product control strategy by January 15, 2016.

Discussion: The Division noted that the response was received on January 8, 2016.

4. Postmarketing Requirements/Postmarketing Commitments

As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in your Agreed iPSP for DESCovy.

Discussion: No discussion occurred.

5. Major Labeling Issues

The Division provided labeling comments on December 17, 2015 prior to today’s LCM. The response was received on January 8, 2016. The Division will continue labeling discussions and send further labeling proposals after the next Division labeling meeting scheduled for January 19, 2016.

Discussion: No discussion occurred.

6. Review Plans

Continue with labeling review and discussions.

Discussion: No discussion occurred.

7. Wrap-up and Action Items

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

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

/s/

ISLAM R YOUNIS
01/21/2016