CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207561Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #: 207561/Original Submission SUPPL #: N/A HFD #: 530

Trade Name: GENVOYA

Generic Name: elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) 150/150/200/10 mg fixed-dose combination tablet

Applicant Name: Gilead Sciences, Inc.

Approval Date, If Known: November 5, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(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.

N/A

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

5 years under 21CFR § 314.108(b)(2)
3 years under 21 CFR§ 314.108(b)(4)

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 # 203093	VITEKTA (elvitegravir) 85 and 150 mg Tablets
NDA # 203094	TYBOST (cobicistat) 150 mg Tablet
NDA # 203100	STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Fixed-Dose Combination 150 mg/150 mg/200 mg/300mg Tablets

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:

N/A

(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:

GS-US-292-0104 entitled "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-292-0111 entitled "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"

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:

N/A

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:

N/A

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"):

GS-US-292-0104 entitled "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-292-0111 entitled "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"

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 # 111,007	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 111,007	YES ☒	! NO ☐
		! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Myung-Joo Patricia Hong, M.S.
Title: Senior Regulatory Project Manager
Date: August 25, 2015

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
08/25/2015

JEFFREY S MURRAY
08/25/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207561 Original Submission	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: GENVOYA® Established/Proper Name: elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) Dosage Form: 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 draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 5, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other – Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval - 11/5/15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (11/2/15)
• Original applicant-proposed labeling	☒ Included (11/5/14)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (11/2/15)
• Original applicant-proposed labeling	☒ Included (11/5/14)
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included (10/9/15)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	• Grant Letter - 12/11/14 • Review - 12/8/14
❖ Labeling reviews *(indicate dates of reviews)*	• RPM: PLR Format Review - 1/6/15 • DMEPA: 3/4/15 • DMPP/PLT (DRISK): 10/30/15 (consolidated review with OPDP for PPI) • OPDP: 10/30/15 (Memorandum) • SEALD: ☒ None • CSS: ☒ None • Product Quality (PI, Container Label & Access Carton/Container) – Included in Integrated Product Quality Assessment Review (page 192 - 201) - 7/9/15 • Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review - January 7, 2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC September 9, 2015 If PeRC review not necessary, explain:	
❖ 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 decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	11/10/14, 1/14/15, 1/22/15, 2/4/15 (x2), 2/24/15, 3/9/15, 3/30/15, 4/1/15, 5/5/15, 5/6/15 (x2), 5/7/15, 5/8/15, 5/26/15, 5/28/15, 6/5/15, 6/25/15 (x2), 6/29/15, 7/9/15, 7/10/15, 7/13/15, 7/17/15,7/20/15, 8/11/15, 8/25/15, 9/17/15, 10/1/15, 10/6/15, 10/14/15, 10/28/15, 10/29/15, 10/30/15 (x3), 11/2/15
❖ 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
• Pre-NDA/BLA meeting *(indicate date of mtg)*	**May 30, 2014** - Pre-NDA meeting scheduled; however, Gilead cancelled after receiving FDA's preliminary comments sent 5/28/14 - Preliminary comments included
• EOP2 meeting *(indicate date of mtg)*	**December 17, 2012** - Minutes included
• Mid-cycle Communication *(indicate date of mtg)*	**April 13, 2015** - Minutes included
• Late-cycle Meeting *(indicate date of mtg)*	**August 4, 2015** - Minutes included
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	**October 30, 2014** - Type C meeting scheduled to discuss the summary of results from pivotal trials; however, Gilead cancelled after receiving FDA's preliminary comments sent 10/27/14 - Preliminary comments included
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	November 4, 2015
Division Director Summary Review *(indicate date for each review)*	October 19, 2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	October 1, 2015
PMR/PMC Development Templates *(indicate total number)*	2

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Please see CDTL Review
• Clinical review(s) *(indicate date for each review)*	• Filing Review - 2/4/15 • Approval - 7/29/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Included in clinical review - located in Section 3.3, Page 17 - 20
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	• DBRUP Review - 3/25/15 • DCRP Review-5/29/15 & 10/1/15 • DDDP Review - 6/4/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	No REMS required - 8/17/15
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	• Inspection Review Summary - 6/5/15 • OSI Letters - 4/1/15, 4/21/15 (x2), 5/14/15, 5/27/15, 6/24/15, 6/26/15 & 9/17/15
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	• Filing Review - 3/11/15 • Approval - 7/10/15 & 10/26/15 (Amended)
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	• Filing Review - 1/14/15 • Approval - 7/10/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	• Filing Review - 1/20/15 • Approval - 7/10/15 & 10/14/15 (Review of additional analyses)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	• Filing Review - 1/9/15 • Approval - 7/10/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	• Filing Review - 12/18/14 • Approval - 7/9/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Method Validation Review - 7/9/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Granted - Included in Integrated Product Quality Assessment Review (page 130) - 7/9/15
☐ Review & FONSI *(indicate date of review)*	N/A
☒ Review & Environmental Impact Statement *(indicate date of each review)*	Included in Integrated Product Quality Assessment Review (page 130) - 7/9/15
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ 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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

---

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
11/05/2015

From: Hong, Myung-Joo P.
To: "Erik Berglund"
Cc: Regulatory Archives
Subject: NDA 207561.Label
Date: Friday, October 30, 2015 3:57:07 PM

Erik, for your question #1, we are ok for both ways:

1. Option #1 - drug name abbreviations be defined at the first usage in the PI and then abbreviated at subsequent usages
2. Option #2 - drug names (e.g., tenofovir alafenamide and tenofovir disoproxil fumarate) be spelled out throughout the PI

But since GENVOYA contains 4 drugs and spelling out TDF will make the label even lengthier. We recommend Option #1.

The error in Table 5, please use the text from 14 October 2015. We have two additional comments:

(b) (4)

2. Regarding manufacturer information at the end of Section 17, this information should be on the container labels and in the label. The manufacturer information (e.g., name and location of business (street address, city, state and zip code) is required in labeling per 21CFR201.1 and 21CFR201.100(e) and should be located after the PATIENT COUNSELING INFORMATION section at the end of the PI. Please include the manufacturer's information including the location of business at the end of the PI.

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: Erik Berglund [mailto:Erik.Berglund@gilead.com]
Sent: Friday, October 30, 2015 1:50 PM
To: Hong, Myung-Joo P.
Cc: Regulatory Archives
Subject: RE: NDA 207561.Label
Importance: High

Hi Pat,

I acknowledge the receipt of the PI and PPI for Genvoya.

Two questions for clarification:
1: Regarding the Agency's comment on page 3 ("Please re-assess the use of drug names or abbreviations throughout the label to make them consistent across sections, particularly with regard to tenofovir alafenamide and tenofovir disoproxil fumarate. There are ~13 uses of tenofovir disoproxil fumarate and ~14 uses of TDF in the label. Please spell out the drug names in section/subsection headers.") –

Does FDA have a preference regarding the approach for abbreviations - i.e. should the drug name abbreviations be defined at the first usage in the PI and then abbreviated at subsequent usages; or should the drug names (e.g. tenofovir alafenamide and tenofovir disoproxil fumarate) be spelled out throughout the PI?

2: In Table 5 (on page 15), there seem to have occurred an error with the text for "Antibacterials" when the font was corrected. Please clarify if we are to use the text from 14 October 2015?
30 October 2015

(b) (4)

[redacted]

14 October 2015 The original text was:

Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Patients with CL_{cr} greater than or equal to 60 mL/minute: No dosage adjustment of clarithromycin is required. Patients with CL_{cr} between 50 mL/minute and 60 mL/minute: The dosage of clarithromycin should be reduced by 50%.

Warm regards,

Erik

From: Hong, Myung-Joo P. [mailto:Myung-Joo.Hong@fda.hhs.gov]
Sent: Friday, October 30, 2015 9:57 AM
To: Erik Berglund
Subject: NDA 207561.Label

Hi Erik, please find attached our label proposal. I am attaching revised PPI as separate attachment. We started using new format for PPIs and MGs. The boxed format represents DMPP's current recommendation for formatting of MGs and PPIs. Please use this format as the base document making subsequent changes. Please submit your response to our proposal by **11/2/15 (Noon, EST).**

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
10/30/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Subject: NDA 207561.Label
Date: Friday, October 30, 2015 12:56:49 PM
Attachments: 10.30.15.PPI to Gilead.docx
10.30.15.PI to Gilead.docx

Hi Erik, please find attached our label proposal. I am attaching revised PPI as separate attachment. We started using new format for PPIs and MGs. The boxed format represents DMPP's current recommendation for formatting of MGs and PPIs. Please use this format as the base document making subsequent changes. Please submit your response to our proposal by **11/2/15 (Noon, EST).**

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*

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

---

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

/s/

MYUNG JOO P HONG
10/30/2015

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

DATE: **October 29, 2015**

NDA: **207561/Original Submission**

TO: **Erik Berglund, M.D., Ph.D., RAC, Associate Director, Regulatory Affairs**

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

SUBJECT: **Advice/Information Request**

Please refer to your November 5, 2014 submission submitted to NDA 207561. We are requesting your assistance in populating the attached tables for your New Molecular Entity, GENVOYA, currently under review in the Division.

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

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

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

Please provide the requested information by November 2, 2015 (see attached Excel spreadsheet).

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

Baseline Demographic for 5 Pooled Trials (104, 111, 109, 112, and 106)

	GENVOYA N=1930	Comparator N=1264	Total N=3194
Demographic Subgroup			
Sex, n (%)			
Male			
Female			
Age Group, n (%)			
12- 17 years			
18-64 years			
>=65 years			
Race (modify according to the program), n (%)			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Ethnicity, n (%)			
Hispanic or Latino			
Not Hispanic or Latino			

Baseline Demographics for 4 pooled adult trials	GENVOYA N=1907	Comparator N=1264	Total N=3171
Sex, n (%)			
Male			
Female			
Age Group, n (%)			
18-64 years			
>=65 years			
Race (modify according to the program), n (%)			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Ethnicity, n (%)			
Hispanic or Latino			
Not Hispanic or Latino			

Baseline Demographics for Trial 106	All patients (N=23)
Sex, n (%)	
Male	
Female	
Race (modify according to the program), n (%)	
White	
Black or African American	
Asian	
American Indian or Alaska Native	
Native Hawaiian or Other Pacific Islander	
Other	
Ethnicity, n (%)	
Hispanic or Latino	
Not Hispanic or Latino	

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
10/29/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Subject: NDA 207561.Label
Date: Wednesday, October 28, 2015 2:18:33 PM

Hello Erik, we have the following comments for Renal Laboratory Tests. Please see suggested text below for the 3 clinical trial descriptions in Section 6 (Adverse Reactions, subsection Renal Laboratory Tests). We will send you our label proposal as recommended below.

- (b) (4) As a path forward, we recommend providing information on the median UPCR at baseline and following treatment (Week 48) in the two treatment arms.

Treatment Naïve Adults:

In two 48-week randomized, controlled trials in a total of 1733 treatment naïve adults with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL in the GENVOYA and STRIBILD groups from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48 in the GENVOYA group. Median UPCR was 44 mg per gram at baseline and 55 mg per gram at Week 48 in those receiving STRIBILD. (b) (4)

Virologically Suppressed Adults:

In a study of 1436 virologically-suppressed TDF-treated adults with a mean baseline eGFR of 112 mL per minute who were randomized to continue their treatment regimen or switch to GENVOYA, at Week 48 mean serum creatinine was similar to baseline for both those continuing baseline treatment and those switching to GENVOYA. Median UPCR was 61 mg per (b) (4) at baseline and 46 mg per gram at Week 48 in subjects switching to GENVOYA. In subjects remaining on their initial regimen, UPCR was 60 mg per gram at baseline and 63 mg per gram at Week 48. (b) (4)

(b) (4)

(b) (4)

In a 24-week trial in 248 subjects with baseline renal impairment (eGFR 30 to 69 mL per minute) who received GENVOYA, mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24. (b) (4).

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
10/28/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Restricted Archives (Restricted.Archives@gilead.com)
Subject:	NDA207561.PREA PMC Comment and Labeling Proposal
Date:	Wednesday, October 14, 2015 4:32:27 PM
Attachments:	10.14.15.PI to Gilead.pdf 10.14.15.PI to Gilead.docx

Hi Erik, please find attached our labeling proposal. Please submit your response to our labeling proposal by **10/19/15 (3 PM, EST).**

Your proposal to change the PMC comment as written below (in red) is not acceptable:

> "Submit the long-term safety and antiviral activity data for Study GS-US-292-0106. Include data and analyses for the entire study population through Week 48 and for all subjects enrolled in the extension phase [redacted] (b) (4)

To ensure alignment with the PREA PMR, Gilead proposes the following dates for the Clinical/Pediatric PMC:

> Protocol Submission: **Please include date**
> Trial Completion: September, [redacted] (b) (4)
> Final Report Submission: March, [redacted] (b) (4)

We have the following clarification/request for PMC:

- Please provide all the data on the Study 0106 population through the end of the primary study period (Week 48) and all the data from the subjects who roll-over into the extension phase through Week 96 [redacted] (b) (4). The data should be included in one submission, although it may require more than one kind of analysis. This will maximize the amount of long-term follow-up data in a single submission and subsequent submissions will not be necessary.

  For example:

  "Submit the long-term safety and antiviral activity data for Study GS-US-292-0106. Include data and analyses for the entire study population through Week 48 and for all subjects enrolled in the extension phase through 96 weeks of [E/C/F/TAF TRADENAME] dosing."

This may require revision of your proposed timeline.

If you can find a better way to phrase that, please try and send to us. Please submit your response to PMC comment by **10/16/15 (12 PM, EST).**

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*

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

---

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

/s/

MYUNG JOO P HONG
10/14/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Subject: NDA 207561.Information Request
Date: Tuesday, October 06, 2015 4:11:34 PM

Hello Erik, we have the following requests:

1. Please clarify whether Genvoya will be the tradename on the Access bottle and carton labels

2. Please submit a revised set of container labels, with Genvoya replacing "Tradename" as appropriate.

3. On these revised labels, please insert an "and" before tenofovir alafenamide so that the established name reads as "(elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) Tablets"

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
10/06/2015

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

DATE: **October 1, 2015**

NDA: **207561/Original Submission**

TO: **Erik Berglund, M.D., Ph.D., RAC, Associate Director, Regulatory Affairs**

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

SPONSOR: **Gilead Sciences, Inc.**

SUBJECT: **PMR/PMC Comments**

Please refer to your November 4, 2014 submission submitted to NDA 207561. The DAVP is proposing the following postmarketing commitment (PMC) and requirement (PMR). Please provide your response to this request by **October 7, 2015**.

PREA PMR

1. Conduct your deferred pediatric study in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination. At least some of the safety data must be derived from dosing as the GENVOYA fixed dose combination (duration and number of subjects on GENVOYA to be agreed upon with the Agency).

   Protocol Submission: Submitted
   Trial Completion: September, 2017
   Final Report Submission: March, 2018

Clinical/Pediatric PMC

2. Submit the long-term safety and antiviral activity data for Study GS-US-292-0106. Include data and analyses for the entire study population through Week 48 and all subjects enrolled in the extension phase through 96 weeks of GENVOYA dosing.

   Protocol Submission: Submitted
   Trial Completion:
   Final Report Submission:

Comment [MPH1]: Gilead, please propose the dates

Please confirm your acceptance for the proposed timelines for commitments 1 and 2. If the dates proposed above are not appropriate, please provide the justification and propose new dates.

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
10/01/2015

PeRC Meeting Minutes
September 9, 2015

PeRC Members Attending:
Lynne Yao
Linda Lewis
Hari Cheryl Sachs
Lily Mulugeta
Belinda Hayes
Wiley Chambers
Meshaun Payne
George Greeley
Michelle Roth-Cline
Lisa Faulcon
Julia Pinto
Dianne Murphy
Gregory Reaman
Non Responsive
Maura O'Leary (Genvoya, Non Responsive reviews only)
Freda Cooner (Genvoya Non Responsive reviews only)

Agenda

9:00	NDA 207561	Genvoya (E/C/F/TAF) Partial Waiver/Deferral/Plan/Assessment (with Agreed iPSP)	DAVP	Stacey Min	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Non Responsive

Non Responsive

Genvoya (E/C/F/TAF) Partial Waiver/Deferral/Plan/Assessment (with Agreed iPSP)

- Proposed Indication: Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.
- The division noted that tenofovir alafenamide is a new pro-drug, and replaces tenofovir disoproxil fumarate in this 4 drug fixed-dosed combination. Tenofovir alafenamide is predicted to have an improved safety profile compared to tenofovir disoproxil fumarate and is the reason for this new combination product. The data reviewed support the approval of the product down to 12 years of age.
- The division also clarified that the deferred study in 6-12 year old patients would be completed in 2 phases; phase A is intended to establish the PK profile and appropriate dose for EVG and TAF because these drugs have not previously be studied in patients 6-12 years of age. Phase B of the study is designed to assess, PK, safety and tolerability of the 4 drug combination.
- The division noted that it would be desirable to evaluate the to-be-marketed formulation before completing phase B so that it would be clear that the sponsor can, in fact, develop a combination product that can be administered in 6-12 year olds. The division requested assistance in developing language for this PMR to reflect this time line for formulation development.

- *PeRC Recommendations*:
  - The PeRC agreed with the division, that the sponsor's plan to request a partial waiver in pediatric patients from 0 to 28 days and 28 days to < 6 years of age because studies are impossible or highly impractical.
  - The PeRC agreed with the deferral in patients 6 years old to < 12 years of age because additional safety and effectiveness data are needed in this age group.
  - DPMH is available to assist the division with drafting the PREA PMRs for this product (see discussion above).

Non Responsive

7 Pages have been Withheld in Full as Non Responsive 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/

MESHAUN L PAYNE
09/28/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com)
Subject:	NDA 207561.Labeling Proposal
Date:	Thursday, September 17, 2015 5:25:17 PM
Attachments:	9.17.15.PI to Gilead.docx 9.17.15.PI to Gilead.pdf

Hi Erik, please find attached the draft GENVOYA labeling proposal with comments from the review team embedded. Please provide your response by COB on **September 30, 2015**. Please let me know if you have any questions.

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*

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

---

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

/s/

MYUNG JOO P HONG
09/17/2015

From:	Hong, Myung-Joo P.
To:	"erik.berglund@gilead.com"
Cc:	"Regulatory Archives (Regulatory.Archives@gilead.com)"
Subject:	NDA 207561.Clarification
Date:	Tuesday, August 25, 2015 11:04:54 AM

Hi Erik, we acknowledge the submission dated August 14, 2015 which contains the new dataset for Study 0112.

We would like to clarify that we do not intend to analyze and review the datasets for Study 0112 submitted on August 14. It is too late in the review cycle to accept and review new datasets. Submission of new data is recommended only within the first 30 days of filing and usually by prior agreement. I apologize if you misunderstood our request to clarify whether the data had already been submitted with the Safety Update. However, we are considering your most recent labeling comments related to this study based on review of data submitted at the time of filing.

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
08/25/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com)
Subject:	NDA 207561 Request for information
Date:	Tuesday, August 11, 2015 1:14:33 PM

Hello Erik, we have the following requests from review team:

1. During our Late Cycle Meeting held last week you referenced additional safety data for Study 0112. We are unable to locate electronic datasets accompanying the Safety Update submitted on February 24, 2015. Such datasets are needed to corroborate your findings which appear in tabular form and to assess the totality of the safety data regarding Study 292-0112 available when the safety update was compiled. Please clarify whether datasets were submitted and, if so, the location in the submission.

2. Please explain the discrepancy between 48 week measurements in Tables 2 and 4.1.7 in the Safety Update. According to Table 2, (b) (4) of subjects with baseline eGFR < 50 had 48 weeks or more exposure and according to Table 4.1.7, (b) (4) of these subjects had reached 48 weeks.

Please submit your response by August 14/15.

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
08/11/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com); "Theresa Tran"; "Mae Lai"
Subject:	NDA 207561.Labeling Proposal
Date:	Friday, July 17, 2015 7:43:00 PM
Attachments:	7.17.15.PI to Gilead.docx 7.17.15.PI to Gilead.pdf

Hi Erik, please find attached the draft GENVOYA labeling proposal with comments from the review team embedded. Please provide your response by COB on August 7, 2015. Please let me know if you have any questions.

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*

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

---

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

/s/

MYUNG JOO P HONG
07/17/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com); "Theresa Tran"; "Mae Lai"
Subject:	NDA 207561.Information Request
Date:	Monday, July 13, 2015 4:47:00 PM

Hi Erik, we have the following IR from review team:

- Current guidelines for treatment of cholesterol to reduce cardiovascular risk recommend an algorithm-based approach incorporating age, gender, race, cholesterol levels, and presence of other risk factors such as hypertension, diabetes and smoking. Using the data collected in the trials, please assess the subjects enrolled in Studies 0104 and 0111 to determine whether subjects should have received lipid lowering therapy based on current ACC/AHA guidelines.

Please provide your response by August 7, 2015.

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
07/13/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com); "Theresa Tran"; "Mae Lai"
Subject:	NDA 207561.IR
Date:	Friday, July 10, 2015 6:05:00 PM
Sensitivity:	Confidential

Hi Erik, we have the following request from review team:

> In order to maintain some consistency across labels, please provide an analysis of the number of subjects in the pooled Studies 0104 and 0111 and Study 0109 demonstrating either 7% BMD loss in femoral neck ([redacted] (b) (4)) or 5% BMD loss in spine at 48 weeks. [redacted] (b) (4) .

Please submit your response by July 24, 2015.

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
07/10/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com); Theresa Tran; Mae Lai
Subject:	NDA 207561.IR
Date:	Thursday, July 09, 2015 9:45:00 AM

Hello Erik, we have the following comments from review team:

. For Study GS-US-292-0112 in HIV-infected subjects with renal impairment, please perform a statistical PK comparison for the components of E/C/F/TAF between subjects with mild ($eGFR_{CG}$ 60-89 mL/min) or moderate ($eGFR_{CG}$ 30-59 mL/min) renal impairment and historical controls without renal impairment ($eGFR_{CG}$ ≥90 mL/min). Please also summarize the demographic characteristics of subjects contributing PK data by renal impairment category.

Please submit your response by July 22, 2015.

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
07/09/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Subject: NDA 207561.Information Request
Date: Monday, June 29, 2015 1:30:00 PM

Hello Erik, we have the following comments from review team:

1. (b) (4) . For studies where TFV-DP was quantified, insufficient detail was found in the application to consider the TFV-DP bioanalytical method to be validated. Please submit method validation reports for TFV-DP, in particular for Studies 104 and 111.

2. Interference of TAF with quantification of TFV in plasma was detected at the low QC in study GS-US-292-1316. In a response (dated 5/11/2015) to an FDA Information Request, this interference was attributed to the presence of TFV-related impurities in the TAF reference materials. Please describe what steps were taken, if any, to remove these impurities from the TAF reference materials, or to modify the plasma TFV analytical procedure to avoid the interference.

Please submit your response by July 6, 2015.

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
06/29/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Cc: Regulatory Archives (Regulatory.Archives@gilead.com)
Subject: NDA 207561 - Request for Container Label Revision
Date: Thursday, June 25, 2015 4:36:00 PM

Hello Erik, we have the following comments from review team:

- Please revise the container labels for both the US and Access products as follows: "Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg of tenofovir alafenamide fumarate)."

- Please submit the revised labels by July 7, if feasible.

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
06/25/2015

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

DATE: **June 5, 2015**

NDA: **207561/Original Submission**

TO: **Erik Berglund, M.D., Ph.D., RAC, Associate Director, Regulatory Affairs**

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

SUBJECT: **Advice/Information Request**

Please refer to your November 5, 2014 submission submitted to NDA 207561. We have the following requests from the review team.

Clinical

During review of the financial disclosure statements included in NDA 207561, we note substantial numbers of site principal investigators (25-45%, varying by study) participating in Studies 0102, 0104, 0111, 0109 and 0112 are identified in your financial certification and disclosure statement as having received significant payments of greater than $25,000 beyond trial conduct costs or have equity interest of greater than $50,000.

Please perform an aggregate assessment of the potential impact of these financial considerations to include:

- Summary table of principal investigators (PIs)/Sub-investigators with financial disclosures and number of sites and subjects affected, by study and treatment arm.
- Sensitivity analysis of primary efficacy and safety endpoints excluding subjects from sites staffed by PIs/Sub-investigators who received financial considerations from Gilead or have greater than $50,000 equity interest in Gilead Sciences.
- Please provide an analysis of the proportion of adverse events considered drug related for each of the trials comparing subjects enrolled at sites that did or did not receive financial considerations.
- Please provide a comparison of the proportion of site PIs with significant financial considerations participating in the GENVOYA covered studies and other recent Gilead NDAs.
- Please provide an explanation for the high proportion of PIs receiving financial considerations in this development program.

Please provide the requested information and analyses by June 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
06/05/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com)
Subject:	NDA 207561 - Information Request
Date:	Tuesday, May 26, 2015 10:17:00 AM

Hello Erik, we have the following requests:

Population PK

1. Please provide more detail, such as the formulas, on the methods used to calculate the individual steady-state parameters (AUC and Cmax for TAF; AUC, Cmax, and Cmin for TFV) from posthoc parameters.
2. In the population PK report, comprehensive analyses were shown for the separate TAF and TFV models, but only the PK parameter values were shown for the joint TAF and TFV model. As the joint model is of primary interest, for the joint model please provide the same analyses shown previously for the TAF and TFV models.

Please submit your response by June 8, 2015.

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
05/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

LABELING PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

Please refer to your New Drug Application (NDA) dated November 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GENVOYA (elvitegravir/ cobicistat/emtricitabine/tenofovir alafenamide), 150/150/200/10 mg fixed-dose combination tablet.

On March 13, 2015, we received your proposed labeling submission to this application. We have preliminary proposed revisions from our CMC and Virology reviewers that are included as an enclosure. We request that you resubmit labeling that addresses these issues by **May 29, 2015**. 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 42 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 in Section 12.4 (Microbiology).

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

(b) (4)

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

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

---

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

/s/

MYUNG JOO P HONG
05/08/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Cc: Regulatory Archives (Regulatory.Archives@gilead.com)
Subject: RE: NDA 207561.Information Request
Date: Thursday, May 07, 2015 9:36:00 AM

Dear Erik, we have the following additional request to the earlier e-mail below.

- For the exposure-safety analysis in relation to BMD, in addition to looking at TAF we recommend also analyzing TFV and perhaps TAF+TFV. We also recommend including the datasets in the submission.

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, May 06, 2015 11:17 AM
To: erik.berglund@gilead.com
Cc: Regulatory Archives (Regulatory.Archives@gilead.com)
Subject: NDA 207561.Information Request

Dear Erik, we have the following information request from review team:

> As mentioned during our post-mid-cycle communication teleconference, we continue to have some concerns about the potential for TAF to cause changes in bone parameters. We note that while fewer subjects receiving TAF (as Genvoya) had decreases in BMD of ≥ 6% compared to those receiving TDF (as Stribild), there were still a significant number of subjects who reached this level of BMD loss. In a population of adult male subjects, this may still represent tenofovir-associated toxicity.
>
> Please provide an exposure response analysis for safety evaluating TAF exposure and BMD change using the combined Study 0104 and 0111 data. To further characterize potential bone effects of TAF, please correlate BMD loss with changes in TmP/GFR, retinol binding protein, β-2 microglobulin, other renal biomarkers, and

bone adverse events including fractures. In addition, correlate bone biomarkers (i.e., CTX and P1NP) with TmP/GFR and other renal biomarkers.

Please submit your response by May 20, 2015.

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
05/07/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Cc: Regulatory Archives (Regulatory.Archives@gilead.com)
Subject: NDA 207561.Information Request
Date: Wednesday, May 06, 2015 11:16:00 AM

Dear Erik, we have the following information request from review team:

> As mentioned during our post-mid-cycle communication teleconference, we continue to have some concerns about the potential for TAF to cause changes in bone parameters. We note that while fewer subjects receiving TAF (as Genvoya) had decreases in BMD of ≥ 6% compared to those receiving TDF (as Stribild), there were still a significant number of subjects who reached this level of BMD loss. In a population of adult male subjects, this may still represent tenofovir-associated toxicity.
>
> Please provide an exposure response analysis for safety evaluating TAF exposure and BMD change using the combined Study 0104 and 0111 data. To further characterize potential bone effects of TAF, please correlate BMD loss with changes in TmP/GFR, retinol binding protein, β-2 microglobulin, other renal biomarkers, and bone adverse events including fractures. In addition, correlate bone biomarkers (i.e., CTX and P1NP) with TmP/GFR and other renal biomarkers.

Please submit your response by May 20, 2015.

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
05/06/2015

From:	Hong, Myung-Joo P.
To:	erik.berglund@gilead.com
Cc:	Regulatory Archives (Regulatory.Archives@gilead.com)
Subject:	NDA 207561.Information Request
Date:	Wednesday, May 06, 2015 1:59:00 PM
Sensitivity:	Confidential

Dear Erik, we have the following information request regarding Study GS-US-292-0109:

> As a certain number of subjects in the switch Study GS-US-292-0109 were recruited from the Phase 3 trials of STRIBILD in treatment-naïve subjects, we assume some may have baseline BMD data prior to the initiation of a TDF-based regimen in the original trials. In order to better understand the relative impact of switching to GENVOYA on BMD in these subjects compared to their original baseline measurements, please provide a summary of BMD changes from their pre-TDF baseline measurements in the feeder trials through their Baseline visit in Study 0109 and up to Week 48 of Study 0109. Your summary should include subjects who switched to GENVOYA in Study 0109 as well as those who remained on their original TDF-based regimen from their feeder trial.

Please submit your response by May 20, 2015.

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
05/06/2015

From: Hong, Myung-Joo P.
To: erik.berglund@gilead.com
Cc: Regulatory Archives (Regulatory.Archives@gilead.com)
Subject: NDA 207561.Information Request
Date: Tuesday, May 05, 2015 12:23:00 PM

Dear Erik, we have the following information request from review team:

1. In Bioanalytical Sample Analysis Report 60-1411B for Study GS-US-292-1316, GS-7340/FTC/EVG/COBI/Sertraline interfered with measurement of TFV peak area ratio at the low QC (402% difference), but not at the high QC (1.6% difference).

    a. Please further discuss why you concluded "The mean responses (peak area ratios) obtained from the samples in the presence of GS-7340/emtricitabine/GS-9137/GS-9350/sertraline were less than 15% of the samples without GS-7340/emtricitabine/GS-9137/GS-9350/sertraline."
    b. Using the existing data, please conduct the comparison (TFV with and without GS-7340/FTC/EVG/COBI/Sertraline) using concentration instead of peak area ratio.

2. Carryover was detected (>20% of LLOQ area) for several analytes in the combination long-term storage stability report (b) (4) 60-1325. In these cases it was stated that carryover was evaluated per (b) (4)-001 or (b) (4) SOP (b) (4)-002 and there was no impact on the data. Please submit these SOPs and further discuss why carryover did not impact the data.

3. For Study GS-US-292-0106, please repeat the statistical analysis for PK parameters comparing adolescents vs. HIV-infected adults (b) (4)).

4. Please evaluate whether EVG, COBI, FTC, TAF, or TFV interfere with the tests used to measure total cholesterol, LDL, HDL, and triglycerides.

Please submit your responses to #1-3 by **May 12, 2015** and provide an estimated timeframe for response to #4.

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
05/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Erik Berglund, M.D., Ph.D., RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide), 150/150/200/10 mg fixed-dose combination tablet.

We also refer to the teleconference between representatives of your firm and the FDA on April 13, 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, Regulatory Project Manager at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Linda L. Lewis, M.D.
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: April 13, 2015, 11 AM – 12 PM

Application Number: 207561

Product Name: Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide), 150/150/200/10 mg fixed-dose combination tablet

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

Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda Lewis, M.D., Clinical Team Leader
Meeting Recorder: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager

FDA Participants:

Office of Antiviral Products

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Poonam Mishra, M.D., Acting Deputy Director for Safety, Division of Antiviral Products
Linda Lewis, M.D., Clinical Team Leader, Division of Antiviral Products
Peter Miele, M.D.,Clinical Reviewer, Division of Antiviral Products
William Tauber, M.D., Clinical Reviewer, Division of Antiviral Products
Hanan Ghantous, Ph.D., DABT, Nonclinical Team Leader, 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
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager, Division of Antiviral Products
Christine Kim, Pharmacy Student

Office of Clinical Pharmacology

Mario Sampson, PharmD., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV

Office of Pharmaceutical Quality

Stephen Miller, Ph.D., Product Quality CMC-Lead
Akhtar Siddiqui, Ph.D., Office of Testing and Research

Office of Biostatistics

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

Office of Medical Policy

Sharon Mills, BSN, Senior Patient Labeling Reviewer, DMPP

Office of Surveillance and Epidemiology

Felicia Duffy, Risk Management Analyst, DRISK

Eastern Research Group Participants

Christopher Sese, Independent Assessor
Patrick Zhou, Independent Assessor

Gilead Sciences' Participants:

Andrew Cheng, Development Operations
Scott McCallister, Clinical Research
Lijie Zhong, Biometrics
Sean Bennett, Clinical Research
Anne Chester, Drug Safety Evaluation
Xi (Sherry) Zhang, DSPH
Marshall Fordyce, Clinical Research
Mae J. Lai, Regulatory Affairs
Christian Callebaut, Clinical Virology
Joseph Custodio, Clinical Pharmacology
Erik Berglund, Regulatory Affairs
Linda McBride, Regulator Affairs CMC
Richard Yu, Pharmaceutical Development

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 issues were discussed:

Clinical

- Assessment of results of Study GS-US-292-0112 to support the use of Genvoya in patients with mild to moderate renal impairment:

  In study GS-US-292-0112 important discrepancies between the eGFR results obtained using the Cockcroft-Gault equation and those using the cystatin C methodology are noted. These eGFR results form the basis of enrollment of subjects with mild to moderate renal insufficiency in study GS-US-292-0112. As requested during the pre-NDA meeting, multiple eGFR methodologies were used to analyze the study data. Most of those enrolled met the renal function eligibility criteria using the Cockcroft-Gault equation but 125/246 had normal baseline renal function when the cystatin C methodology was used. In addition, all but 6 of the 240 subjects were switched from other ARV regimens including 114 taking regimens containing either ritonavir or cobicistat. Both ritonavir and cobicistat are known to increase serum creatinine without affecting renal function.

  We remain concerned a significant number of subjects may not have had true renal impairment and this eventuality could impact on the interpretability of the results. We intend to seek internal consultation with the Division of Cardiovascular and Renal Products to assist in reviewing the study results and any related labeling.

- Assessment of bone biomarkers and BMD data from the Phase 3 trials:

  Internal consultation with the Division of Bone, Reproductive and Urologic Products (DBRUP) was undertaken to assist in reviewing the bone safety data. DBRUP agrees the mean declines from baseline in BMD of both hip and spine were significantly smaller with Genvoya compared to Stribild. Further, DBRUP agrees that percent increases in bone markers from baseline were smaller in Genvoya subjects at 48 weeks compared to those taking Stribild. (b) (4)

  ecommends placing BMD data in section 6.1 (Adverse Reactions) (b) (4)

(b) (4)

- General safety review and apparent imbalance in rates of selected infections, particularly dental infections, in the Genvoya arms:

  To this point in the review, comparative safety data for Genvoya are overall similar to that seen with Stribild. Exceptions were observed in a variety of infections such as those of skin, gastrointestinal, upper respiratory tract, dental and herpes virus infections which were more prevalent among Genvoya recipients. The imbalance in dental infections was particularly noteworthy. Descriptions of the dental infections were variable and included dental necrosis, dental abscess, tooth abscess, jaw abscess. The lack of descriptive uniformity makes comparisons difficult. There is no clear explanation for this finding. We intend to obtain internal consultation with the Division of Dermatologic and Dental Products (DDDP). We encourage Gilead to investigate this further since protective dental measures may be possible with use of Genvoya.

  Gilead asked if they can provide additional support to explain the findings. The Division re-iterated that there is a 2:1 imbalance in Grade 2-4 events (moderate to severe) and will consult with DDDP to further assess risk.

- Correlation of preclinical findings of posterior uveitis with safety review of the clinical trials:

  Preclinical data included the finding of posterior uveitis in dogs administered the highest exposures. As a result of this finding, special attention was given to AEs in this area during the development of Genvoya. The current data indicate no posterior uveitis was demonstrated in adults, one adolescent experienced intermediate uveitis related to Genvoya and single cases of anterior uveitis were balanced between study arms. There were also balanced retinal detachments. None the less, there remains an increase in numbers of subjects with eye disorders of grade 2 or higher intensity in the pooled Genvoya arms. Further investigation in this area is planned.

- Assessment of changes in serum lipid profile is currently in progress but has not been complete.

3.0 INFORMATION REQUESTS

Product Quality

1. The OPQ noted the two pending information requests. Information requests were conveyed by the review team on March 30 and April 1, 2015. Gilead intends to submit the response to the Mar 30, 2015 request on April 13, 2015. Regarding the

April 1, 2015 request, Gilead's initial e-mail response was received on April 6, 2015 and Gilead plans to submit the complete response around April 17, 2015.

Clinical Pharmacology

2. Bioanalytical:

   a. Provide interference data for each analyte in E/C/F/TAF in the presence of all other analytes in the fixed dose combination (FDC).

   b. Provide more information on how carryover was detected and mitigated during sample analysis.

   c. Provide long-term stability data for samples containing all of the components of E/C/F/TAF.

3. Using the pooled Phase 3 studies dataset, please submit concentration-response analyses for all analytes in E/C/F/TAF, including TFV, in relation to changes from baseline in lipids (total cholesterol, LDL, HDL, triglycerides). Conduct the analysis stratified and unstratified by statin use. Submit datasets so that we may perform further analyses if needed. Please submit within two weeks.

Gilead stated that responses to the information requests are being prepared.

Clinical

4. An information request was sent to Gilead on April 1, 2015 asking for an explanation for the discrepancies between the Cockroft-Gault and cystatin C eGFR methodologies. Gilead responded to this information request and their response is being reviewed.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- There are no major safety concerns identified at this time that warrant the need for a REMS.

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 August 4, 2015. 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 July 22, 2015.

Gilead asked if they would receive any more specific questions and general comments as the NDA review progresses or if all remaining questions would be conveyed during the LCM. The Division responded that it will depend on the timing in the review cycle and will depend on the outstanding review issues. The Division plans to send information requests as issues are identified.

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/

LINDA L LEWIS
04/22/2015

From: Hong, Myung-Joo P.
To: "Erik Berglund"
Subject: NDA 207561.Information Request
Date: Wednesday, April 01, 2015 11:38:00 AM

Erik, we have the following request from review team:

- Please explain the data provided in Listing 26.3 Clinical Laboratory Data: Chemistry (Part III, and Renal-Related Laboratory Tests), Study GS-US-292-0112. This listing demonstrates significant discrepancy between baseline creatinine clearance values calculated for enrollees using eGFR Cystatin C methodology and those calculated using the eGFR Cockcroft Gault methodology. As we interpret these data, 125 of the 247 subjects enrolled had baseline creatinine clearances > 70ml/min when the Cystatin C methodology was used. Additionally, the Cystatin C eGFR methodology only identifies a total of 38 subjects with baseline creatinine clearances of ≤ 50 ml/min. We understood one of the purposes of Study GS-US-292-0112 was to provide data supportive of the expansion of indicated population beyond what is recommended with Stribild® to include those with creatinine clearances at or above 30ml/min. This data discrepancy may have impact on labeling decisions.

Would you provide your response by April 6, 2015?

Best 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
04/01/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE

Date: **March 9, 2015**

NDA: **207561**

Drug: **GENVOYA (elvitegravir, cobicistat, emtricitabine, tenfovir alafenamide (E/C/F/TAF) fixed-dose combination tablet (FDC))**

To: **Erik Berglund, MD, PhD., RAC, Associate Director**

Sponsor: **Gilead Sciences, Inc.**

From: **Stacey Min, Pharm.D., Senior Regulatory Project Manager**

Subject: **Clinical Virology Information Request**

Please refer to your NDA 207561 for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) fixed-dose combination tablet) for the treatment of HIV-1 infection. We also refer to your November 5, 2014, submission consisting of your original NDA application. We are reviewing your submission and have the following information request.

Clinical Virology Information Request:

Please submit the resistance data (both genotypic and phenotypic) for the following virologic failure subjects from Studies -0104 and -0111 that had "data pending" and any other subjects who had additional resistance data since the NDA filing.

0104-2734-4394
0111-1790-5185
0111-2480-5585
0111-2704-5057
0104-1541-4150
0111-2106-5415

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

_____

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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
03/09/2015

Erik

Erik O. Berglund, MD, PhD, RAC (US & EU)
Associate Director, Regulatory Affairs| Gilead Sciences, Inc.
333 Lakeside Drive, Foster City, CA 94404
Direct: 650-524-3984 | Fax: 650-522-5489

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
02/04/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE

Date: **February 4, 2015**

NDA: **207561**

Drug: **GENVOYA (elvitegravir, cobicistat, emtricitabine, tenfovir alafenamide (E/C/F/TAF) fixed-dose combination tablet (FDC))**

To: **Erik Berglund, MD, PhD., RAC, Associate Director**

Sponsor: **Gilead Sciences, Inc.**

From: **Stacey Min, Pharm.D., Senior Regulatory Project Manager**

Subject: **Biometrics Information Request**

Please refer to your NDA 207561 for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) fixed-dose combination tablet) for the treatment of HIV-1 infection. We also refer to your November 5, 2014, submission consisting of your original NDA application. We are reviewing your submission and have the following information request.

Biometrics Comment:

The results in the report below can be reproduced from the variable V48_S5C in ADEFFOUT.

(b) (4)

Nonetheless, there are some minor discrepancies between the subject level data in ADEFFOUT and the visit level data in ADHIVOUT. These do not change the overall conclusion of clinical non-inferiority but we would appreciate your clarifying the discrepancies.

- 9 Subjects in trial -0111 are listed as suppressed at week 48 in ADEFFOUT but have no week 48 HIV in the HIV dataset (ADHIVOUT).

- 4 subjects in trial -0102 are listed as suppressed at week 24 and two of them are also listed as suppressed at week 48 but none have any HIV data at week 24 or 48 in the HIV dataset. Admittedly, the week 24 could be interpolated as suppressed from visits before and after week 24.

- 12 Subjects in trial -0109 are listed as suppressed at week 48 but have no week 48 HIV in the HIV dataset.

In the attachment below, we list the subjects who are discrepant between ADEFFOUT and ADHIVOUT, followed by the week by week records from ADHIVOUT.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

_____

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

15 Page(s) 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/

STACEY MIN
02/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

METHODS VALIDATION
MATERIALS RECEIVED

Gilead Sciences, Inc.
Attention: Erik Berglund
333 Lakeside Dr.
Foster City, CA 94404

Dear Erik Berglund:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elvitegravir/cobicistat/emtricitabine/Tenofovir alafenamide, fixed dose combination tablets and to our December 19, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 20, 2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
01/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

Please refer to your New Drug Application (NDA) dated and received, November 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF)) 150/150/200/10 mg fixed-dose combination tablet.

We also refer to your amendments dated November 10, 2014, November 25, 2014 and December 5, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is November 5, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 17, 2015. In addition, the planned date for our internal mid-cycle review meeting is March 31, 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.

We note that Study GS-US-216-0114 entitled, "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of ATV/co versus ATV/r Each Administered with FTC/TDF in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults (Week-144 update)" and Study GS-US-236-0112 entitled, "A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents" will not be reviewed under this application as these studies are not necessary to complete the review of GENVOYA.

We request that you submit the following information:

Product Quality:

1. When the drug substance TAF fumarate (2:1) was first reported in the May 2011 amendment to IND 63737, it was described as: [redacted (b) (4)]" NDA 207561 seems to be silent on whether the [redacted (b) (4)]. Please provide the available information and your conclusions about whether the TAF fumarate drug substance is a [redacted (b) (4)].

2. Include a complete dissolution method development report supporting the selection of the proposed dissolution test. The report should include the following information:

   a. Justification for the dissolution parameters; specifically, selection of apparatus, rotation speed, and justification for the amount of surfactant used.
   b. Complete dissolution profile data (individual, mean, SD, and profiles). We recommend the use of at least 12 samples per testing variable and sampling time points of 10, 15, 20, 30, 45, 60, 90, and 120.
   c. Demonstration of the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables).

3. For the dissolution method TM-233 a brief four page Validation Report QAVAL-1664R.01 is provided. This report refers to three attachments which appear to be complete Methods Validation reports. Please provide copies of these reports.

4. In Section P.5.4 three batches of white tablets (CP1105B, CP1201B, and CP1203B) are described. Please confirm that these differ from the commercial product only in regards to [redacted (b) (4)]

5. Please clarify what steps in the Emtricitabine manufacturing process are carried out by [redacted] (b) (4)

Pharmacology/Toxicology:

6. Please provide your final study report for study TX-120-2021 "4-Week Oral Gavage Toxicity and Toxicokinetic Bridging Study with GS-7340-03 in Sprague Dawley Rats" submitted under impurity studies as soon as possible.

PRESCRIBING INFORMATION

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

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

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

1. All headings in Highlights (HL) must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column). Some of the headings have horizontal lines that do not extend the entire width of the columns.

2. White space should be presented before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. The spacing throughout HL is inconsistent. There should be no extra space between the subheading title and the content below it. There is also extra white space between the heading and the content below the Contraindications section.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 30, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), 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 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 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 Stacey Min, Pharm.D., 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

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
01/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

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:	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) 150/150/200/10 mg fixed-dose combination tablet
Date of Application:	November 5, 2014
Date of Receipt:	November 5, 2014
Our Reference Number:	NDA 207561

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 4, 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

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

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

If you have any questions, call me at (301) 796-4253 or the main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Stacey Min, Pharm.D.
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/

STACEY MIN
11/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111007

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

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

We also refer to your July 31, 2014, correspondence, requesting a meeting to discuss the Phase 3 clinical data to support the NDA submission.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (301) 796-4253 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: Other

Meeting Date and Time: October 30, 2014; 11:00 AM – 12:00 PM, EST
Meeting Location: Teleconference

Application Number: IND 111007
Product Name: elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) fixed-dose combination tablet
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative)
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
Takashi Komatsu, Ph.D., RAC, Clinical Virology Reviewer, DAVP
Lisa Naeger, Ph.D., Clinical Virology Reviewer
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Mario Sampson, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, Ph.D., Clinical Pharmacology Team Lead, DCP IV
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoixing Soon, Ph.D., Biometrics Team Lead, DB IV
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Lead, DAVP
Fuqiang Liu, Ph.D., Division of New Drug Quality Assessment V (DNDQA II, Branch V)
Stephen Miller, Ph.D., CMC Lead, DNDQA II, Branch V
Elizabeth Thompson, M.S., Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Senior Regulatory Project Manager, DAVP

SPONSOR ATTENDEES
Andrew Cheng, MD, PhD, Senior Vice President, Development Operations
Mike Wulfsohn, MD, PhD, Vice President, Biometrics
Brian Kearney, PharmD, Vice President, Clinical Pharmacology
Scott McCallister, MD, Senior Director, Clinical Research
Erin Quirk, MD, Senior Director, Clinical Research
Anne Chester, PhD, DABT, Senior Director, Drug Safety Evaluation
Marshall Fordyce, MD, Director, Clinical Research

Mae J. Lai Director, Regulatory Affairs
Christian Callebaut, PhD, Sr. Research Scientist II, Clinical Virology
Joseph Custodio, PhD, Senior Clinical Pharmacologist, Clinical Pharmacology
Erik Berglund, MD, PhD, Associate Director, 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 30, 2014; 11:00 AM – 12:00 PM, EST 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 pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On March 18, 2014, Gilead requested a pre-NDA meeting for IND 111007 to discuss the proposed clinical studies to be included in the NDA as well as the statistical analyses to be conducted for the Phase 3 studies and the content and format of the NDA Safety Update. The face-to-face pre-NDA meeting was scheduled on March 30, 2014 but the meeting was cancelled by Gilead after receiving the Division's May 28, 2014 preliminary comments. In the May 28, 2014 preliminary comments, the Division requested a summary of the topline results for all pivotal trials as soon as the data were available. The Division advised Gilead to schedule a Type C meeting to discuss these results before submitting the original NDA application. Gilead has requested this Type C meeting with the summary of results from their pivotal trials.

2.0 DISCUSSION

Question 1: Does the Agency agree that safety and efficacy data from the Phase 3 studies to be included in the NDA will support the proposed indication in adults and pediatric patients 12 years of age and older for E/C/F/TAF FDC tablets?

Agency Response: Yes, we agree that the safety and efficacy data from the Phase 3 studies as provided in the meeting package appear to be adequate to support submission of the NDA package. As part of your original NDA, in addition to deaths, SAEs and all discontinuations,

please provide narratives for all subjects who experienced a TEAE with symptoms consistent with posterior uveitis and those TEAE diagnosed as myocardial infarction or stroke. For subjects experiencing myocardial infarction or stroke, please provide a subject profile that includes available lipid values to include total cholesterol, LDL, HDL and triglycerides. In addition, please be advised that we plan to consult our colleagues in the Division of Reproductive and Urologic Products to assist in evaluating and labeling BMD/bone biomarker data.

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 October 29, 2013. Please submit your Agreed PSP with your original NDA submission.

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
10/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111007

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

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

We also refer to your March 18, 2014, correspondence, received March 18, 2014, requesting a pre-NDA meeting to discuss:

- The proposed clinical studies to be included in the E/C/F/TAF FDC NDA to support the proposed indication
- The statistical analyses to be conducted for the Phase 3 clinical studies and the content, format, and proposed pooling strategy to generate the Integrated Summaries of Efficacy and Safety
- The content and format of the E/C/F/TAF FDC NDA and NDA Safety Update

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, call me at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 30, 2014; 2:30 – 4:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 111007
Product Name:	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed-dose combination tablet
Indication:	Treatment of HIV-1 infection
Sponsor/Applicant Name:	Gilead Sciences, Inc.

FDA ATTENDEES (tentative)

Edward Cox, M.D., MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, M.D., MPH, Deputy Director, OAP
David Roeder, 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, Deputy Director for Safety, DAVP
Kyong Hyon, Safety Project Manager, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Takashi Komatsu, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Mario Sampson, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, Ph.D., Clinical Pharmacology Team Lead, DCP IV
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Lead, DAVP
Fuqiang Liu, Ph.D., Division of New Drug Quality Assessment V (DNDQA II, Branch V)
Stephen Miller, Ph.D., CMC Lead, DNDQA II, Branch V
Althea Cuff, M.S., CMC Project Manager, DNDQA II, Branch V
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoixing Soon, Ph.D., Biometrics Team Lead, DB IV
Suzanne Strayhorn, M.Sc., Regulatory Project Manager, DAVP
Elizabeth Thompson, M.S., Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Senior Regulatory Project Manager, DAVP

Danyal Chaudhry, M.S., OSE Project Manager
Tony El-Hage, Ph.D., OSI

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 30, 2014; 2:30- 4:00 PM at White Oak, Building 22, Room 1311 between Sponsor 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. 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). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On 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 February 17, 2011, Gilead submitted IND 111007 elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) fixed-dose combination tablet (FDC) for the treatment of HIV-1 infection. E/C/F/TAF is being compared to Gilead's approved drug, Stribild (E/C/F/TDF), in an ongoing Phase 2 study, GS-US-292-0102, and two Phase 3 studies, GS-US-292-0104 and GS-US-292-0111, in treatment-naïve adults. Gilead is seeking registration of E/C/F/TAF for the treatment of HIV- infection in adults and children 12 years of age and older who are treatment-naïve or virologically-suppressed with no resistance to E/C/F/TAF tablet.

Gilead plans to submit the following phase 3 trials to support the registration of E/C/F/TAF NDA:

- GS-US-292-0104: Phase 3, randomized, double-blinded study of E/C/F/TAF compared with E/C/F/TDF (1:1 randomization) in HIV-1 infected, ART-naïve adult subjects
- GS-US-292-0111: Phase 3, randomized, double-blinded study of E/C/F/TAF compared with E/C/F/TDF (1:1 randomization) in HIV-1 infected, ART-naïve adult subjects
- GS-US-292-0106: Phase 2/3, open-label study of E/C/F/TAF in HIV-1 infected, ART-naive adolescent subjects
- GS-US-292-0112: Phase 3 study of E/C/F/TAF in HIV-1 infected, ART-naive adult subjects with mild to moderate renal impairment

- GS-US-292-0109: Phase 3 switch study of E/C/F/TAF in HIV-1 infected, ART-experienced, virologically suppressed adult subjects previously treated with TDF-containing regimens
- (b) (4)

IND 111007 (E/C/F/TAF) was granted Fast Track designation on January 28, 2013. (b) (4) The anticipated NDA submission is December 2014. Gilead submitted the pre-NDA meeting request on March 18, 2014 and the meeting was granted on April 1, 2014. The meeting package was submitted on April 30, 2014.

2.0 DISCUSSION

E/C/F/TAF Submission Strategy Questions

Question 1: Does the Agency agree that the studies described above will support the proposed indication shown in Section 2.2.1 for the E/C/F/TAF FDC tablet?

FDA's Response to Question 1: Overall, the studies described in the background package will support an NDA submission; whether they support the proposed indication will be a review issue. We doubt that the limited data available from study (b) (4) will add much to the submission and we think it is premature to submit this study for review.

NDA Format and General Content Questions

Question 2a: Does the Agency agree with the proposed draft NDA TOC?

FDA's Response to Question 2a: Yes. However, the leaf title of the m4 document should indicate that it is a link to the actual document, located in m5.

Please clarify how studies are listed in the draft NDA TOC. Does the TOC include all studies that will be submitted and/or cross-referenced? Many of the studies listed appear to be related to TDF, EVG, and COBI and have previously been submitted to those NDAs. We prefer that studies previously submitted not be resubmitted (regardless of whether submitted to an IND or an NDA) if they can be cross-referenced and hyperlinked.

Question 2b: Does the Agency agree with the proposed locations of nonclinical study reports using human matrices and nonclinical virology study reports in the E/C/F/TAF FDC tablet NDA?

FDA's Response to Question 2b: We agree with the proposed locations of the nonclinical virology study reports. While you state that the clinical virology study reports will be included in section 5.3.5.4, this report is not mentioned in your proposed NDA Table of Contents. Please clarify that the clinical virology study report (in section 5.3.5.4) and the virology summary (in section 2.7.2.4) will be included in the NDA submission.

Question 3: Does the Agency agree with the proposal to cross-reference previously submitted nonclinical and clinical studies with TDF, EVG, COBI, and FTC to their respective NDAs?

FDA's Response to Question 3: Yes, your 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.

- 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.

- To use the second option (cross-application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross-application links are used, it's strongly recommended that a cross-reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross-reference" and application number (e.g. Cross Ref to NDA 123456). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

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

To submit an eCTD cross-application links sample, you 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

Question 4: Does the Agency agree with this proposal for the provision of references?

FDA's Response to Question 4: This proposal is acceptable.

Question 5: Does the Agency agree with this proposal for inclusion of the clinical study report for the thorough QT/QTc study in the E/C/F/TAF FDC tablet NDA and that associated electronic datasets and ECG waveforms will not be resubmitted?

FDA's Response to Question 5: This proposal is acceptable.

Question 6: Does the Agency agree with this proposal for the locations of the ISE and ISS?

FDA's Response to Question 6: Yes, this proposal is acceptable.

Question 7: Does the Agency agree with the proposal regarding the provision of study narratives and CRFs?

FDA's Response to Question 7: Please clarify your proposal for narrative and CRF submission. Narratives should be submitted for all deaths, serious adverse events, and pregnancies, and those discontinuations considered due to adverse events. It is acceptable to submit CRFs for deaths, SAEs and discontinuations due to AEs. Please provide a specific TOC for the narratives and group them according to category (i.e., deaths, SAEs, discontinuations).

Clinical/Statistical Questions

Question 8: Does the Agency agree with the proposal for the timing and content of the E/C/F/TAF FDC tablet Safety Update?

FDA's Response to Question 8: Overall, your proposal is acceptable. Please clearly distinguish deaths, SAEs, AE-related discontinuations, and pregnancies that have occurred since the original data cut-off and provide narratives as described in Question 7.

Question 9: Does the Agency agree with the proposal for the analyses included in the ISE?

FDA's Response to Question 9: In general, your proposal for the ISE is acceptable.

Question 10: Does the Agency agree with the proposal for the analyses included in the ISS?

FDA's Response to Question 10: In general, your proposal for the ISS is acceptable. See additional responses under Question 12.

Question 11: For all studies in the E/C/F/TAF FDC tablet clinical development program, the Cockcroft-Gault equation for estimating the glomerular filtration rate (GFR) has been used to assess study eligibility and changes in renal function during the studies and will be used for final data analyses. While other equations will be used as supportive analyses, the principal method for assessing GFR remains the CG equation.

Does the Agency agree with this approach?

FDA's Response to Question 11: The Cockcroft-Gault equation is acceptable for your primary safety analyses, however, we expect you to evaluate other methods of determining eGFR as well to further characterize potential differences between TAF and TDF.

Question 12a: Does the Agency agree that 24-week results for 23 subjects in Study GS-US-292-0106 will support an indication for the use of the E/C/F/TAF FDC tablet in adolescents (12 years of age and older)?

FDA's Response to Question 12a: In most dedicated adolescent clinical trials submitted for review, a larger number of subjects are enrolled (about 50). Depending on the quality of the data and the safety findings, the number proposed may be adequate to support an indication. This will be a review issue.

Question 12b: (b) (4)

FDA's Response to Question 12b: In general, cross-study comparisons are not adequate to support regulatory decisions. Differences between TAF and TDF may be relatively subtle and analyses comparing uncontrolled trials may be difficult to interpret, especially if the patient populations are small and potentially different in demographic or disease characteristics. A comparative analysis may be interesting to include in the text of the ISS but will probably not be adequate to include in labeling.

Virology Question

Question 13a: Does the Agency agree with the presentation of virology analyses for all Phase 3 studies in a single VSR in lieu of individual summaries located within each CSR?

FDA's Response to Question 13a: Please see our response to comment 13b.

Question 13b: Does the Agency have any comments on the draft VAP?

FDA's Response to Question 13b: Your proposal for the resistance analysis plan is acceptable. Please include the Phase 2 study GS-US-292-0102 in your resistance analyses (including the datasets). As we have previously stated, if the uptake of TAF and formation of tenofovir diphosphate is significantly greater than that of TFV, the resistance profile may be different. Therefore, all novel substitutions that developed in multiple virologic failures should be analyzed as there could be additional resistance pathways.

Nonclinical Question

Question 14: Does the Agency agree that the current nonclinical program will support the registration of E/C/F/TAF FDC?

FDA's Response to Question 14: Yes, we agree.

Label/Target Product Label Questions

Question 15: Does the Agency have any comments on the E/C/F/TAF FDC tablet TPL?

FDA's Response to Question 15: As noted above, it is unlikely that data from studies (b) (4) will be displayed in labeling.

Recommendations regarding labeling best practices are frequently updated by the Agency and we recommend you check the most recent published labeling guidances prior to submission.

Question 16: Does the Agency agree with the use of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) as the generic name?

FDA's Response to Question 16: In keeping with recent approvals, we prefer the use of commas to separate components in a fixed dose combination product (see Complera and Stribild labels).

Pre-NDA and NDA Review Questions

Question 17: Based on the nonclinical and clinical information that has been previously submitted to IND 063737 for TAF Single Agent (SA), (b) (4) the available data from Phase 2 study GS-US-292-0102 (Attachment 1), and the ongoing review of safety and efficacy data from the clinical program, a Type C meeting (November 2014) prior to the submission of the E/C/F/TAF FDC tablet NDA will not be requested unless considered warranted upon receipt of the Phase 3 data.

Does the Agency agree with this proposal?

FDA's Response to Question 17: Please provide a summary of the topline results of all pivotal trials as soon as those data are available. You should be prepared to schedule a Type C meeting/teleconference at that time if we have any specific concerns related to the study results or recommendations for additional analyses.

Question 18: Does the Agency agree that a REMS should not be included in the NDA?

FDA's Response to Question 18: 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.

Question 19: Based on the nonclinical and clinical information that has been previously submitted to IND 063737 for TAF SA, (b) (4) , does the Agency anticipate that the NDA for the E/C/F/TAF FDC tablet will be the subject of an FDA Advisory Committee Meeting?

FDA's Response to Question 19: Based on the information currently available, we do not believe that an Advisory Committee meeting will be necessary. We will make a final determination regarding the need for an AC early in the NDA review cycle.

Additional Comments:

1. From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:

   - When providing a table in m1.4.4. (cross-referencing to other applications), if possible, provide hyperlinks for ease of review.

- For eCTD sections M1.6.3 (Correspondence regarding meetings) and m1.11.3 (information amendment not covered under m2-m5) – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.

- The synopses of individual studies in m2.7.6 should be in tabular format and linked to the referenced studies in m5.

- M5.2 (tabular listing) should be provided in a tabular format and also linked to the referenced studies in m5.

- Providing two 3.2.p sections (i.e. Tablet and Access Module) is not necessary. A single 3.2.p. section should be provided and use leaf titles to differentiate between documents.

- Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of 4.3 Literature Reference, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form".

2. 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 NDA application in the appropriate module so it can be reviewed accordingly.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 1, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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 October 29, 2013.

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.				

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
05/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111007

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Michelle Hack, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Hack:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to discuss the (b) (4) registration (b) (4) for (b) (4) the E/C/F/TAF FDC tablet NDA in HIV treatment-naïve patients. Specific objectives of the meeting include:

(b) (4)

- Discuss whether the proposed Phase 3 clinical studies are adequate to support registration of E/C/F/TAF FDC for the proposed indication

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, Pharm.D., Regulatory Project Manager at (301) 796-4253.

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:	End of Phase 2
Meeting Date and Time:	December 17, 2012; 3:00 – 3:30 PM
Meeting Location:	White Oak Building 22; Conference Room 1415
Application Number:	111007
Product Name:	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed-dose combination tablet (FDC)
Indication:	Treatment of HIV-1 naïve patients
Sponsor/Applicant Name:	Gilead Sciences, Inc. (Gilead)
Meeting Chair:	Stacey Min, Pharm.D., Regulatory Project Manager
Meeting Recorder:	Stacey Min, Pharm.D., Regulatory Project Manager

FDA ATTENDEES

David Roeder, Associate Director of Regulatory Affairs, Office of Antimicrobial Products (OAP)
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Linda Lewis, MD, Medical Team Lead, DAVP
William Tauber, MD, Medical Officer, DAVP
Takashi Komatsu, PhD, Clinical Virology Reviewer, DAVP
Julian O'Rear, PhD, Clinical Virology Team Lead, DAVP
Vikram Arya, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, PhD, Clinical Pharmacology Team Lead, DCP IV
Shirley Seo, PhD, Clinical Pharmacology Team Lead, DCP IV
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead, DAVP
Mohammed Bourdi, PhD, Pharmacology/Toxicology Reviewer, DAVP
Celia Cruz, PhD, Product Quality Reviewer, Division of New Drug Quality Assessment V (DNDQA II, Branch V)
Rao Kambhampati, PhD, Product Quality Reviewer, DNDQA II, Branch V
Stephen Miller, PhD, CMC Lead, DNDQA II, Branch V
Thomas Hammerstrom, PhD, Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoxing Soon, PhD, Biometrics Team Lead, DV IV
Katherine Schumann, MS, Regulatory Project Manager, DAVP
Stacey Min, PharmD, Regulatory Project Manager, DAVP
Morgan Walker, PharmD, MBA, Reviewer, Division of Medication Error and Prevention and Analysis (DMEPA)

Jamie Wilkins Parker, PharmD, Team Lead, DMEPA

SPONSOR ATTENDEES

Andrew Cheng, MD, PhD - Senior Vice-President, Development Operations
Michael Miller, PhD - Senior Director, Biology
Scott McCallister, MD - Senior Director, Clinical Research
Brian Kearney, PharmD - Senior Director, Clinical Pharmacology
Michael Wulfsohn, MD, PhD - Vice President, Biometrics
Anne Chester, PhD, DABT - Senior Director, Drug Safety Evaluation
Lijie Zhong, PhD - Director, Biostatistics
Richard Yu, PhD - Senior Director, Process Development
Mae J. Lai - Director, Regulatory Affairs
Michelle Hack - Associate Director, Regulatory Affairs

BACKGROUND

On November 28, 2011, Gilead submitted IND 63737, tenofovir alafenamide (TAF), an oral prodrug of tenofovir (TFV) that has longer plasma half-life compared to TFV for the treatment of HIV-1 infection. On February 17, 2011, Gilead submitted IND 111007 elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) fixed-dose combination tablet (FDC) for the treatment of HIV-1 infection. Gilead proposes to submit (b) (4) the E/C/F/TAF FDC NDA, (b) (4) for the treatment of HIV-1 in treatment-naïve patients. (b) (4)

The purpose of this EOP2 meeting is to discuss (b) (4) the E/C/F/TAF FDC tablet NDA in HIV treatment-naïve patients. Specific objectives of the meeting included:

- Discuss the adequacy of the completed nonclinical program to support registration of (b) (4) E/C/F/TAF FDC
- (b) (4)
- Discuss whether the proposed Phase 3 clinical studies are adequate to support registration of E/C/F/TAF FDC for the proposed indication
- Discuss whether the development plan will support the target labeling claims for (b) (4) E/C/F/TAF FDC as described in the Target Product Profiles (TPPs)
- (b) (4)

Gilead submitted eight, multi-part questions in the meeting package. After receiving the Division's December 14, 2012, preliminary comments, Gilead requested to discuss Question 3b and 4 during the teleconference.

DISCUSSION

Questions submitted by Gilead in the November 16, 2012, meeting background page are in **bold** font, the Division's December 14, 2012, preliminary responses are noted in *italicized* font and discussions at the December 17, 2012, teleconference are noted in regular font.

Question 1: Waiver for Peri/postnatal Study in Rats

Does the Agency agree that a peri/postnatal study in rats is not required for TAF registration, due to the lack of TAF exposure in rats and lower TFV exposure compared to TDF?

Yes, we agree.

No discussion.

Question 2: Nonclinical Safety Program

a. Does the Agency agree that the current nonclinical toxicology program will support the registration of (b) (4) E/C/F/TAF STR?

Yes, we agree.

No discussion.

b. Does the Agency agree that data from the current nonclinical program support studies of TAF-containing products in HIV-positive adolescents and children?

Yes, we agree.

No discussion.

Question 3: E/C/F/TAF STR Registration Plan

a. Does the Agency agree that the two planned Phase 3 E/C/F/TAF STR studies support registration of this STR for the indication being sought in adult patients who are antiretroviral TN or have no known substitutions associated with resistance to the components of E/C/F/TAF?

We do not agree that the study design of both planned Phase 3 E/C/F/TAF FDC studies will provide the basis for registration of TAF (b) (4) *as a part of an FDC. Of the two planned Phase 3 studies, only the study design of GS-US-292-0104 permits a clean assessment of the contribution of TAF to the regimen (by direct comparison of TAF and TDF).* (b) (4) *Other study designs isolating the comparison of TAF and TDF would be preferred to meet the standard of two adequate and well-controlled clinical trials to support a new molecular entity. Examples of such designs might include Efavirenz/FTC/TAF versus Atripla (* (b) (4) *or cobicistat boosted atazanavir/FTC/TDF compared with boosted atazanavir/FTC/TAF.* (b) (4)

We note that the inclusion criteria of both GS-US-292-0104 (b) (4) *specify subject participants be treatment-naïve with no known substitutions associated with resistance to the components of the FDC. The data from studies of this population will not support an indication for treatment of treatment experienced subjects whose recovered virus has no known substitutions associated with resistance.*

Please include the HIV-1 protease in your resistance analyses for study GS-US-292-0104. Additionally, please provide a detailed resistance analysis plan.

The list of resistance-associated amino acid substitutions (Appendix 6) needs to be updated. For example, amino acid substitutions K101T, K103S, E138K/G, V179I/L, V189I, H221Y, and F227C/L for NNRTI resistance-associated amino acid substitutions are missing (please refer to current labels for efavirenz and rilpivirine).

Gilead acknowledges that Study (b) (4) does not provide a direct comparison between TAF and TDF. Therefore, Gilead proposes conducting another Phase 3 study, a duplicate of Study GS-US-292-0104, differing only in the geographical area of the study. The Division stated that this is generally acceptable (b) (4)

b. Does the Agency agree with the planned statistical analysis using a 12% margin for noninferior efficacy as the primary efficacy endpoint?

We agree with the use of a 12% margin for noninferior efficacy for studies that permit the efficacy contribution of TAF vs TDF to be adequately compared such as in study GS-US-292-0104.

No discussion.

c. Does the Agency agree that the proposed renal and AE lab assessments are appropriate (b) (4)

The proposed renal and AE lab assessments are appropriate to study. (b) (4) *will be a review issue.*

No discussion.

d. Does the Agency have any additional comments on protocols GS-US-292-0104 and (b) (4)

We note a possible increased incidence of rhabdomyolysis among TAF recipients in studies (b) (4) *and GS-US-292-0102. Although you intend to collect CPK as part of safety*

monitoring, we would recommend you consider incorporating additional laboratory monitoring especially in the setting of increased CPK or muscle symptomatology into these protocols.

No discussion.

Question 4: (b) (4)

(b) (4)

(b) (4)

Question 5: Safety Database

Does the Agency agree that the proposed safety database is adequate to support (b) (4) for the indications being sought?

The proposed safety database appears to be adequate (b) (4) However, refer to reservations expressed in response to #4 above.

The proposed safety database comprised of data from studies (b) (4) would provide experience from nearly (b) (4) subjects and should be adequate to support the E/C/F/TAF FDC (b) (4) (b) (4)

No discussion.

Question 6: Renal Impairment Dosing

a. Does the Agency agree that the data from this clinical study could support dosing of E/C/F/TAF STR in patients with impaired renal function (eGFR ≥30 mL/min) as described in the E/C/F/TAF STR TPP?

The approach, as outlined, is acceptable; however, the decision on whether the pharmacokinetic data (b) (4) *supports dosing of E/C/F/TAF FDC* (b) (4) *in patients with eGFR ≥ 30 mL/min is a review issue. The systemic exposures of FTC are expected to increase in patients with eGFR ≥ 30 mL/min who are administered the FDC; therefore, adequate safety data to support these higher FTC exposures will be required.*

No discussion.

b. (b) (4)

Please see response above.

No discussion.

Question 7: Switch Study (TDF-based regimen to E/C/F/TAF STR)
If maintenance of virologic effect as well as improvements in BMD and/or kidney-related effects (as shown by AE-related discontinuations, bone mineral density testing, bone biomarkers, and renal lab testing) is observed in patients who are switched from a TDF-based regimen to E/C/F/TAF STR, would the Agency consider the inclusion of this clinical study in the label as outlined in the E/C/F/TAF STR TPP?

Study GS-US-292-109, the switch study, may provide valuable information regarding the safety of E/C/F/TAF FDC. The study design provides for varying proportions of 4 different regimens to be compared with E/C/F/TAF FDC. It seems unlikely with so many comparisons possible that meaningful differences in safety parameters will be discernable but this remains a review issue. We will be better able to answer this question when the data are available for review.

No discussion.

Question 8: Priority Review

a. Does the Agency agree that intensive pharmacokinetic data and 24-week safety and efficacy results from Study GS-US-292-0106 could support an indication in adolescents (ages 12 to < 18 years) (b) (4) **?**

Appropriate PK and safety data in adolescents could support an indication in this age group. (b) (4)

(b) (4) *The determination of priority review for the NDAs will be made at the time of the filing meeting.*

No discussion.

b. (b) (4)

This is a review issue and a priority review determination will be made at the time that the data are provided.

No discussion.

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan (PSP) within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

- Gilead will submit another Phase 3 clinical trial, comparing E/C/F/TAF with Stribild in a treatment naïve population.

- Gilead will submit the PREA pediatric study plan within 60 days of the EOP2 meeting, by February 15, 2013.

- FDA will provide official comments on Study GS-US-292-0104 by early January 2013, (b) (4) and GS-US-292-0109 (switch study).

ATTACHMENTS AND HANDOUTS

None.

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
01/14/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

LATE-CYCLE MEETING MINUTES

Gilead Sciences, Inc.
Attention: Erik Berglund, M.D., Ph.D., RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF)) 150/150/200/10 mg fixed-dose combination tablet.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 4, 2015.

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

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

Sincerely,

{See appended electronic signature page}

Linda L. Lewis, M.D.
Clinical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
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: August 4, 2015, 1-2 PM
Meeting Location: Teleconference

Application Number: NDA 207561
Product Name: GENVOYA
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda L. Lewis, M.D., Cross Discipline Team Leader
Meeting Recorder: Myung-Joo Patricia Hong, M.S, Senior Regulatory Project Manager

FDA ATTENDEES

OND/Office of Antiviral Products

John Farley, M.D., Deputy Director, Office of Antiviral Products

OND/OAP/Division of Antiviral Products

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Linda Lewis, M.D., Clinical Team Leader, Division of Antiviral Products
Peter Miele, 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
Stacey Min, PharmD, Associate Director for Labeling, Division of Antiviral Products
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager, Division of Antiviral Products

OTS/Office of Clinical Pharmacology

Mario Sampson, PharmD., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV
Vikram Arya, PharmD., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV

Office of Pharmaceutical Quality

Navi Bhandari, PharmD., Product Quality BRPM

Office of Biostatistics

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

Office of Surveillance and Epidemiology

Monica Calderon, PharmD., BCPS, DMEPA Reviewer
Jasminder Kumar, Risk Management Analyst, DRISK

ODEIII/DBRUP (Division of Reproductive and Urologic Products)

Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Clinical Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES

Andrew Cheng, Development Operations
Marshall Fordyce, Clinical Research
Moupali Das, Clinical Research
Dana Pizzuti, Regulatory
Mae J. Lai, Regulatory Affairs
Erik Berglund, Regulatory Affairs
Shan-Shan Chen, Biometrics
Anne Chester, Drug Safety Evaluation
David Voong, DSPH
Christian Callebaut, Clinical Virology
Joseph Custodio, Clinical Pharmacology
Sonja Tong, Regulatory Affairs Labeling

1.0 BACKGROUND

NDA207561 was submitted on November 5, 2014 for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) 150/150/200/10 mg fixed-dose combination tablet.

Proposed Indication: Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

PDUFA Goal Date: November 5, 2015

FDA issued a Background Package in preparation for this meeting on July 20, 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.

2. Discussion of Discipline Review Letters and Substantive Review Issues

- The Division noted that no discipline review letters have been issued and no substantive review issues have been identified to date.

3. Discussion of Upcoming Advisory Committee Meeting

- The Division noted that no advisory committee meeting is planned.

4. REMS or Other Risk Management Actions

- The Division noted that as discussed during the Mid-Cycle Communication on April 13, 2015, the Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS), at this time.

5. Discussion of Minor Review Issues

a. We are continuing our review of serum lipid profile changes associated with use of GENVOYA. Although we recognize the study populations enrolled in the pooled Studies 0104 and 0111 were younger than the study population enrolled in Study 0109, it appears that the proportion of subjects receiving lipid lowering therapy was very low (4-5% compared to 11%) at baseline. In spite of significant elevations in lipid parameters during the trials, very few additional subjects initiated lipid lowering therapy. We have assessed the study population using older guidelines of total cholesterol and LDL cut-offs and it appears that many subjects may not have been appropriately treated for elevated lipids. However, current guidelines for treatment of cholesterol to reduce cardiovascular risk

recommend an algorithm-based approach incorporating age, gender, race, cholesterol levels, and presence of other risk factors such as hypertension, diabetes and smoking. Therefore, additional analyses are needed to determine whether the proposed labeling accurately captures clinically relevant information. Using the data collected in the trials, we would like you to assess the subjects enrolled in Studies 0104 and 0111 to determine whether subjects should have received lipid lowering therapy based on current ACC/AHA guidelines.

Discussion: The Division asked if there is any progress on analyses as requested and if there are any preliminary results available for review. Gilead stated that they are working on additional analyses using current ACC/AHA guidelines as recommended. Gilead also stated that they are ahead of schedule and may be able to submit the re-analysis results before the requested due date (August 21, 2015). The Division stated that we are waiting to see the completed analysis.

b. (b) (4)

Therefore, we recently forwarded a request for reanalysis of the BMD data to evaluate proportions of subjects experiencing ≥7% BMD loss in femoral neck and ≥5% BMD loss in spine at week 48.

Discussion: The Division and the consultants from Division of Reproductive and Urologic Products (DBRUP) noted that there were still a number of subjects receiving GENVOYA with substantial loss in BMD. Gilead understands the Division's rationale to choose ≥7% BMD loss in femoral neck and ≥5% BMD loss in spine at week 48 for re-analysis of the BMD data to evaluate the proportions of subjects with significant bone loss. Gilead submitted an initial response to Division's request on July 22, 2015. (b) (4)

c. We consider the TFV-diphosphate bioanalytical method to be unvalidated. In the method qualification report sent in response to our Information Request, long term stability at (b) (4) °C was not established (concentrations were changed 272% at day 35 compared to day 0). Also, in the pivotal studies, quality controls were not included in the TFV-diphosphate runs. (b) (4)

Discussion: Gilead acknowledged the request and agreed (b) (4) Gilead plans to discuss requirements for validation of intracellular bioanalytical methods with the agency in the future.

6. Information Requests

- The Division notes the following pending requests:

Clinical

a. In order to maintain some consistency across labels, please provide an analysis of the number of subjects in the pooled Studies 0104 and 0111 and Study 0109 demonstrating either 7% BMD loss in femoral neck ((b) (4) or 5% BMD loss in spine at 48 weeks. Your original proposal to describe (b) (4)% decline in BMD may be less clinically relevant.

Discussion: The requested information was submitted on July 22, 2015.

b. Current guidelines for treatment of cholesterol to reduce cardiovascular risk recommend an algorithm-based approach incorporating age, gender, race, cholesterol levels, and presence of other risk factors such as hypertension, diabetes and smoking. Using the data collected in the trials, please assess the subjects enrolled in Studies 0104 and 0111 to determine whether subjects should have received lipid lowering therapy based on current ACC/AHA guidelines.

Discussion: Gilead requested additional time to complete the requested analysis using current ACC/AHA guidelines and the request was granted. Gilead acknowledged the extension of time and will submit the requested information by August 21, 2015.

Clinical Pharmacology

c. For Study GS-US-292-0112 in HIV-infected subjects with renal impairment, please perform a statistical PK comparison for the components of E/C/F/TAF between subjects with mild ($eGFR_{CG}$ 60-89 mL/min) or moderate ($eGFR_{CG}$ 30-59 mL/min) renal impairment and historical controls without renal impairment ($eGFR_{CG} \geq 90$ mL/min). Please also summarize the demographic characteristics of subjects contributing PK data by renal impairment category.

Discussion: Gilead stated that they acknowledged the request and the requested information were submitted on July 22, 2015.

7. Postmarketing Requirements (PMRs)/Postmarketing Commitments (PMCs)

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

  Discussion: At this time of review, the Division doesn't have any additional PMRs/PMCs requests to propose. (b) (4) [redacted]

8. Major Labeling Issues

- *The Division provided labeling comments on July 17, 2015 prior to the LCM scheduled for August 4, 2015.*

  a. The Indication statement should include the populations studied, i.e., the switch study population as enrolled in Study 0109 should be described in the indication, similar to the language in the current STRIBILD label.

     Discussion: Gilead acknowledged the label proposal by the Division and agreed to revise the label as recommended. The counter-proposal from Gilead will be submitted by August 7, 2015.

  b. We expect that additional Warnings and Precautions (W & P) will be required including:

     - Risk of adverse reactions or loss of virologic response due to drug interactions.

       Discussion: Gilead agreed to include additional W & P section (Section 5.4) in the label. The Division's proposal for this section was a very generic statement similar to that included in the recent labels for COBI or ritonavir boosted agents.

     - New onset or worsening renal impairment

       Discussion: The Division consulted the Division of Cardiovascular and Renal Products (DCRP) regarding renal safety issues. DCRP agreed that there was not enough data available to fully assess the safety profile for subjects with CrCL clearance level < 50mL/min. The product is not entirely benign in that population. Gilead noted that this patient population has not been well studied for other regimens. They note these patients do not have access to a good once daily regimen. The Division agreed that this patient population has not been well studied. The Division would like to review safety data at 48 weeks for the whole study population but the primary safety data submitted is at 24 weeks. If there are more data available, the Division will have further discussion with the DCRP consultant. Gilead stated they have provided additional information on this population through 48 weeks in the 4 month safety

update. The Division will review the analysis as provided. The Division reminded Gilead that a safety update is usually very limited, i.e., only limited clinical events are included. If additional analysis of safety data is needed, it should be planned at the time of the NDA filing, not during the review cycle. The Division's concern is that the kidney and bone are target organs for tenofovir in all the animal toxicology studies. (b) (4)

- Bone effects of tenofovir

  Discussion: Gilead agreed to include this section in W & P (Section 5.8)

c. Placement of data related to safety endpoints – Section 6.1 Adverse Reactions

Discussion: No discussion occurred.

d. (b) (4)

Discussion: Gilead requested some clarification between validated versus non-validated biomarkers. The Division stated that the validated biomarkers are those that have been confirmed to be predictive of renal toxicity. Since our DCRP colleagues cannot join the call, the Division will have further discussion with DCRP and request some input from them. The Division will follow-up with Gilead regarding biomarkers. (b) (4)

e. (b) (4)

FDA guidance (2010 FDA Clinical Pharmacology renal impairment guidance), which incorporates the K/DOQI definitions (normal=≥90 mL/min, mild=60-89 mL/min, moderate=30-59 mL/min). Please propose revisions across the label taking this into account. One possible solution is to only use eGFR values (b) (4)

Discussion: Gilead acknowledged that there is inconsistency in the label (b) (4) and leave numerical renal function descriptions.

f. (b) (4)

Discussion: (b) (4)

(b) (4) After a label proposal is submitted from Gilead, the Division will review the proposal and make a decision. (b) (4)

- *As discussed above, Gilead will submit the full documentation for label proposal by August 7, 2015.*

9. Other Discussion

- Gilead proposed two questions in regards to CMC issues:

  a. Is the CMC review complete? There are some M3 CTD sections that still require updating based on responses to IRs and Gilead would like to confirm the CMC review is complete before submitting them.

     Discussion: The OPQ representative noted that the CMC review is complete.

  b. It was noted that the facility inspections are believed to be complete. Does this include the GMP inspections?

     Discussion: The OPQ representative noted that the facility inspection is complete.

10. Review Plans

  a. Continue with labeling review and discussions

     Discussion: No discussion occurred.

  b. Financial disclosure

     Discussion: The Division stated that we were very surprised to see the high proportion of principal investigators with a financial interest in Gilead. We cross checked with other divisions but no other product has been identified with such a high proportion of principal investigators with potential financial conflicts of interest. Gilead stated that they were also very surprised. They believe it may have to do with the "Sunshine Act" and new requirements for financial disclosure among clinician-investigators. Gilead agrees with the Agency's concern and plans to look closer regarding this financial issue. The Division stated that there were not identifiable differences in efficacy across sites with and without financial interests. However, there was a suggestion of down-graded adverse events (i.e., lower severity grades) among the group from sites with financial interests versus no financial interests but the results are not reproducible for other assessments. The Division thanked Gilead for their plan to mitigate the problem but the Division cannot share the information from other divisions or other sponsors with Gilead. The Division recommended Gilead inform their upper management regarding the Division's concerns for financial issues with the study

investigators. Discussions within the Division and with FDA upper management are continuing.

11. 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.

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/

MYUNG JOO P HONG
08/24/2015

LINDA L LEWIS
08/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

LATE CYCLE MEETING
BACKGROUND PACKAGE

Gilead Sciences, Inc.
Attention: Erik Berglund, MD, PhD, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Berglund:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) 150/150/200/10 mg fixed-dose combination tablet.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 4, 2015. 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: August 4, 2015, 1-2 PM
Meeting Location: Teleconference

Application Number: NDA 207561
Product Name: GENVOYA
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 April 13, 2015, the Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS).

LCM AGENDA

1. Introductory Comments – 5 minutes (Myung-Joo Patricia Hong, M.S./Linda Lewis, M.D.)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 10 minutes

   a. We are continuing our review of serum lipid profile changes associated with use of GENVOYA. Although we recognize the study populations enrolled in the pooled Studies 0104 and 0111 were younger than the study population enrolled in Study 0109, it appears that the proportion of subjects receiving lipid lowering therapy was very low (4-5% compared to 11%) at baseline. In spite of significant elevations in lipid parameters during the trials, very few additional subjects initiated lipid lowering therapy. We have assessed the study population using older guidelines of total cholesterol and LDL cut-offs and it appears that many subjects may not have been appropriately treated for elevated lipids. However, current guidelines for treatment of cholesterol to reduce cardiovascular risk recommend an algorithm-based approach incorporating age, gender, race, cholesterol levels, and presence of other risk factors such as hypertension, diabetes and smoking. Therefore, additional analyses are needed to determine whether the proposed labeling accurately captures clinically relevant information. Using the data collected in the trials, we would like you to assess the subjects enrolled in Studies 0104 and 0111 to determine whether subjects should have received lipid lowering therapy based on current ACC/AHA guidelines.

   b. (b) (4)

   Therefore, we recently forwarded a request for reanalysis of the BMD data to evaluate proportions of subjects experiencing ≥7% BMD loss in femoral neck and ≥5% BMD loss in spine at week 48.

   c. We consider the TFV-diphosphate bioanalytical method to be unvalidated. In the method qualification report sent in response to our Information Request, long term stability at (b) (4) °C was not established (concentrations were changed 272% at day 35 compared to day 0). Also, in the pivotal studies, quality controls were not included in the TFV-diphosphate runs. (b) (4)

(b) (4)

3. Information Requests (Pending Requests) – 5 minutes

Clinical

a. In order to maintain some consistency across labels, please provide an analysis of the number of subjects in the pooled Studies 0104 and 0111 and Study 0109 demonstrating either 7% BMD loss in femoral neck (b) (4) or 5% BMD loss in spine at 48 weeks. Your original proposal to describe (b) (4)% decline in BMD may be less clinically relevant.

b. Current guidelines for treatment of cholesterol to reduce cardiovascular risk recommend an algorithm-based approach incorporating age, gender, race, cholesterol levels, and presence of other risk factors such as hypertension, diabetes and smoking. Using the data collected in the trials, please assess the subjects enrolled in Studies 0104 and 0111 to determine whether subjects should have received lipid lowering therapy based on current ACC/AHA guidelines.

Clinical Pharmacology

c. For Study GS-US-292-0112 in HIV-infected subjects with renal impairment, please perform a statistical PK comparison for the components of E/C/F/TAF between subjects with mild ($eGFR_{CG}$ 60-89 mL/min) or moderate ($eGFR_{CG}$ 30-59 mL/min) renal impairment and historical controls without renal impairment ($eGFR_{CG} \geq 90$ mL/min). Please also summarize the demographic characteristics of subjects contributing PK data by renal impairment category.

4. Postmarketing Requirements/Postmarketing Commitments – 1 minute

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

5. Major Labeling Issues – 30 minutes

a. The Indication statement should include the populations studied, i.e., the switch study population as enrolled in Study 0109 should be described in the indication, similar to the language in the current STRIBILD label.

b. We expect that additional Warnings and Precautions will be required including:

- Risk of adverse reactions or loss of virologic response due to drug interactions
- New onset or worsening renal impairment
- Bone effects of tenofovir

c. Placement of data related to safety endpoints – Section 6.1 Adverse Reactions.

d. (b) (4).

e. (b) (4)
K/DOQI definitions (normal=≥90 mL/min, mild=60-89 mL/min, moderate=30-59 mL/min). Please propose revisions across the label taking this into account. One possible solution is to only use eGFR values rather (b) (4)

f. (b) (4)

6. Review Plans – 5 minutes
   a. Continue with labeling review and discussions
   b. Financial disclosure

7. Wrap-up and Action Items – 5 minutes

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

/s/

DEBRA B BIRNKRANT
07/20/2015