

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208464Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #: 208464/Original Submission

SUPPL # N/A

HFD # 530

Trade Name: VEMLIDY®

Generic Name: tenofovir alafenamide (TAF), 25 mg Tablet

Applicant Name: Gilead Sciences, Inc.

Approval Date, If Known: November 11, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1) Original Submission

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

The current application seeks approval of a drug product (the "TAF" product), containing a single drug substance (tenofovir alafenamide fumarate), which itself contains a single active moiety (tenofovir alafenamide or TAF). The current application provides for a new use (new indication) of the TAF active moiety, which has previously been approved by the FDA.

The applicant requested 3 years of exclusivity under 21CFR 314.108(b)(4).

In addition, the sponsor requested "umbrella exclusivity" policy for the tenofovir alafenamide active moiety in the current application. Because the F/TAF product in NDA 208215 (DESCOVY, approved on April 7, 2016) and the E/C/F/TAF product in NDA 207561 (GENVOYA, approved on November 5, 2015) both contain the drug substance TAF, the applicant requested 5 years under "umbrella exclusivity" policy. The "umbrella exclusivity" will apply to the tenofovir alafenamide active moiety in the TAF product during any remaining portion of, and to the same extent as, the E/C/F/TAF product's NCE exclusivity.

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

YES NO

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

No

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA # 207561	GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), Fixed-Dose Combination Tablet 150 mg/150 mg/200 mg/10mg
NDA # 208215	DESCOVY (emtricitabine and tenofovir alafenamide), Fixed-Dose Combination Tablet 200 mg/25mg

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#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES NO

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

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

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

YES NO

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

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:

N/A

(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:

N/A

(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:

Investigation #1:

- **Study GS-US-320-0108** entitled "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Negative, Chronic Hepatitis B"

Investigation #2:

- **Study GS-US-320-0110** entitled "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive, Chronic Hepatitis B"

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"):

Investigation #1:

Study GS-US-320-0108 entitled "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Negative, Chronic Hepatitis B"

Investigation #2:

Study GS-US-320-0110 entitled "A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive, Chronic Hepatitis B"

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

YES NO

If yes, explain:

=====

Name of person completing form: Myung-Joo Patricia Hong, M.S.
Title: Senior Regulatory Project Manager
Date: 10/3/16

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

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
10/03/2016

JEFFREY S MURRAY
10/03/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208464 Original Submission	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: VEMLIDY® Established/Proper Name: tenofovir alafenamide (TAF) Dosage Form: 25 mg 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: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>November 11, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> 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*)

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	• Approval – November 10, 2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included (11/2/16)
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included (1/11/16)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included (1/11/16)
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	<ul style="list-style-type: none"> • Grant Letter - 3/6/16 • Review - 3/2/16
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: PLR Format Review - 2/1/16 DMEPA: 6/22/16 & 9/30/16 DMPP/PLT (DRISK): 10/27/16 (consolidated review with OPDP for PPI) OPDP: 10/27/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: PI & Container Label - Included in Integrated Product Quality Assessment Review (page 70-79) - 10/11/16 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	• RPM Filing Review - 3/2/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> 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.

<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>September 21, 2016</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	1/12/16, 1/21/16, 2/18/16 (x2), 2/29/16, 3/3/16, 3/8/16, 3/11/16, 3/17/16, 4/1/16, 4/19/16 (x2), 4/25/16, 5/3/16, 5/10/16, 5/25/16, 5/27/16, 6/3/16, 6/10/16, 6/23/16 (e-mailed on 6/22/16; darrr't'd on 6/23/16), 7/14/16, 7/15/16, 7/29/16 (x2), 8/29/16, 8/30/16 (x2), 9/14/16, 9/27/16, 9/30/16, 10/4/16, 10/6/16, 10/13/16, 10/20/16, 10/24/16, 10/28/16, 11/1/16
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	June 18, 2015 - Pre-NDA Meeting scheduled under IND 115561; however, Gilead cancelled after receiving FDA's preliminary comments sent on 6/16/15 - Preliminary comments included
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	June 17, 2013 – Minutes included
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	Type C Meeting to discuss topline data - granted as WRO - Response sent on 12/16/15 included

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	• Approval – November 10, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	• Approval – October 21, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	PMR - 7 Templates PMC - 2 Templates
Clinical	
• Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review (included in CDTL Review)
• Clinical review(s) (<i>indicate date for each review</i>)	• Approval - 10/6/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Included in clinical review - located in Section 13.2, Page 107 - 110
• Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	• DCRP Review - 7/29/16 • DBRUP Review - 8/1/16 • DTOP Review - 8/1/16
• Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
• Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
• OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	• Inspection Summary - 8/10/16 • Letters - 6/16/16, 8/9/16 (x2), 10/7/16
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	• Approval - 10/6/16 & 10/13/16 (Rhee) • Approval - 10/6/16 (Donaldson)
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	• Approval - 10/6/16

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	• Approval - 10/7/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	• Approval - 10/11/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	• Approval -10/11/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Granted - Included in Integrated Product Quality Assessment Review (page 66-67) -10/11/16
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Included in Integrated Product Quality Assessment Review (page 66-67) - 10/11/16

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

MYUNG JOO P HONG
11/10/2016

From: [Hong, Myung-Joo P.](#)
To: "sara.snow@gilead.com"
Subject: NDA 208464.Labeling Proposal
Date: Tuesday, November 01, 2016 2:52:00 PM
Attachments: [11.1.16.PI to Gilead.docx](#)

Hi Sara, attached please find our final label proposal. We made very minor edit in page 20. Please respond by 11/2/16 (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

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/s/

MYUNG JOO P HONG
11/01/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Labeling Proposal
Date: Friday, October 28, 2016 11:41:00 AM
Attachments: [10.28.16.PI to Gilead.docx](#)
[NDA 208464.DMPP-OPDP PPI.10.27.16.Marked.doc](#)

Hi Sara, please find attached our labeling proposal for VEMLIDY. I am attaching PI and PPI as separate documents to preserve the changes made by Patient Labeling Team and OPDP. Please response by 10/31/16 (NOON, EST).

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
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/s/

MYUNG JOO P HONG
10/28/2016



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

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: October 24, 2016

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

Total no. of pages including cover: pages

Comments: NDA 208464

Document to be mailed: YES NO

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

DATE: October 24, 2016

NDA: 208464/Original Submission

TO: Sara Snow, PharmD, MBA, Manager, Regulatory Affairs

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

SPONSOR: Gilead Sciences, Inc.

SUBJECT: PMC Comment

Please refer to your original NDA submitted on January 11, 2016. The DAVP is proposing the following additional postmarketing commitment. Please provide your response to this request by **October 25, 2016**.

Post Marketing Commitment

1. Submit the long-term efficacy, safety and antiviral activity data for Studies GS-US-320-0108 and GS-US-320-0110. Include data and analyses for the entire study population through Week 144.

Protocol Submission:

Trial Completion:

Final Report Submission:

Please propose timelines for the above commitment. In general, we expect study reports to be completed and submitted about 6 months after the final subject visits. If the dates proposed above are not appropriate, please provide the justification and propose new dates.

We 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

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/s/

MYUNG JOO P HONG
10/24/2016

From: [Hong, Myung-Joo P.](#)
To: "sara.snow@gilead.com"
Subject: NDA 208464.Labeling Proposal and Response to (b) (4)
Date: Thursday, October 13, 2016 4:06:00 PM
Attachments: [10.13.16.PI to Gilead.docx](#)

Hello Sara, please find attached our labeling proposal. Would you submit your response by 10/17/16?

In regards to your request to (b) (4), we have the following response:

PMC #8 Proposed by DAVP:

- Phenotype Week-48 virus samples from Subjects 4296-5147 and 8758-5188 in the TAF group and Subjects 1507-4546 and 9035-4845 in the TDF group in Study GS-US-320-0110.

Gilead Requested:

(b) (4)

DAVP's Response:

(b) (4)

Please submit the final report for PMC #8 by June, 2017.

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

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/s/

MYUNG JOO P HONG
10/13/2016



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

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: October 6, 2016

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

Total no. of pages including cover: pages

Comments: NDA 208464

Document to be mailed: YES NO

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

DATE: October 6, 2016

NDA: 208464/Original Submission

TO: Sara Snow, PharmD, MBA, Manager, 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 original NDA submitted on January 11, 2016. The DAVP is proposing the following postmarketing requirements and postmarketing commitment. Please provide your response to this request by **October 11, 2016**.

Post Marketing Requirements

PREA

1. Conduct the deferred pediatric study to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 12 to less than 18 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

Protocol Submission: March, 2016 (submitted)
Trial Completion: June, 2019
Final Report Submission: December, 2019

2. Conduct the deferred pediatric study to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 2 to less than 12 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

Protocol Submission: January, 2017
Trial Completion: September, 2021
Final Report Submission: March, 2022

Clinical Virology

3. Perform genotypic (also phenotypic if qualified) resistance analysis of baseline virus samples from all HBeAg-positive nucleos(t)ide reverse transcriptase inhibitor-experienced subjects and of Week-48 virus samples from all evaluable subjects, regardless of their Week 96 virologic outcome.

Study Completion:

Final Report Submission: March, 2017

Comment [MPH1]: Gilead, please propose the dates for comment #3, 4, 5, 6, 7 and 8

4. Evaluate the anti-HBV activity of TAF in combination with sofosbuvir.

Study Completion:

Final Report Submission: June, 2017

5. To evaluate resistance pathways, (b) (4) sequence the baseline and Week 48 time-points (by population sequencing or NGS) for all evaluable subjects who had HBV DNA >69 IU/mL and provide a study report that includes resistance data analysis.

Study Completion:

Final Report Submission:

6. Subjects 4296-4510, 5613-1163, and 9035-5187 had HBV DNA titers at the last PCR assessment that were >159 IU/mL, qualifying them for deep sequencing analysis. To evaluate resistance pathways, (b) (4) provide a study report that includes resistance data analysis and submit the fastq files and analyses for (b) (4).

Study Completion:

Final Report Submission:

7. (b) (4) for subjects 8006-5282 and 8600-4558 who had HBV DNA titers at the last PCR assessment that were >159 IU/mL; (b) (4)

(b) (4) provide a study report that includes resistance data analysis and submit the fastq files and analyses (b) (4)

Study Completion:

Final Report Submission:

Post Marketing Commitment

Clinical Virology

8. Phenotype Week-48 virus samples from Subjects 4296-5147 and 8758-5188 in the TAF

group and Subjects 1507-4546 and 9035-4845 in the TDF group in Study GS-US-320-0110.

Study Completion:

Final Report Submission: March, 2017

Please confirm the proposed timelines for commitments 1 and 2, taken from your Agreed iPSP and propose the timelines for requirements 3 thru 8. In general, we expect study reports to be completed and submitted about 6 months after the final subject visits. If the dates proposed above are not appropriate, please provide the justification and propose new dates.

We 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

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/s/

MYUNG JOO P HONG
10/06/2016

From: [Hong, Myung-Joo P.](#)
To: ["Michele Anderson"; "Sara Snow"](#)
Cc: ["Regulatory Archives"](#)
Subject: NDA 208464.Labeling Proposal
Date: Tuesday, October 04, 2016 11:19:00 AM
Attachments: [10.4.16.PI to Gilead.docx](#)

Hello Michele and Sara, attached please find our labeling proposal. We corrected the numbers in Table 8 (b) (4). Can you submit your proposal by 10/6/16?

Warm Regards,
Pat

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

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MYUNG JOO P HONG
10/04/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Labeling Proposal
Date: Friday, September 30, 2016 3:16:00 PM
Attachments: [9.30.16.PI to Gilead.docx](#)

Hi Sara, attached please find our labeling proposal. Would you submit your proposal by 10/6/16?

*Warm Regards,
Pat*

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

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MYUNG JOO P HONG
09/30/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Tuesday, September 27, 2016 2:24:00 PM

Hi Sara, we have the following information request from review team:

- This is in reference to “Table 3: Estimated Safety Margins of TAF Based on AUCs When Comparing Animal NOAELS” in your module 2.4 “Nonclinical overview.” Please clarify which AUC data for maternal exposures were used to calculate exposure multiples comparing human exposures with animal exposures (at the NOAEL) of the embryo fetal development and perinatal/postnatal studies as seen in “Table 3: Estimated Safety Margins of TAF BASED on AUCs When Comparing Animal NOAELS” (see also footnote c in this table).

Please respond by 9/30/16.

Warm Regards,
Pat

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

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/s/

MYUNG JOO P HONG
09/27/2016



NDA 208464

LABELING COMMENTS

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

Please refer to your New Drug Application (NDA) dated January 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for VEMLIDY (tenofovir alafenamide), 25 mg tablet.

We also refer to our March 8, 2016, letter in which we notified you of our target date of October 14, 2016 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On March 18, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by September 22, 2016. The resubmitted labeling will be used for further labeling discussions.

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

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

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

In addition, we have the following comment from the review team regarding our recommended labeling change for carton and container labeling.

Carton and Container Labeling

- Replace “TRADENAME” with the conditionally acceptable proprietary name, VEMLIDY.

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

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MYUNG JOO P HONG
09/14/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Tuesday, August 30, 2016 1:12:00 PM

Hello Sara, we have the following information request:

- We note that the difference in efficacy between the HBeAg+ treatment naïve and treatment experienced subjects was significant. Please provide a high level summary of the 96 week efficacy for these two groups as soon as possible.

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

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/s/

MYUNG JOO P HONG
08/30/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Tuesday, August 30, 2016 4:15:00 PM

Hi Sara, we have the following information request:

- The Division would like clarification modality of identification of cirrhosis in NDA 208464. Please provide a table with the subject ID, modality of determining cirrhosis diagnosis, and the result of that assessment.

Please respond by 9/6/16.

Warm Regards,
Pat

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

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/s/

MYUNG JOO P HONG
08/30/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Monday, August 29, 2016 12:50:00 PM

Hello Sara, we have the following information request:

- Please provide information on the cell-culture anti-HBV activity of TAF when combined with sofosbuvir.

Please respond by 9/6/16.

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA | CDER | OAP | DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

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✉ myung-joo.hong@fda.hhs.gov

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/s/

MYUNG JOO P HONG
08/29/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Friday, July 29, 2016 4:00:00 PM

Hi Sara, we have the following information request from review team:

- We are currently reviewing cases of glycosuria in NDA 208464. Please provide narratives for 0108-0429-1006, 0108-05691-1422, 0108-1041, 0110-01069-4541, 0110-04074-4645, 0110-08645-5085, and 110-09680-5341.

Please respond by COB 8/8/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6235
Silver Spring, MD 20993-0002
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/s/

MYUNG JOO P HONG
07/29/2016



NDA 208464

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Snow:

Please refer to your New Drug Application (NDA) dated and received January 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenofovir alafenamide Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response for #3 by Aug 5 and responses to the remaining comments by Aug 12, 2016 in order to continue our evaluation of your NDA.

1. For the (b)(4) for the proposed container closure system, provide a letter of authorization for DMF (b)(4)
2. Based on the stability data and statistical projection, we recommend (b)(4) the acceptance criterion for total degradation products from NMT (b)(4)% to NMT (b)(4)%.
3. (b)(4)
(b)(4) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. Revise your drug product specification and other related sections to provide commitment to test microbial limits for each drug product release batch.

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200170330
8, cn=Bamidele F. Aisida -A
Date: 2016.07.29 08:36:03 -04'00'

**Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research**

From: [Hong, Myung-Joo P.](#)
To: ["Sara Snow"](#)
Cc: ["Regulatory Archives"](#)
Subject: NDA 208464.Information Request
Date: Friday, July 15, 2016 7:20:00 PM

Hello Sara, please provide the following information:

- We are concerned about the number of cases of Grade 3 and 4 amylase increases (some symptomatic) observed in Studies 0108 and 0110. Please provide the following information:
 1. A comprehensive integrated assessment of any and all reports of asymptomatic and symptomatic Grade 3 and 4 amylase increases across all studies of TAF-containing regimens. For each report, please provide a complete assessment of the clinical course of the event and any action taken regarding TAF.
 2. A similar analysis of any and all post-marketing reports of asymptomatic and symptomatic Grade 3 and 4 amylase increases.
 3. A comprehensive integrated assessment of asymptomatic and symptomatic Grade 3 and 4 amylase increases in patients treated with TDF-containing regimens containing the same information requested under #1 above.
 4. Proposed verbiage for inclusion in the TAF label.

*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: Sara Snow [mailto:Sara.Snow@gilead.com]
Sent: Thursday, July 14, 2016 2:57 PM
To: Hong, Myung-Joo P.
Cc: Regulatory Archives

Subject: RE: NDA 208464.Information Request

Hi Pat,

As narratives for most of these subjects do not currently exist, would the review team be able to provide clarification regarding what event(s) the narratives should be written for these patients?

Thanks!

Sara

Sara Snow, PharmD, MBA
Manager, HBV & HIV Regulatory Affairs
Gilead Sciences Inc | 333 Lakeside Drive | Foster City, CA 94404
☎ 650.425.8310 | ✉ Sara.Snow@gilead.com

From: Hong, Myung-Joo P. [<mailto:Myung-Joo.Hong@fda.hhs.gov>]
Sent: Thursday, July 14, 2016 7:25 AM
To: Sara Snow
Subject: NDA 208464.Information Request

Hello Sara, we have the following information request from review team:

- **Please provide brief narratives for subjects below by COB July 22, 2016.**

- - GS-US-320-0108-01069-1159
 - GS-US-320-0108-02019-1187
 - GS-US-320-0108-02080-1180
 - GS-US-320-0108-02145-1011
 - GS-US-320-0108-02757-1275
 - GS-US-320-0108-02865-1023
 - GS-US-320-0108-04037-1249
 - GS-US-320-0108-05552-1295
 - GS-US-320-0108-05610-1060
 - GS-US-320-0108-06963-1340
 - GS-US-320-0108-08312-1093
 - GS-US-320-0108-08600-1041
 - GS-US-320-0108-04029-1123
 - GS-US-320-0108-08017-1038
 - GS-US-320-0110-02757-4647
 - GS-US-320-0110-04074-4645
 - GS-US-320-0110-06758-5257
 - GS-US-320-0110-06958-5118
 - GS-US-320-0110-06963-5041
 - GS-US-320-0110-06970-4567

GS-US-320-0110-08313-4933
GS-US-320-0110-08599-5171
GS-US-320-0110-00481-5268
GS-US-320-0110-01069-5079
GS-US-320-0110-05691-5343
GS-US-320-0110-06758-4763
GS-US-320-0110-06758-4987
GS-US-320-0110-08599-4880
GS-US-320-0110-09695-5213

*Warm Regards,
Pat*

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA | CDER | OAP | DAVP
10903 New Hampshire Ave
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 301-796-0807
 301-796-9883 (fax)
 myung-joo.hong@fda.hhs.gov

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/s/

MYUNG JOO P HONG
07/15/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Thursday, July 14, 2016 10:24:00 AM

Hello Sara, we have the following information request from review team:

- **Please provide brief narratives for subjects below by COB July 22, 2016.**

-
GS-US-320-0108-01069-1159
GS-US-320-0108-02019-1187
GS-US-320-0108-02080-1180
GS-US-320-0108-02145-1011
GS-US-320-0108-02757-1275
GS-US-320-0108-02865-1023
GS-US-320-0108-04037-1249
GS-US-320-0108-05552-1295
GS-US-320-0108-05610-1060
GS-US-320-0108-06963-1340
GS-US-320-0108-08312-1093
GS-US-320-0108-08600-1041
GS-US-320-0108-04029-1123
GS-US-320-0108-08017-1038
GS-US-320-0110-02757-4647
GS-US-320-0110-04074-4645
GS-US-320-0110-06758-5257
GS-US-320-0110-06958-5118
GS-US-320-0110-06963-5041
GS-US-320-0110-06970-4567
GS-US-320-0110-08313-4933
GS-US-320-0110-08599-5171
GS-US-320-0110-00481-5268
GS-US-320-0110-01069-5079
GS-US-320-0110-05691-5343
GS-US-320-0110-06758-4763
GS-US-320-0110-06758-4987
GS-US-320-0110-08599-4880
GS-US-320-0110-09695-5213

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
07/14/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request from DMEPA
Date: Wednesday, June 22, 2016 4:56:00 PM

Hi Sara, we have the following request from DMEPA:

1. As presented, the label for Vemlidy does not have any distinctive characteristics helping to differentiate it from the currently marketed Viread label. Please provide a proposal to help differentiate the labels to prevent wrong drug selection errors.
2. Please replace "TRADENAME" with the conditionally acceptable proprietary name, Vemlidy.

Please submit your response by July 5, 2016.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
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/s/

MYUNG JOO P HONG
06/23/2016

From: [Hong, Myung-Joo P.](#)
To: "sara.snow@gilead.com"; "[Mae Lai \(Mae.Lai@gilead.com\)](mailto:Mae.Lai@gilead.com)"
Subject: NDA 208464.Information Request
Date: Friday, June 10, 2016 4:21:00 PM

Hi Sara, we have the following information request from review team:

- We found a discrepancy with the numbers of subjects on lipid modifying therapy at the beginning of the trials. The values we discover are lower than 4.6% in the TAF arm and 3.7% in the TDF arm. Please describe what data set was used and what codes were used to calculate these numbers. Which SAS program was used for this analysis? We see the footnote at the bottom of Table 5.1 in the Safety Summary that the program for analysis was t-lipid.sas, but this program does not appear to have been included in the NDA application. Please send a text file with the t-lipid.sas program.

Please respond by 6/20/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
06/10/2016

From: [Hong, Myung-Joo P.](#)
To: "[Mae Lai \(Mae.Lai@gilead.com\)](mailto:Mae.Lai@gilead.com)"; "sara.snow@gilead.com"
Subject: NDA 208464.Information Request
Date: Friday, June 03, 2016 3:34:00 PM

Hi Mae, we have the following comments:

- We are concerned about blank samples where TAF or TFV were detected (i.e., a peak is showing in the chromatogram). We were not able to identify the analytical runs to which these blank samples belong to and we are requesting you to identify these runs. These chromatograms for blank samples can be found by looking at the sample analysis reports submitted to the NDA corresponding to the studies and analytes listed in the table below.

Table 1. Studies affected by potential contamination.

Study	Analyte	Potential contamination
120-0107	TAF	Blank + IS Extracted blank
120-0117	TFV	Extracted blank
320-0101	TAF	Blank + IS Extracted blank
320-0101	TFV	Extracted blank (report B)
320-0110	TAF	Blank + IS
320-1228	TAF	Blank + IS Extracted blank

*Warm Regards,
Pat*

Myung-Joo Patricia Hong, M.S.
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✉ myung-joo.hong@fda.hhs.gov

From: Sara Snow
Sent: Tuesday, May 31, 2016 12:02 PM
To: 'Hong, Myung-Joo P.'

Cc: Regulatory Archives
Subject: RE: NDA 208464.Information Request

Hi Pat,

Thank you for your email. I have shared the information request with our team and they have the following question:

- Would you please clarify any specific runs for each study in which the contamination was observed?

Thanks!

Sara

Sara Snow, PharmD, MBA
Manager, HBV & HIV Regulatory Affairs
Gilead Sciences Inc | 333 Lakeside Drive | Foster City, CA 94404
☎ 650.425.8310 | ✉ Sara.Snow@gilead.com

From: Hong, Myung-Joo P. [<mailto:Myung-Joo.Hong@fda.hhs.gov>]
Sent: Friday, May 27, 2016 10:45 AM
To: Sara Snow
Subject: NDA 208464.Information Request

Hi Sara, we have the following information request from review team:

- Your previous response (SDN 16) contained specific acceptance criteria in the SOP for addressing carryover. Specific acceptance criteria in the SOP were lacking with regard to contamination: "If contamination rather than carryover is suspected, valid scientific justification and an assessment to determine the impact on study concentrations will be documented in the study data and approved by the Principal Investigator." We identified potential contamination in blanks for several studies (Table 1). Please detail how potential contamination was addressed in the studies listed in Table 1. Please respond by June 3, 2016.

Table 1. Studies affected by potential contamination.

Study	Analyte	Potential contamination
120-0107	TAF	Blank + IS Extracted blank
120-0117	TFV	Extracted blank
320-0101	TAF	Blank + IS Extracted blank
320-0101	TFV	Extracted blank (report B)
320-0110	TAF	Blank + IS

320-1228	TAF	Blank + IS Extracted blank
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*Warm Regards,
Pat*

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
06/03/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Friday, May 27, 2016 1:44:00 PM

Hi Sara, we have the following information request from review team:

- Your previous response (SDN 16) contained specific acceptance criteria in the SOP for addressing carryover. Specific acceptance criteria in the SOP were lacking with regard to contamination: "If contamination rather than carryover is suspected, valid scientific justification and an assessment to determine the impact on study concentrations will be documented in the study data and approved by the Principal Investigator." We identified potential contamination in blanks for several studies (Table 1). Please detail how potential contamination was addressed in the studies listed in Table 1. Please respond by June 3, 2016.

Table 1. Studies affected by potential contamination.

Study	Analyte	Potential contamination
120-0107	TAF	Blank + IS Extracted blank
120-0117	TFV	Extracted blank
320-0101	TAF	Blank + IS Extracted blank
320-0101	TFV	Extracted blank (report B)
320-0110	TAF	Blank + IS
320-1228	TAF	Blank + IS Extracted blank

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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MYUNG JOO P HONG
05/27/2016

From: [Aisida, Bamidele \(Florence\)](#)
To: "Sara Snow"
Cc: [Hong, Myung-Joo P.](#)
Subject: NDA 208464 CMC INFORMATION REQUEST
Date: Wednesday, May 25, 2016 4:33:41 PM

Dear Ms. Snow,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, June 08, 2016:

1. The provided dissolution data do not support the proposed dissolution acceptance criterion of $Q = \text{(b)} \text{(4)}\%$ at $\text{(b)} \text{(4)}$ minutes and it is not acceptable. Implement the following dissolution acceptance criterion for your proposed drug product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

$Q = \text{(b)} \text{(4)}\%$ at 15 min

Please confirm receipt of this email.

Thanks,

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 | Bamidele.aisida@fda.hhs.gov

From: [Hong, Myung-Joo P.](#)
To: "sara.snow@gilead.com"
Subject: NDA 208464.Information Request
Date: Tuesday, May 10, 2016 2:15:00 PM

Hello Sara, we have the following information request from review team.

Regarding bioanalytical methods:

1. Please provide the storage temperatures of plasma samples (for PK) at the clinical sites for each clinical study or refer us to where this information is documented in the protocols or CSRs.
2. Submit the following method validation reports (or links if previously submitted):
 - a. Gilead Bioanalytical Validation Report V_FTC_TFV_HUMAN_and_CANINE_PLASMA_V9, 15401v9: Determination of Emtricitabine and Tenofovir in Human Plasma and Canine Plasma by LC/MS/MS
 - b. (b) (4) 60N-1419
3. In Studies 320-0108 and 320-0110, what was the maximum time between sample collection and bioanalysis for TFV-DP samples?
4. In sample analysis reports for several studies, analyte with peak areas >10% of the LLOQ peak area were detected for TAF and/or TFV blanks (such as blank + IS, extracted blank, and carryover blank). Please provide SOPs documenting run acceptance criteria for when interference is detected.
5. In Study 320-0110, report (b) (4) 60-1357C Amendment 1, samples were stored at -70°C but validated duration of stability data is cited for -80°C. Using the validated duration of stability at -70°C, not all samples were measured within the duration of stability. Of the 1400 samples measured in this report, please specify the number of samples not measured within 340 days of collection.

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
05/10/2016

From: [Hong, Myung-Joo P.](#)
To: "sara.snow@gilead.com"
Subject: NDA 208464.Information Request
Date: Tuesday, May 03, 2016 11:12:00 AM

Hello Sara, we have the following information request from review team:

- Subject 5691-5109 in Study 110 died due to HCC. In Table 7 of the study report, this subject's age is listed as 50 while in the death narrative it is 62. Please explain this discrepancy.
- In Study 108 you list three TAF subjects as having abnormal baseline fundoscopic exams; two of which remained abnormal at Week 48. Please provide each subject's baseline and Week 48 abnormality.
- In Study 108, you list one TAD subject as having an abnormal baseline fundoscopic exam which was determined to be normal at Weeks 24 and 48. Please provide this subject's baseline abnormality.
- In Study 110, you list three TAF subjects as having an abnormal baseline fundoscopic exam, one of which remained abnormal at Week 48. Please provide this subject's baseline and Week 48 abnormality.
- In Study 110, you list nine TDF subjects who were included in the fundoscopic exam substudy but failed to provide any information about these subjects. Please provide details of any and all baseline and Week 24 or 48 abnormalities.

Please respond by COB 05/04/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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 myung-joo.hong@fda.hhs.gov

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/s/

MYUNG JOO P HONG
05/03/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464 - Information Request
Date: Monday, April 25, 2016 1:39:00 PM

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

- The Division recently became aware that the double-blind portion of Studies 0108 and 0110 has been extended to 144 weeks. Please provide a reference to an IND submission describing this revision, or provide the amendment as soon as possible.

Please submit your response by 5/2/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
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/s/

MYUNG JOO P HONG
04/25/2016



NDA 208464

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Snow:

Please refer to your New Drug Application (NDA) dated and received January 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenofovir alafenamide (TAF) Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by May 3, 2016.

- 1. In your stability report, it has been noted that degradation product content in the proposed drug product has been analyzed by an analytical method (STM-2214) with multiple updates including a change of sample (b)(4) preparation. Provide data to demonstrate that the contents of degradation products from the same sample analyzed by different versions of the method (STM-2214) remain the same.*
- 2. Lactose monohydrate is listed in FDA guidance for industry, Pharmaceutical Components at Risk for Melamine Contamination. Provide a melamine free certificate for lactose monohydrate.*
- 3. Investigate the effect of rotation speed on the dissolution profile of TAF tablets. Provide the full profile dissolution data (mean, individual, SD, figure, n=12) for TAF tablets using the speeds of 50 rpm and 60 rpm in the proposed medium.*

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: cn=US, o=US Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001703308,
cn=Bamidele F. Aisida -A
Date: 2016.04.19 16:15:20 -0400'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464 - Information Request
Date: Tuesday, April 19, 2016 11:26:00 AM

Hello Sara, we have the following information request from review team:

1. Please provide possible explanations for differences between TAF and TDF with respect to ALT normalization in the face of comparable antiviral activity. How would TAF provide better liver targeting?
2. Please provide results for ALT fractionation from muscle in addition to ALT fractionation from liver from the ALT results in Study 0108 and 0110.

Please respond by April 27, 2016.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
04/19/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.IR
Date: Friday, April 01, 2016 4:10:00 PM

Hello Sara, would you submit the narratives for Subject 381-1218 in Study 108 and Subject 2145-4641 in Study 110? Please respond by 4/7/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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MYUNG JOO P HONG
04/01/2016

From: [Hong, Myung-Joo P.](#)
To: "Sara Snow"
Cc: "Regulatory Archives"
Subject: NDA-208464 Information Request
Date: Thursday, March 17, 2016 11:00:00 AM

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

- We note that there were compounds in the TAF fumarate drug substance (b) (4) that were controlled as mutagenic impurities. Per ICH M7, the HIV indication was considered to involve 1-10 year use for the great majority of patients. Please describe the control strategy for mutagenic impurities that will be in place for TAF fumarate, given that the level of control for the Hepatitis B indication (chronic dosing scenario) will involve a lower default TTC (1.5 $\mu\text{g}/\text{day}$) and lower class-specific TTC for (b) (4) $\mu\text{g}/\text{day}$."

Please submit your response by 3/25/16.

Warm Regards,
Pat

Myung-Joo Patricia Hong, M.S.
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/s/

MYUNG JOO P HONG
03/17/2016



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

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 11, 2016

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

Total no. of pages including cover: pages

Comments: NDA 208464

Document to be mailed: YES NO

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

DATE: March 11, 2016
NDA: 208464/Original Submission
TO: Sara Snow, Manager, Regulatory Affairs
FROM: Myung-Joo Patricia Hong, M.S., Senior Regulatory Project Manager
SUBJECT: Advice/Information Request

Please refer to your Original NDA submitted on January 11, 2016. We have the following comments from the review team.

Clinical/Statistical

The data provided had some deficiencies that need to be reconciled for our analysis. Two of them are described below in red box:

1. Table of “Neither Start Date/Time of Disposition Event (DSSTDTC), Date/Time of Collection (DSDTC) nor Study Day of Start of Disposition Event (DSSTDY) are populated for 52% of records in both studies SDRG”
 - No dates collected for study completion records.

Missing Data Findings Examples

- ▶ Neither Start Date/Time of Disposition Event (DSSTDTC), Date/Time of Collection (DSDTC) nor Study Day of Start of Disposition Event (DSSTDY) are populated for 52% of records in both studies
 - Example from 108 DS domain:

Domain	USUBJID	DSDECOD	DSSCAT	DSDTC	DSSTDTC	DSSTDY
DS	GS-US-320-0108-01057-1043	ADVERSE EVENT	STUDY COMPLETION			
DS	GS-US-320-0108-02145-1007	COMPLETED	STUDY DRUG COMPLETION - BLINDED			
DS	GS-US-320-0108-08601-1079	PHYSICIAN DECISION	STUDY COMPLETION			

2. Table of “Missing value for Origin (QORIG) variable for domains in both studies”

- Study 108: SUPPAE (15%), SUPPDV (100%)
- Study 110: SUPPAE (16%), SUPPDM (16%), SUPPDV (100%)
- SDRG: “Not entered”

Missing Data Findings Examples

- ▶ Missing value for Origin (QORIG) variable for domains in both studies
 - Examples from 110 SUPPAE domain:

RDOMAIN	USUBJID	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
AE	GS-US-320-0110-00340-4973	1	AEDICVR	Coding Dictionary and Version	MedDRA 18	Assigned
AE	GS-US-320-0110-00342-4700	1	AEBONCAT	Selected AE Bone Event Category	BONE DISORDERS	Derived
AE	GS-US-320-0110-00381-4570	6	AEACNOL	Action Taken for Open-Label TAF	NOT APPLICABLE	
AE	GS-US-320-0110-00595-4502	2	AEACNOL	Action Taken for Open-Label TAF	DOSE NOT CHANGED	

Please reconcile data and submit your response by March 18, 2016. In addition to making corrections to errors identified in the SDTM datasets please identify and correct any corresponding errors in the analysis datasets.

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

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/s/

MYUNG JOO P HONG
03/11/2016



NDA 208464

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

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

Please refer to your New Drug Application (NDA) dated January 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for VEMLIDY (tenofovir alafenamide) 25 mg tablet.

We also refer to your amendments dated January 12, January 25, February 24, and February 26, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 11, 2016.

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 October 14, 2016.

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

PRESCRIBING INFORMATION

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

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

During our preliminary review of your submitted labeling, we have the following labeling comment:

- Please add drug interaction information for use of HIV antiretrovirals with TAF in the prescribing information.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **March 25, 2016**. 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 request 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. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies in children less than 2 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
03/08/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 115561
NDA 208464

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs

Dear Dr. Snow:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and to your New Drug Application (NDA) dated and received January 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tenofovir Alafenamide Tablets, 25 mg.

We also refer to:

- Your correspondence to your IND, dated and received November 4, 2015, requesting review of your proposed proprietary name, Vemlidy
- Your correspondence to your NDA, dated and received January 12, 2016, requesting review of your proposed proprietary name, Vemlidy

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

If **any** of the proposed product characteristics as stated in your January 12, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
03/05/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/06/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@gilead.com"](mailto:sara.snow@gilead.com)
Subject: NDA 208464.Information Request
Date: Thursday, March 03, 2016 2:52:00 PM

Hello Sara, we have the following request from review team:

- Please provide a brief description of reason for subjects who withdrew consent and discontinued study for reasons other than viralogic failure and adverse events.

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

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/s/

MYUNG JOO P HONG
03/03/2016

From: [Hong, Myung-Joo P.](#)
To: ["sara.snow@qilead.com"](mailto:sara.snow@qilead.com)
Subject: NDA 208464.Information Request
Date: Monday, February 29, 2016 11:33:00 AM

Hello Sara, we have the following request from review team:

- Please provide rationale for assuming the applicability of foreign data in the submission to the U.S. population or provide where in the submitted NDA application this information is located.

Please provide your response by COB Thursday.

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
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✉ myung-joo.hong@fda.hhs.gov

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MYUNG JOO P HONG
02/29/2016

From: [Hong, Myung-Joo P.](#)
To: sara.snow@gilead.com
Subject: NDA 208464.IR.AEs Coding
Date: Thursday, February 18, 2016 7:48:59 PM

Hello Sara, we have the following request from review team.

- Please code the AEs below in your datasets.
 - o WORSENING BACK PAIN DUE TO MOTOR VEHICLE ACCIDENT
 - o LEUKOURIA

Please submit your response by 2/26/16.

Warm Regards,
Pat

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

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/s/

MYUNG JOO P HONG
02/18/2016

From: [Hong, Myung-Joo P.](#)
To: sara.snow@gilead.com
Subject: NDA 208464.Clinical Virology IR
Date: Thursday, February 18, 2016 12:43:00 AM

Hello Sara, we have the following request from review team.

- Please identify HBV serologic assays (qualitative for HBeAg, HBeAb, HBsAg, and HBsAb) utilized in Studies 108 and 110, and the assay used to determine HBV genotypes (A through H) at baseline (or screening).

Please submit your response by 2/24/16.

Warm Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA | CDER | OAP | DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

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/s/

MYUNG JOO P HONG
02/18/2016

From: [Hong, Myung-Joo P.](#)
To: sara.snow@gilead.com
Subject: NDA 208464.Information Request
Date: Thursday, January 21, 2016 9:41:22 AM

Hello Sara, we have the following information request:

- Please locate (or provide) the dataset (SAS transport file) for the baseline INNO-LiPA results summarized in Study Report PC-320-2009 (Appendix 8).

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

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/s/

MYUNG JOO P HONG
01/21/2016



NDA 208464

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

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: tenofovir alafenamide (TAF), 25 mg Tablet

Date of Application: January 11, 2016

Date of Receipt: January 11, 2016

Our Reference Number: NDA 208464

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 March 11, 2016 in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MYUNG JOO P HONG
01/12/2016



IND 115561

**MEETING REQUEST-
WRITTEN RESPONSES**

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, M.B.A.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

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

We also refer to your submission dated October 9, 2015, containing a Type C meeting request. The purpose of the requested meeting was to share and discuss topline data from the two Phase 3 studies (Study GS-US-320-0108 and Study GS-US-320-0110) in advance of the NDA filing.

Further reference is made to our Meeting Granted letter dated October 16, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the question contained in your November 23, 2015 background package.

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:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C Meeting
Meeting Category: Other

Application Number: IND 115561
Product Name: tenofovir alafenamide (TAF)
Indication: Treatment of chronic HBV Infection
Sponsor/Applicant Name: Gilead Sciences, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Tenofovir alafenamide (TAF) is an investigational prodrug of tenofovir for the treatment of chronic hepatitis B (CHB) in treatment-naïve and treatment-experienced patients. TAF is more stable in plasma than tenofovir disoproxil fumarate (TDF), provides higher intracellular levels of the active phosphorylated metabolite, tenofovir diphosphate (TFV-DP) to target cells (e.g., HBV-infected hepatocytes and HIV-infected lymphoid cells), and demonstrates approximately 90% lower circulating levels of TFV relative to TDF when given at a lower dose than TDF. The unique metabolism of TAF offers the potential for an improved clinical safety profile compared with TDF.

The proposed TAF Phase 3 development program and registration plan for the treatment of chronic hepatitis B were discussed at the End-of-Phase 2 Meeting on June 17, 2013. The proposed NDA submission is targeted for January 2016.

The two pivotal Phase 3 non-inferiority studies to support the proposed indication for the TAF tablet for chronic hepatitis B are:

- Study GS-US-320-0108 in HBeAg-negative treatment-naïve and -experienced subjects
- Study GS-US-320-0110 in HBeAg-positive treatment-naïve and -experienced subjects

On April 17, 2015, Gilead requested a pre-NDA meeting to discuss the NDA for the TAF tablet and to agree on key aspects related to the content and format of the application, as well as plans for the NDA Safety Update. After receiving the Agency's preliminary comments (June 16, 2015), Gilead cancelled the pre-NDA meeting. Gilead submitted a response to the Agency's preliminary comments on July 2, 2015.

Gilead submitted a Type C Meeting Request on October 9, 2015. The Division granted the meeting as a Type C Written Response Only on October 16, 2015. Gilead provided a background package on November 23, 2015. The objectives of this meeting are to share and discuss topline data from the two Phase 3 studies in advance of the NDA filing.

2.0 QUESTIONS AND RESPONSES

Sponsor questions are in *bold italicized font* and DAVP comments are in standard font.

2.1. Clinical

Q1. Gilead is providing an executive summary of the key efficacy and safety data from the following Phase 3 Studies in the meeting information package:

- Study GS-US-320-0108: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B.
- Study GS-US-320-0110: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Positive, Chronic Hepatitis B.

Does the Division agree that the Phase 3 data to be included in the NDA will support the proposed indication for TAF tablets?

FDA Response: The Division agrees that the data from Studies 0108 and 0110 would be sufficient to support submission of an NDA for TAF tablets.

The Division notes the extremely low enrollment of Black/African Americans into these trials. Such low enrollment may preclude an assessment of efficacy in this important population, and could lead to a requirement for additional data.

The Division notes that subjects will remain on randomized treatment through Week 96 and then will be rolled to open-label TAF. The Division recommends that subjects remain on their assigned treatment for a longer duration in order to better understand the long-term safety and efficacy of TAF.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 reference the Agreed iPSP dated February 28, 2014. Please provide the Agreed iPSP, along with any requests for waivers and deferrals, in your NDA submission.

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/s/

MYUNG JOO P HONG
12/16/2015



IND 115561

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, M.B.A.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

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

We also refer to your April 10, 2015, correspondence requesting a pre-NDA meeting to reach agreement with the Agency on the strategy for the submission of the TAF tablet NDA in January 2016 and to agree on key aspects related to the content and format of the NDA application as well as plans for the 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.

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 (240) 402-4247.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 18, 2015
Meeting Location: Teleconference

Application Number: 115561
Product Name: tenofovir alafenamide (TAF)
Indication: Treatment of hepatitis B virus infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 18, 2015, 2:00 - 3:30 PM, between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. 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

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits the hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase/reverse transcriptase (pol/RT) and the HIV-1 reverse transcriptase. Tenofovir disoproxil fumarate (TDF), a prodrug of TFV, is a nucleotide reverse transcriptase inhibitor (NtRTI) that is indicated for the treatment of chronic hepatitis B (CHB) in adults and pediatric patients 12 years of age and older. While TDF is used broadly in the treatment of both CHB and HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown.

Tenofovir alafenamide (TAF) is an investigational prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV

relative to TDF. The unique metabolism of TAF offers the potential for an improved clinical safety profile compared with TDF.

The safety/tolerability, PK, and antiviral results from the Phase 1b study (GS-US-320-0101) in subjects with CHB and the proposed TAF Phase 3 development program and registration plan for the treatment of CHB were discussed at the End-of-Phase 2 (EOP2) Meeting on June 17, 2013.

Two pivotal non-inferiority studies were conducted to support the proposed indication:

- Study GS-US-320-0108 in HBeAg-Negative, CHB subjects
- Study GS-US-320-0110 in HBeAg-Positive, CHB subjects

The primary purpose of the meeting is to reach agreement with the Agency on the strategy for the submission of the NDA and to agree on key aspects related to the content and format of the application as well as plans for the NDA Safety Update for the TAF tablet.

The proposed NDA submission is targeted for January 2016.

2.0 DISCUSSION

Your summary and questions are in ***bold italicized font*** and our responses are shown in standard font.

2.1. TAF Submission Strategy

Q1. *The development program for the TAF tablet is planned to support a label for the use of the TAF tablet in treatment-naïve and treatment-experienced adults with CHB.*

The proposed indication for the TAF tablet is based on the following two Phase 3 non-inferiority studies:

- ***Study GS-US-320-0108: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B.***
- ***Study GS-US-320-0110: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Positive, Chronic Hepatitis B.***

A tabular presentation of the Phase 3 clinical studies characterizing the safety and efficacy of the TAF tablet is provided in Table 1.

Table 1. Phase 3 Clinical Studies Characterizing the Safety and Efficacy of the TAF Tablet

<i>Study Number</i>	<i>Description</i>	<i>Number of Subjects Planned</i>	<i>Number of Subjects Treated</i>	<i>Format</i>
<i>GS-US-320-0108</i>	<i>Phase 3, randomized, double-blind study of TAF compared with TDF (2:1 randomization) in HBeAg-negative CHB infected, treatment-naive and treatment-experienced adult subjects</i>	<i>390</i>	<i>425</i>	<i>48 Week Interim CSR</i>
<i>GS-US-320-0110</i>	<i>Phase 3, randomized, double-blind study of TAF compared with TDF (2:1 randomization) in HBeAg-positive CHB infected, treatment-naive and treatment-experienced adult subjects</i>	<i>864</i>	<i>873</i>	<i>48 Week Interim CSR</i>

Does the Agency agree that the studies described above will support the proposed indication for the TAF tablet for treatment of CHB in adults?

Division Response:

The types and designs of the trials proposed for the NDA are comparable to those that have been submitted for previous applications for the treatment of chronic hepatitis B; however, in the absence of clinical data the Division is unable to answer this question. When you have top-line efficacy and safety data from these trials you are encouraged to submit a summary to the Division prior to submitting the NDA for further feedback on this question..

2.2. NDA Format and General Contents

Q2. *The NDA Table of Contents for the TAF tablet NDA is provided in Attachment 2. Gilead plans to submit all pertinent clinical and nonclinical study reports that have not previously been submitted as part of an NDA. Lists of nonclinical (Attachment 3) and clinical (Attachment 4) studies cross-referenced in the application will be provided in m1.4.4 of the TAF tablet NDA.*

Gilead plans to utilize cross-application links to TAF drug substance in the E/C/F/TAF fixed-dose combination (FDC) NDA 207561.

Nonclinical in vitro metabolism studies using human matrices will be located in Module 5.3.2, with cross-reference from the appropriate sections of Module 4. Similarly, nonclinical virology study reports will be located in Module 5.3.5.4–Other Study Reports with cross-reference included from the appropriate sections of Module 4.

a) *Does the Agency have any comments regarding the NDA Table of Contents and the draft clinical and nonclinical m1.4.4 documents for the TAF tablet NDA?*

Division Response:

Overall the proposed “NDA Table of Contents” and draft clinical documents for the TAF tablet NDA are acceptable. With respect to the clinical pharmacology information, please add to the Table of Contents, Section 5.3.1.4, the bioanalytical reports for atazanavir, norgestimate, and ethinyl estradiol.

- b) Does the Agency agree that clinical and nonclinical studies previously submitted to another NDA(s) do not need to be resubmitted in the TAF tablet NDA to facilitate review of the NDA?***

Division Response:

We agree that clinical and nonclinical studies previously submitted to another NDA do not need to be resubmitted in the TAF tablet NDA. Please provide cross-links to any previously submitted data.

- c) Does the Agency agree that CMC information previously submitted for the TAF drug substance in E/C/F/TAF FDC NDA do not need to be resubmitted but instead will be provided via cross-application links to Module 3.2.S in the E/C/F/TAF NDA?***

Division Response:

Yes, we agree with your use of cross-application links to NDA 207561 for this situation, provided that the facilities involved with manufacturing or testing of TAF fumarate drug substance are included in 3.2.S.2 and listed on the 356h form. If applicable, justification that the TAF fumarate drug substance specification is appropriate for manufacture of the TAF tablet could be included in 3.2.S.2.S.4 in addition to the cross-application link to NDA 207561.

- d) Does the Agency agree with the proposed locations of nonclinical study reports using human matrices and nonclinical virology study reports in the TAF tablet NDA?***

Division Response:

There are no comments on the NDA Table of Contents and we agree with the location.

- Q3. *Gilead is committed to making TAF tablets available in the developing world through the Gilead Access Program. The trade dress intended for the US market, along with the alternate trade dress that Gilead is developing for the Access program, is described in Table 2.***

Table 2. TAF Tablets – US and Access Trade Dress

Tablet Shape and Dimensions	US Trade Dress	Access Program Trade Dress
Round, 7.9 mm in diameter	Debossing: GSI/25 Color: Yellow, (b) (4)	Debossing: GSI/T2 Color: White, (b) (4)

Gilead plans to include in the NDA submission the required quality information in Module 3 for this alternate trade dress, including the required stability data to support the use of the tablet in climatic zones where the drug will be distributed as part of the Gilead Access Program. In Module 1 of the NDA, Gilead will include the container and carton for the Access presentation.

Does the Agency agree with this proposal?

Division Response:

We agree, under the assumption that the quality information provided in the initial NDA submission to support the alternative trade dress will include stability data at 30°C/75%RH and comparative dissolution profiles. Including the draft container and carton labels for the Access table in Module 1 is also appropriate from our perspective.

- Q4. *In the TAF tablet NDA, Gilead proposes to include literature references cited only in the Nonclinical and Clinical Overviews (Modules 2.4 and 2.5, respectively). References to guidelines, prescribing information for approved products and other similar documents will not be included in the application. All other documents referenced in the application will be available upon request.***

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

Division Response:

Yes we agree with the proposal.

- Q5. *Per FDA’s Guidance for Industry entitled “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” (April 2009), Gilead proposes to provide the Integrated Summary of Efficacy (ISE) text for the Summary of Clinical Efficacy and the ISS text for the Summary of Clinical Safety in Module 2.7.3 and Module 2.7.4, respectively. A cross-reference link to Module 2.7.3 for the ISE and Module 2.7.4 for the ISS will be provided in Module 5.3.5.3 together with supporting statistical outputs and electronic datasets.***

Does the Agency agree with this proposal for the ISE and the ISS?

Division Response:

Yes, we agree with the proposal.

- Q6. *Narratives will be provided in the clinical study reports for deaths, serious adverse events, pregnancies, and discontinuations due to adverse events. Additionally, case report forms (CRFs) for deaths, serious adverse events, pregnancies, and discontinuations due to adverse events will be provided in the application. All other CRFs will be available upon request.***

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

Division Response:

Yes, we agree with the proposal.

2.3. Clinical/Statistical

- Q7. *The primary efficacy endpoint is the proportion of subjects with HBV DNA < 29 IU/mL at Week 48. Due to the expected differences in antiviral response to treatment in the HBeAg-negative and the HBeAg-positive CHB populations for studies GS-US-320-0108 and GS-US-320-0110, respectively, Gilead does not plan to pool or group the efficacy data from the Phase 3 studies. However, the efficacy results from the two Phase 3 studies will be displayed in a side by side comparison in the ISE.***

Given the design of the two Phase 3 pivotal studies, does the Agency concur that efficacy data for the ISE will be summarized by a side-by-side comparison of each of the individual studies?

Division Response:

Yes, we concur with this approach.

- Q8. *For the purpose of the ISS, Gilead plans to conduct integrated analyses on pooled data from the two pivotal Phase 3 studies (GS-US-320-0108 and GS-US-320-0110) in treatment-naïve and treatment-experienced CHB subjects. A statistical analysis plan (SAP) for the ISS is provided in Attachment 5.***

Does the Agency agree with the proposal for the analyses to be included in the ISS?

Division Response:

Yes, we agree with this proposal.

- Q9. *Individual SAPs for the two pivotal Phase 3 studies (GS-US-320-0108 and GS-US-320-0110) are provided in Attachment 6 and Attachment 7, respectively.***

Does the Agency agree with the proposal for the planned primary and key secondary analyses in studies GS-US-320-0108 and GS-US-320-0110?

Division Response:

Yes, we agree with this proposal.

Q10. Per 21 CFR 314.50(d)(5)(vi)(b), Gilead proposes to submit a Safety Update 90 days (priority review) or 120 days (standard review) following the submission of the TAF tablet NDA in January 2016. The Safety Update will include cumulative deaths, serious adverse events, pregnancies, and discontinuations due to adverse events for the ongoing Phase 3 clinical studies shown in the table below. The projected data cut-off for inclusion in the safety update for each study is listed in Table 3.

Table 3. Safety Update from Ongoing Studies Included in the TAF Tablet NDA

<i>Study Number</i>	<i>Description</i>	<i>Data Cut-off for Safety Update</i>
<i>GS-US-320-0108</i>	<i>Phase 3, randomized, double-blind study of TAF compared with TDF (2:1 randomization) in HBeAg-negative CHB infected, treatment-naïve adult subjects and treatment-experienced adult subjects</i>	<i>Jan 2016</i>
<i>GS-US-320-0110</i>	<i>Phase 3, randomized, double-blind study of TAF compared with TDF(2:1 randomization) in HBeAg-positive CHB infected, treatment-naïve adult subjects and treatment-experienced adult subjects</i>	<i>Jan 2016</i>

Does the Agency agree with the proposal for the timing and content of the TAF tablet Safety Update?

Division Response:

Yes, we agree with the timing (120 days after NDA submission) of the safety update.

Q11. Gilead is unaware of any preferred FDA format for analysis datasets for HBV submissions. Therefore, Gilead plans to base the SDTM and ADaM datasets on the CDISC convention. Further, Gilead plans to submit the ADVR dataset in the same format as the Viread GS-US-174-0102/GS-US-174-0103 Week 384 sNDA submission (NDA 021356, SN 0728).

a) Does the Agency require a preferred format for HBV submissions, similar to the FDA preferred formats for HCV and HIV?

Division Response:

A submission for a HBV therapy should be similar to the format used to submit applications for other viral infections, such as HIV and HCV.

b) Does the Agency agree with the proposed format for the submission of the ADVR dataset?

Division Response:

Yes, we agree with the proposed format.

2.4. Clinical Virology

Q12. *To facilitate the Agency's review of virology data from the two Phase 3 studies listed in Table 1, Gilead plans to develop a free-standing virology study report (VSR) to be located in Module 5.3.5.4. In the VSR, Gilead will provide summaries of virology analyses for each individual Phase 3 study together with an integrated summary of resistance data from the pivotal studies GS-US-320-0108 and GS-US-320-0110. The individual clinical study reports will include a cross reference to the VSR. However, virology analyses will not be included in the study reports.*

The draft VAP (PC-320-2002) is provided in Attachment 8. The VAP summarizes the criteria that will be used to determine if a subject qualifies for genotypic or phenotypic analysis in all clinical trials that evaluate TAF for the treatment of CHB.

a) *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?*

Division Response:

Your plan to submit a separate virology report in Module 5.3.5.4 describing the analyses of virology data, in lieu of individual summaries located within each CSR is acceptable. Please include in the report detailed descriptions of virology assays utilized in the Phase 3 studies (e.g., HBV DNA quantification, HBV genotype determination, HBV antigen and antibody detection, population-based nucleotide sequencing, clonal sequencing, phenotypic assay, site-directed mutagenesis).

b) *Does the Agency have any comments on the VAP?*

Division Response:

In general, the proposed virology analysis plan (VAP) for resistance analyses for Studies GS-US-320-0108 and GS-US-320-0110 is acceptable. We agree with your plan to perform genotypic resistance testing on virus samples from subjects who are viremic with no evidence of virologic breakthrough at Weeks 96 and 144 (not at Week 48) in addition to any subjects who experience breakthrough. But, it is recommended to include Week-48 viremic samples from subjects who are viremic with no evidence of virologic breakthrough at Weeks 96 and 144 in your genotypic resistance analysis. Please confirm that baseline isolates will be also evaluated of all subjects whose post-baseline isolates are genotyped in your resistance analysis. If population-based sequencing of post-baseline samples (or pharmacokinetic data) cannot explain a viral load rebound or non-response, please perform additional genotypic analyses on the on-treatment and baseline samples using a method sufficiently sensitive to detect minority variants.

Q13. *As summarized in the draft VAP, Gilead plans to use the following criteria to identify the subset of the subjects in the pivotal Phase 3 studies (GS-US-320-0108 and GS-US-320-0110) that qualify for phenotypic analysis:*

- *Subjects on treatment that experience confirmed virologic breakthrough, regardless of genotypic changes*
- *Subjects with an emerging amino acid substitution observed at a conserved residue of pol/RT*
- *Subjects with an emerging amino acid substitution observed at a polymorphic residue of pol/RT, if it is observed in more than one subject*

Gilead plans to include the genotypic resistance analyses for the two pivotal Phase 3 studies at the time of the TAF tablet NDA submission. However, the phenotypic resistance analyses will not be completed until approximately 6 months following the last patient last visit date for each study. Therefore, Gilead proposes to submit the genotypic data for the Phase 3 studies with the TAF tablet NDA and to submit the phenotypic data during the TAF tablet NDA review period.

a) Does the Agency agree with the proposed criteria for phenotypic analysis for the pivotal Phase 3 studies?

Division Response:

Yes, we agree with the proposed criteria.

b) Does the Agency agree with the proposal that the phenotypic data be submitted during the TAF tablet NDA review period?

Division Response:

Delayed submission of phenotypic data may be acceptable. Please provide the anticipated date during the review period that the data will be submitted for review.

2.5. Nonclinical

Q14. *TAF has been well characterized for antiviral activity, drug metabolism and pharmacokinetics (DMPK), and potential for toxicity. A waiver for carcinogenicity studies of TAF was granted by the FDA on 19 July 2012 (Reference ID: 3161161) as it was agreed that carcinogenicity studies in mice and rats with TAF would not add to the overall risk evaluation of the drug based on TAF PK and toxicity data, as well as the available nonclinical data for TDF. Additionally, the nonclinical safety program was summarized in the meeting information package for the End of Phase 2 (EOP2) meeting for TAF Single Agent (SA) and E/C/F/TAF FDC which was held on 17 December 2012. In the EOP2 preliminary meeting comments, the Agency agreed that the current nonclinical toxicology program supported the TAF tablet and that a peri/postnatal study in rats was not required for registration of the TAF tablet (Reference ID: 3231054).*

Does the Agency agree that the current nonclinical program will support the registration of the TAF tablet?

Division Response:

Yes, we agree the current nonclinical program will support submission of the NDA.

2.6 Pre-NDA and NDA Review

Q15. *Gilead believes that upon approval of the E/C/F/TAF FDC tablet NDA, the TAF tablet NDA will be considered a non-NME NDA, and therefore will not be subject to the provisions of “The Program” under the Prescription Drug User Fee Act (PDUFA) V.*

Gilead has not identified any safety concerns in the TAF Phase 3 program to date. However, based on previous recommendations from the Agency, Gilead plans to request a Type C meeting and provide a topline summary of Phase 3 results as soon as they become available.

a) *If the NDA for the E/C/F/TAF FDC tablet is approved in advance of the submission of the TAF NDA, does the agency agree that;*

i) the TAF tablet NDA will not be reviewed under “The Program” in accordance with PDUFA V?

Division Response:

Yes, we agree.

(a) the review goals for the TAF NDA would be within 10 months and 6 months of the receipt date for a standard and priority review, respectively?

Division Response:

We agree that the review goals for the TAF NDA will likely be 10 months.

(b) mid-cycle and late-cycle communications could still be scheduled by the Agency to facilitate interactions with the sponsor?

Division Response:

We will determine the need for additional interactions with you.

b) *Does the Agency agree that a Type C, Phase 3 data review meeting may be granted prior to the submission of the NDA?*

Division Response:

The Division’s preference is to have a discussion of the clinical safety and efficacy data well ahead of the planned NDA submission in order to determine if there are additional analyses that must be conducted or regulatory issues that require addressing. It is difficult to agree on any aspects of the acceptability of an NDA or the likelihood of approval in the absence of such clinical data. However, as stated above

you are encouraged to submit a summary of your topline efficacy and safety data when available and depending on results a meeting may be warranted for additional discussions of any potential review issues.

Q16. Based on the nonclinical and clinical information that has been previously submitted to INDs 063737 and 115561 for the TAF tablet, IND 111007 and NDA 207561 for the E/C/F/TAF FDC tablet, and IND 111851 and NDA 208215 for the F/TAF FDC tablet, the available data from the Phase 1b study GS-US-320-0101 (Attachment 1), and the ongoing review of safety data from the clinical program, Gilead does not intend to include a Risk Evaluation and Mitigation Strategy (REMS) in the NDA for the TAF tablet.

Does the Agency agree with this proposal?

Division Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE) have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Q17. Based on the nonclinical and clinical information that has been previously submitted to INDs 063737 and 115561 for the TAF tablet, IND 111007 and NDA 207561 for the E/C/F/TAF FDC tablet, and IND 111851 and NDA 208215 for the F/TAF FDC tablet, does the Agency anticipate that the NDA for the TAF tablet will be the subject of an FDA Advisory Committee Meeting?

Division Response:

At this time, we believe that an Advisory Committee (AC) will be unlikely. This opinion may change once the application has been submitted and the review initiated.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 20, 2015 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>

4.0 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 your Agreed iPSP submitted on January 31, 2014. Your Agreed iPSP, along with any requests for waivers or deferrals, should be included in your New Drug Application.

5.0 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](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in 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.

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

6.0 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.				

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at

this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site

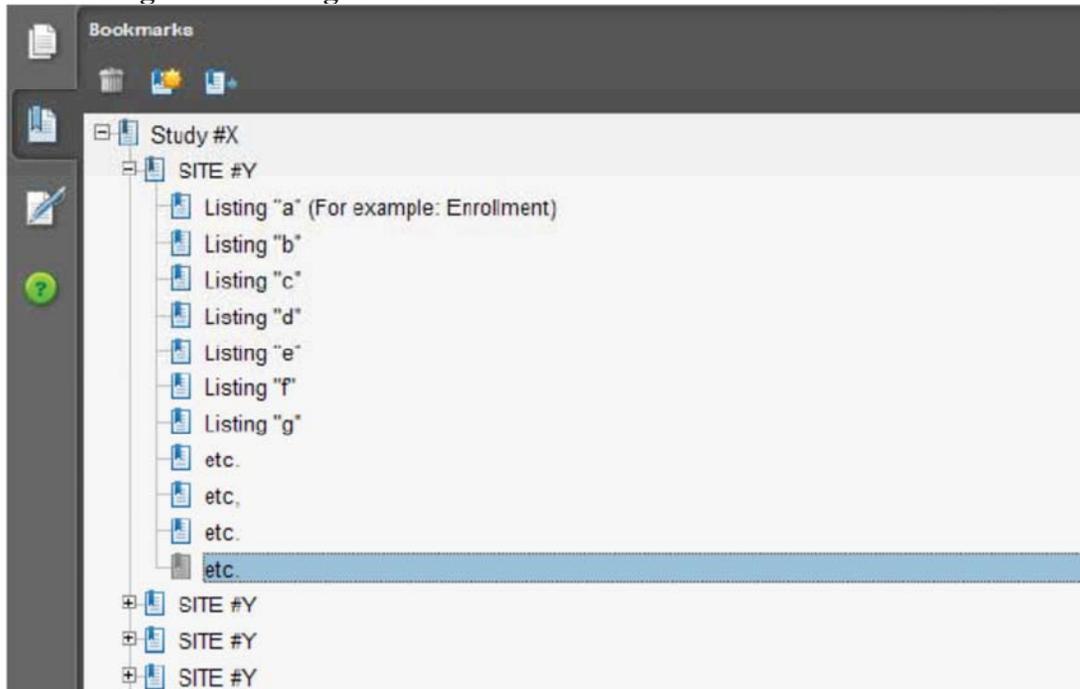
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

- j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@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/

SUZANNE K STRAYHORN
06/16/2015



IND 115561

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Joel Lintao, RAC
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Mr. Lintao:

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

We also refer to the teleconference between representatives of your firm and the FDA on June 17, 2013. The purpose of the meeting was to discuss the proposed clinical and nonclinical development programs that are intended to support the use of TAF for the treatment of chronic hepatitis B virus infection.

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., Senior 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: June 17, 2013; 10:30 am – 11:00 am
Meeting Location: Teleconference
Application Number: IND 115561
Product Name: Tenofovir alafenamide (TAF)
Indication: Treatment of hepatitis B infection
Sponsor/Applicant Name: Gilead Sciences, Inc.
Meeting Chair: Linda Lewis, M.D., Medical Team Lead
Meeting Recorder: Stacey Min, Pharm.D., Senior Regulatory Project Manager

FDA ATTENDEES

David Roeder, M.S., Associate Director of Regulatory Affairs, Office of Antimicrobial Products (OAP)
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Kendall Marcus, M.D., Deputy Director for Safety, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Sung Rhee, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, Ph.D., Acting Clinical Pharmacology Team Lead, DCP IV
Janice Lansita, Ph.D., DABT, Pharmacology/Toxicology Reviewer, DAVP
Peyton Myers, Ph.D., DABT, Acting Pharmacology/Toxicology Team Lead, DAVP
Guoxing Soon, Ph.D., Biometrics Team Lead, DV IV
Antoine El Hage, Ph.D., Reviewer, Office of Scientific Investigation (OSI)
Elizabeth Thompson, M.S., Acting Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Senior Regulatory Project Manager, DAVP
Nina Mani, Ph.D., MPH, MS, Regulatory Project Manager, DAVP
Linda Cong, Regulatory Information Specialist, eData Management Solutions Team

SPONSOR ATTENDEES

John McHutchison, MD, Senior Vice-President, Liver Disease Therapeutics
Mani Subramanian, MD, PhD, Vice President, Clinical Research Liver Disease Therapeutics
John Flaherty, PharmD, Project Lead/Director, Clinical Research
Neby Bekele, PhD, Senior Director, Biostatistics

Michael Miller, PhD, Senior Director, Virology
Adrian S. Ray, PhD, Principal Scientist, Drug Metabolism
Anne Chester, PhD, DABT, Senior Director, Drug Safety Evaluation
Mae J. Lai Director, Regulatory Affairs
Erik Berglund, MD, PhD, Associate Director, Regulatory Affairs

BACKGROUND

On July 30, 2012, Gilead submitted IND 115561, tenofovir alafenamide (TAF), an oral prodrug of tenofovir (TFV) that has longer plasma half-life compared to TFV for the treatment of hepatitis B virus (HBV) infection. This original IND was opened with Phase 1 Study GS-US-320-0101 entitled “A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment- Naive Adults with Chronic Hepatitis B (CHB) Infection”. TAF is currently being studied under IND 63737 for the treatment of HIV-1 infection. In addition, there are two combination INDs consisting of TAF; IND 111007 (elvitegravir/cobicistat/emtricitabine/TAF) and IND 111851 (emtricitabine/TAF) both for the treatment of HIV-1 infection. There are 8 Phase 1/2 and Phase 2 clinical trials of TAF that have been completed or are currently ongoing. In advance of the meeting briefing package, Gilead submitted two Phase 3 studies (one each in HBeAg-positive and HBeAg-negative subjects) have been submitted to IND 115561 for review.

- GS-US-320-0108 entitled “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B”
- GS-US-320-0110 entitled “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive, Chronic Hepatitis B”

The purpose of this EOP2 meeting is to discuss whether the two proposed Phase 3 studies will support the New Drug Application (NDA) registration of TAF for the treatment of chronic hepatitis B infection in treatment-naïve and treatment-experienced patients. In addition, Gilead would like to seek the Division’s feedback on whether the completed nonclinical toxicology studies are adequate to support the registration of TAF for the proposed indication. Lastly, Gilead would like to discuss the use of viral suppression (HBV DNA <69 IU/mL) as the primary endpoint at Week 48 for the two Phase 3 noninferiority studies comparing TAF to TDF.

DISCUSSION

Questions submitted by Gilead in the May 16, 2013, meeting background package are in **bold** font, the Division’s June 13, 2013 preliminary responses are noted in *italicized* font and discussions at the June 17, 2013, teleconference are noted in regular font.

Question 1: TAF HBV Registration Plan

- 1a. Does the Agency agree that HBV DNA suppression (<69 IU/mL at Week 48) is acceptable as the primary endpoint to support registration of TAF for the treatment of chronic hepatitis B infection?**

There are unique aspects of the development of tenofovir alafenamide fumarate (TAF) as treatment of chronic hepatitis B infection that must be acknowledged in our reply. From a regulatory perspective, HBV DNA suppression alone does not meet the criteria as a validated surrogate endpoint and may not be adequate as the sole primary endpoint to support registration of a new molecular entity for HBV treatment. Historically, a histologic endpoint has served as a co-primary but we understand that histologic endpoints may no longer be acceptable to the research community. TAF and its comparator tenofovir disoproxil fumarate (TDF, Viread) are both prodrugs producing the same intracellular active metabolite, tenofovir diphosphate. In this situation, the amount of viral suppression should correspond to the amount of tenofovir diphosphate delivered to its target cells and the degree of histologic improvement. Because the active moiety is shared, it might be possible to support non-inferiority of TAF compared with TDF based upon comparison of HBV DNA suppression.

However, HBV DNA suppression as a primary endpoint for comparison of these two agents should be evaluated as rigorously as possible. First, lower limit of quantification of HBV DNA should be utilized as the primary measure (< 29 IU/mL at Week 48). Secondary efficacy endpoints should be robust, widely acknowledged as supportive of efficacy, and based on precedent from earlier HBV treatment approvals. Endpoints such as normalization of ALT or HBeAg or HBsAg seroconversion are suitable. The secondary efficacy endpoints you have proposed in both studies evaluate bone mineral density loss and renal injury of TAF relative to TDF. These expected imaging/laboratory findings are more appropriately considered safety endpoints. Lastly, demonstration of durability of virologic suppression for at least 96 weeks or longer is appropriate in supporting the validity of HBV DNA suppression as a sole primary endpoint in this unique situation.

Gilead agreed to use < 29 IU/mL as the primary measure of HBV DNA suppression at Week 48 and will submit a protocol amendment for both studies to reflect this change. Gilead indicated that secondary endpoints, ALT normalization, loss of HBeAg and HBe antigen seroconversion will be clarified in the protocol amendment for both studies. Gilead also agreed that bone changes in DEXA scan and renal outcomes are key safety endpoints and will control Type 1 error by statistical outcome. Gilead clarified that they plan to file the NDA based on 48 week data but will extend the study to 96 weeks to get safety and virologic suppression data.

The Agency confirmed that this was acceptable.

- 1b. Does the Agency agree that the noninferiority studies GS-US-320-0108 and GS-US-320-0110, that compare TAF 25 mg to TDF 300 mg in HBeAg-negative and**

HBeAg-positive subjects, respectively, are adequately designed to support registration of TAF for the treatment of chronic hepatitis B infection?

Studies GS-US-320-0108 and GS-US-320-0110 are appropriately designed Phase 3 studies. The determination of non-inferiority and approval of TAF for the treatment of chronic hepatitis B will be review issues. Please provide a more detailed justification for a non-inferiority margin based on an endpoint of HBV DNA < 29 IU/mL and a clinical margin (M2) that reflects a clinically tolerable amount of potential treatment effect loss (in terms of HBV DNA suppression) of TAF compared to TDF.

Gilead again agreed to amend the protocols with 10% noninferiority margin using < 29 IU/mL as the primary endpoint. Gilead stated that treatment benefit of TDF will not change much from using <29 IU/mL vs. <69 IU/mL as the primary endpoint. The Agency stated that TDF and TAF should be nearly identical and from a clinical perspective, 10 % is a large margin. Gilead expects the point estimate for efficacy between TAF and TDF will be nearly identical but expects to see better bone and renal benefits with TAF.

1c. Is the proposal to include both treatment-naïve and nucleos(t)ide-experienced (e.g. lamivudine, adefovir, entecavir) subjects with CHB in the Phase 3 studies appropriate to obtain a labeled indication for TAF for the treatment of chronic HBV infection in these populations?

We disagree with enrolling subjects who are well controlled on nucleos(t)ides (lamivudine, adefovir, entecavir) in these Phase 3 studies to support an indication for TAF in treatment experienced. Please confirm that you are not planning this to be a “switch study.” In our view, “treatment experienced” describes individuals whose anti-HBV treatment regimen is failing because of viral resistance or drug tolerability issues. If you desire a labeled indication for TAF for the treatment of chronic hepatitis B infection in “treatment experienced” patients, it is essential that you include a sufficient number of subjects in the proposed Phase 3 studies with resistance to current or prior NRTI treatment (baseline virus with detectable rt substitutions associated with NRTI resistance by the INNO-LiPA HBV Multi-DR assay and/or population based genotypic analysis). Care should be taken to ensure that such patients are enrolled with balanced allocation to both TAF and TDF.

Gilead confirmed that the two planned Phase 3 studies will not be switch studies. Gilead agrees that treatment-experienced patients are those who were uncontrolled in the past including patients who failed treatments with high levels of replicating DNA. These are patients who failed lamivudine, adefovir, entecavir, or telbivudine in the past. Gilead commented that randomization will be stratified based on antiviral treatment status.

Question 2: Nonclinical Safety Program

2. Does the Agency agree that the toxicology program will support the registration of TAF for use in CHB subjects?

Yes, the toxicology program appears to support the registration of TAF for CHB subjects. If in vivo metabolism data in the dog are available that measure the levels of Metabolite X, alaninyl TFV and Metabolite Y, isopropylalaninyl TFV, please provide a comparison of these metabolites in the dog and human. This information can be provided in the NDA submission.

Gilead acknowledged the Agency's comments and stated that details around metabolite X and metabolite Y will be provided in the NDA submission. Gilead commented that in the recent human ADME study with radiolabeled TAF, neither metabolite X nor metabolite Y were found in plasma, urine or feces. Gilead stated that a comparison of metabolite levels in nonclinical species and humans will be submitted in the NDA.

The Agency agreed that this is acceptable.

Additional Clinical Comments (June 13, 2013):

- 1. As differences in the clinical safety profile between TAF and TDF may be subtle, we strongly recommend you continue the double blinded portion of Studies GS-US-320-0108 and GS-US-320-0110 for at least 96 weeks. This should permit further delineation of the potential bone and renal advantages, if any, of TAF compared to TDF.*

Gilead agreed to extend both studies to 96 weeks.

- 2. Please confirm that the ALT values of 60 U/L for males and 38 U/L for females in your central laboratory correspond to the 2x ULN for ALT as specified by the AASLD guidelines or if not, please explain their derivation.*

Gilead confirmed that the values cited above do conform to the AASLD guidelines of 2x ULN for ALT as determined by their central laboratory.

Additional Clinical Virology Comments (June 13, 2013):

- 3. In addition to genotypic resistance testing, perform phenotypic resistance testing for (1) viruses that harbor treatment-emergent amino acid substitutions at conserved sites of the HBV rt or at polymorphic sites if the change was observed in more than one subject and (2) viruses from subjects experiencing on-treatment virologic rebound regardless of genotypic changes in the proposed Phase 3 studies.*

Gilead agreed with this overall approach. Gilead commented that it is rare to see virologic breakthrough in subjects who are adherent and will monitor adherence based on tenofovir levels. Gilead will include this information in the overall plan to demonstrate resistance. The Agency requested that the expression and enzymatic activity of cathepsin A and CES1

be evaluated in cells used for phenotypic resistance testing.

4. *All HBV genotypes commonly found in the US should be well represented in the proposed study subject populations.*

Gilead agreed to include all genotypes, a through e.

5. *We recommend using “<29 IU/mL, target detected” or “<29 IU/mL, target not detected” for subjects with HBV DNA <29 IU/mL at Weeks 48, 96, and 144. Please evaluate the proportion of subjects with HBV DNA <29 IU/mL, target not detected at Week 48 as a secondary efficacy endpoint.*

Gilead agreed with the Agency’s comment to include the analysis.

6. *Please provide the median change (Min, Max) in HBV DNA at Day 28 from Baseline by HBV genotype in subjects who received TAF in Study GS-US-320-0101.*

Gilead commented that results from recent study showed HBV DNA reductions ranging from 2.2 log₁₀ to 2.8 log₁₀ IU/mL across all genotypes.

Additional Clinical Pharmacology Comment (June 13, 2013):

7. *CES1, the enzyme responsible for conversion of TAF to TFV in hepatocytes, is polymorphic; several nonsynonymous genetic variants (e.g. G143E and D260fs) have been associated with reduced enzymatic function. Please characterize the potential for these variants to influence the rate and extent of TAF hydrolysis in vitro.*

Gilead agreed to conduct an *in vitro* study to evaluate the effect of CES1 SNPs on TAF hydrolysis. The Agency recommended that Gilead review the paper describing the clinical relevance of G143E SNP on oseltamivir activation.

ADDITIONAL DISCUSSION:

- Gilead agreed to submit the PSP within 60 days of the EOP2 meeting.



- The Agency advised Gilead to look at available information on the FDA's website on constructing datasets for NDA submission. The Agency also advised Gilead to contact the electronic submission group with any questions.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, 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

Action Item/Description	Owner	Due Date
Gilead agreed to submit the PSP within 60 days of the EOP2 meeting	Gilead	August 16, 2013
The Division will provide additional comments on the two proposed Phase 3 protocols in the next few weeks	Agency	Few weeks

ATTACHMENTS AND HANDOUTS

No attachments or handouts were provided.

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
07/09/2013



IND 115561

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Joel Lintao, RAC
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Mr. Lintao:

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

We also refer to your correspondence, dated and received March 18, 2013, requesting an End-of-Phase 2 (EOP2) meeting to discuss the proposed clinical and nonclinical development programs that are intended to support the use of TAF for the treatment of chronic hepatitis B infection.

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: End of Phase 2 (EOP2)
Meeting Date and Time: June 17, 2013; 10:30 AM – 12:00 PM
Meeting Location: White Oak, Building 22; Room 1419
Application Number: IND 115561
Product Name: Tenofovir alafenamide (TAF)
Indication: Treatment of hepatitis B virus (HBV) infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative)

Edward Cox, M.D., MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, M.S., Associate Director of Regulatory Affairs, OAP
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Kendall Marcus, M.D., Deputy Director for Safety, DAVP
Linda Lewis, M.D., Medical Team Lead, DAVP
William Tauber, M.D., Medical Officer, DAVP
Sung Rhee, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Lead, DAVP
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, Ph.D., Acting Clinical Pharmacology Team Lead, DCP IV
Janice Lansita, Ph.D., DABT, Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Lead, DAVP
Rao Kambhampati, Ph.D., Division of New Drug Quality Assessment V (DNDQA II, Branch V)
Stephen Miller, Ph.D., CMC Lead, DNDQA II, Branch V
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoxing Soon, Ph.D., Biometrics Team Lead, DV IV
Antoine El Hage, Ph.D., Reviewer, Office of Scientific Investigation (OSI)
Elizabeth Thompson, M.S., Acting Chief Project Management Staff, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Regulatory Project Manager, DAVP
Danyal Chaudhry, M.S., Project Manager, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES

John McHutchison, MD, Senior Vice-President, Liver Disease Therapeutics
Mani Subramanian, MD, PhD, Vice President, Clinical Research Liver Disease Therapeutics
John Flaherty, PharmD, Project Lead/Director, Clinical Research
Neby Bekele, PhD, Senior Director, Biostatistics
Michael Miller, PhD, Senior Director, Virology

Adrian S. Ray, PhD, Principal Scientist, Drug Metabolism
Anne Chester, PhD, DABT, Senior Director, Drug Safety Evaluation
Mae J. Lai Director, Regulatory Affairs
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 meeting scheduled for June 17, 2013 from 10:30 AM to 12:00 PM, at White Oak Building 22; Room 1419 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. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

On July 30, 2012, Gilead submitted IND 115561, tenofovir alafenamide (TAF), an oral prodrug of tenofovir (TFV) that has longer plasma half-life compared to TFV for the treatment of hepatitis B virus (HBV) infection. This original IND was opened with Phase 1 Study GS-US-320-0101 entitled "A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment- Naive Adults with Chronic Hepatitis B (CHB) Infection". TAF is currently being studied under IND 63737 for the treatment of HIV-1 infection. In addition, there are two combination INDs consisting of TAF; IND 111007 (elvitegravir/cobicistat/emtricitabine/TAF) and IND 111851 (emtricitabine/TAF) both for the treatment of HIV-1 infection. There are 8 Phase 1/2 and Phase 2 clinical trials of TAF that have been completed or are currently ongoing. In advance of the meeting briefing package, Gilead submitted two Phase 3 studies (one each in HBeAg-positive and HBeAg-negative subjects) have been submitted to IND 115561 for review.

- GS-US-320-0108 entitled “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B”
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The purpose of this EOP2 meeting is to discuss whether the two proposed Phase 3 studies will support the New Drug Application (NDA) registration of TAF for the treatment of chronic hepatitis B infection in treatment-naïve and treatment-experienced patients. In addition, Gilead would like to seek the Division’s feedback on whether the completed nonclinical toxicology studies are adequate to support the registration of TAF for the proposed indication. Lastly, Gilead would like to discuss the use of viral suppression (HBV DNA <69 IU/mL) as the primary endpoint at Week 48 for the two Phase 3 noninferiority studies comparing TAF to TDF.

DISCUSSION

Question 1: TAF HBV Registration Plan

- 1a. Does the Agency agree that HBV DNA suppression (<69 IU/mL at Week 48) is acceptable as the primary endpoint to support registration of TAF for the treatment of chronic hepatitis B infection?**

There are unique aspects of the development of tenofovir alafenamide fumarate (TAF) as treatment of chronic hepatitis B infection that must be acknowledged in our reply. From a regulatory perspective, HBV DNA suppression alone does not meet the criteria as a validated surrogate endpoint and may not be adequate as the sole primary endpoint to support registration of a new molecular entity for HBV treatment. Historically, a histologic endpoint has served as a co-primary but we understand that histologic endpoints may no longer be acceptable to the research community. TAF and its comparator tenofovir disoproxil fumarate (TDF, Viread) are both prodrugs producing the same intracellular active metabolite, tenofovir diphosphate. In this situation, the amount of viral suppression should correspond to the amount of tenofovir diphosphate delivered to its target cells and the degree of histologic improvement. Because the active moiety is shared, it might be possible to support non-inferiority of TAF compared with TDF based upon comparison of HBV DNA suppression.

However, HBV DNA suppression as a primary endpoint for comparison of these two agents should be evaluated as rigorously as possible. First, lower limit of quantification of HBV DNA should be utilized as the primary measure (< 29 IU/mL at Week 48). Secondary efficacy endpoints should be robust, widely acknowledged as supportive of efficacy, and based on precedent from earlier HBV treatment approvals. Endpoints such as normalization of ALT or HBeAg or HBsAg seroconversion are suitable. The

secondary efficacy endpoints you have proposed in both studies evaluate bone mineral density loss and renal injury of TAF relative to TDF. These expected imaging/laboratory findings are more appropriately considered safety endpoints. Lastly, demonstration of durability of virologic suppression for at least 96 weeks or longer is appropriate in supporting the validity of HBV DNA suppression as a sole primary endpoint in this unique situation.

1b. Does the Agency agree that the noninferiority studies GS-US-320-0108 and GS-US-320-0110, that compare TAF 25 mg to TDF 300 mg in HBeAg-negative and HBeAg-positive subjects, respectively, are adequately designed to support registration of TAF for the treatment of chronic hepatitis B infection?

Studies GS-US-320-0108 and GS-US-320-0110 are appropriately designed Phase 3 studies. The determination of non-inferiority and approval of TAF for the treatment of chronic hepatitis B will be review issues. Please provide a more detailed justification for a non-inferiority margin based on an endpoint of HBV DNA < 29 IU/mL and a clinical margin (M2) that reflects a clinically tolerable amount of potential treatment effect loss (in terms of HBV DNA suppression) of TAF compared to TDF.

1c. Is the proposal to include both treatment-naïve and nucleos(t)ide-experienced (e.g. lamivudine, adefovir, entecavir) subjects with CHB in the Phase 3 studies appropriate to obtain a labeled indication for TAF for the treatment of chronic HBV infection in these populations?

We disagree with enrolling subjects who are well controlled on nucleos(t)ides (lamivudine, adefovir, entecavir) in these Phase 3 studies to support an indication for TAF in treatment experienced. Please confirm that you are not planning this to be a “switch study.” In our view, “treatment experienced” describes individuals whose anti-HBV treatment regimen is failing because of viral resistance or drug tolerability issues. If you desire a labeled indication for TAF for the treatment of chronic hepatitis B infection in “treatment experienced” patients, it is essential that you include a sufficient number of subjects in the proposed Phase 3 studies with resistance to current or prior NRTI treatment (baseline virus with detectable rt substitutions associated with NRTI resistance by the INNO-LiPA HBV Multi-DR assay and/or population based genotypic analysis). Care should be taken to ensure that such patients are enrolled with balanced allocation to both TAF and TDF.

Question 2: Nonclinical Safety Program

2. Does the Agency agree that the toxicology program will support the registration of TAF for use in CHB subjects?

Yes, the toxicology program appears to support the registration of TAF for CHB subjects. If *in vivo* metabolism data in the dog are available that measure the levels of Metabolite X, alaninyl TFV and Metabolite Y, isopropylalaninyl TFV, please provide a comparison

of these metabolites in the dog and human. This information can be provided in the NDA submission.

Additional Clinical Comments:

1. As differences in the clinical safety profile between TAF and TDF may be subtle, we strongly recommend you continue the double blinded portion of Studies GS-US-320-0108 and GS-US-320-0110 for at least 96 weeks. This should permit further delineation of the potential bone and renal advantages, if any, of TAF compared to TDF.
2. Please confirm that the ALT values of 60 U/L for males and 38 U/L for females in your central laboratory correspond to the 2x ULN for ALT as specified by the AASLD guidelines or if not, please explain their derivation.

Additional Clinical Virology Comments:

3. In addition to genotypic resistance testing, perform phenotypic resistance testing for (1) viruses that harbor treatment-emergent amino acid substitutions at conserved sites of the HBV rt or at polymorphic sites if the change was observed in more than one subject and (2) viruses from subjects experiencing on-treatment virologic rebound regardless of genotypic changes in the proposed Phase 3 studies.
4. All HBV genotypes commonly found in the US should be well represented in the proposed study subject populations.
5. We recommend using “<29 IU/mL, target detected” or “<29 IU/mL, target not detected” for subjects with HBV DNA <29 IU/mL at Weeks 48, 96, and 144. Please evaluate the proportion of subjects with HBV DNA <29 IU/mL, target not detected at Week 48 as a secondary efficacy endpoint.
6. Please provide the median change (Min, Max) in HBV DNA at Day 28 from Baseline by HBV genotype in subjects who received TAF in Study GS-US-320-0101.

Additional Clinical Pharmacology Comment:

7. CES1, the enzyme responsible for conversion of TAF to TFV in hepatocytes, is polymorphic; several nonsynonymous genetic variants (e.g. G143E and D260fs) have been associated with reduced enzymatic function. Please characterize the potential for these variants to influence the rate and extent of TAF hydrolysis in vitro.

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- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, 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>

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/s/

STACEY MIN
06/13/2013