

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203093Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203093/Original Submission

SUPPL # 0

HFD #: 530

Trade Name: VITEKTA®

Generic Name: elvitegravir

Applicant Name: Gilead Science, Inc.

Approval Date, If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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# 203,100

STRIBILD (elvitegravir/ cobicistat/ emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) Fixed-Dose Combination 150 mg/150 mg/200 mg/300mg)

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

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:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations

submitted in the application that are essential to the approval:

Study GS-US-183-0145 entitled – “A Multicenter, Randomized, Double-Blind, Double Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) versus Raltegravir (RAL) Each Administered with a background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults”

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

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study GS-US-183-0145 entitled – “A Multicenter, Randomized, Double-Blind, Double Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) versus Raltegravir (RAL) Each Administered with a background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults”

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

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

Investigation #1
IND # 72,177 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO

Explain:

! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Myung-Joo Patricia Hong, M.S.
Title: Regulatory Project Manager
Date: September 5, 2014

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

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

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

/s/

MYUNG JOO P HONG
09/09/2014

JEFFREY S MURRAY
09/10/2014

Debarment Certification

Gilead Sciences, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 203-093, EVG tablets).

[See appended electronic signature]

Andrew Cheng, MD, PhD
SVP, HIV Therapeutics & Development Operations
Gilead Sciences, Inc.

1.3.3 Debarment Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd hh:mm)
Andrew Cheng	Clinical eSigned	2012-01-04 10:20

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203093 Original Submission	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: VITEKTA [®] Established/Proper Name: elvitegravir Dosage Form: 85 and 150 mg Tablets		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)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____ <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 4, 2014</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> 	<ul style="list-style-type: none"> Complete Response - 4/26/2013 Approval - 9/24/2014 	
❖ 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	

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, (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).

❖ Application Characteristics ³	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <i>(confirm chemical classification at time of approval)</i></p> <p> <input checked="" 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 </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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 checked="" type="checkbox"/> Yes <input 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.

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

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> Copies of all action letters (<i>including approval letter with final labeling</i>) 	<ul style="list-style-type: none"> Complete Response - 4/26/2013 Approval - 9/24/2014
Labeling	
<ul style="list-style-type: none"> ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) <ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included <input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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>) <ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) Original applicant-proposed labeling 	<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 <input checked="" type="checkbox"/> Included <input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) <ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	<ul style="list-style-type: none"> Grant Letter - 9/20/12 & 6/14/14 Reviews - 9/20/12, 3/13/13 & 6/11/14
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews</i>) 	<input checked="" type="checkbox"/> RPM - PLR Format Review - <ul style="list-style-type: none"> 8/7/12 (Original Submission) <input checked="" type="checkbox"/> DMEPA <ul style="list-style-type: none"> 3/1/13 (Original Submission) 7/14/14 (Re-submission) <input checked="" type="checkbox"/> DMPP/PLT (DRISK) <ul style="list-style-type: none"> 4/12/13 (Original Submission) 9/9/14 (Re-submission) <input checked="" type="checkbox"/> ODPD (DDMAC) <ul style="list-style-type: none"> 4/15/13 (Original Submission) 9/11/14 (Re-submission) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other

Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee 	RPM Filing Review - 8/17/12 <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (approvals only) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>April 3, 2013</u> If PeRC review not necessary, explain: _____ 	
<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) (do not include previous action letters, as these are located elsewhere in package) 	6/27/12, 7/3/12, 9/6/12, 9/27/12, 10/10/12, 11/5/12, 11/29/12, 12/12/12, 12/13/12, 1/18/13, 1/22/13, 2/4/12, 2/7/13, 2/13/13, 2/26/13, 2/27/13, 3/15/13, 3/19/13, 4/5/13 (x2), 4/16/13, 4/19/13, 9/17/13, 12/17/13, 1/16/14 (Preliminary Comments), 3/24/14, (b)(4) 4/14/14, 4/17/14, 4/30/14, 8/19/14, 9/9/14, 9/12/14, 9/19/14
<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) 	<ul style="list-style-type: none"> • April 26, 2013 - Informal T-con with Gilead to inform Complete Response Action - Internal meeting minutes included (4/30/13)
<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 (indicate date of mtg) • Pre-NDA/BLA meeting (indicate date of mtg) • EOP2 meeting (indicate date of mtg) 	No meeting <ul style="list-style-type: none"> • March 5, 2012 - Pre-NDA was scheduled under IND 72,177; however, Gilead cancelled after receiving FDA's preliminary comments (3/1/12) - preliminary comments included • March 12, 2010 - EOP 2 meeting held for IND 101,283 (cobcicstat) - Some discussion of EVG are included in the minutes - minutes included (4/9/10) • No EOP 2 meeting held for IND 72,177

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

• Mid-cycle Communication (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	<ul style="list-style-type: none"> • January 13, 2009 - Type C meeting was scheduled to discuss the integrated development plan for STRIBILD, elvitegravir (EVG), and cobicistat (COBI); however; Gilead cancelled after receiving FDA's preliminary comments (1/13/2009) - preliminary comments included • January 22, 2014 - Type A meeting was scheduled to discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta[®] (elvitegravir) tablets and Tybost[®] (cobicistat) tablets - minutes included (2/11/14)
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
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>)	<ul style="list-style-type: none"> • Complete Response - 4/26/2013 • Approval - 9/19/2014 (Comment Included in CDTL Review)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<ul style="list-style-type: none"> • Contingent Approval - pending resolution of facility inspections - 4/5/2013 • Approval - 9/19/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	PMR Template (1)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Please see CDTL Review
• Clinical review(s) (<i>indicate date for each review</i>)	<ul style="list-style-type: none"> • Filing Review - 8/21/2012 • Approval (OS) - 3/22/2013 • Approval (re-submission) - 9/4/14
• 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 the clinical review dated 3/22/13 (located in Section 3.3, page 11 - 12)

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> 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>)	<ul style="list-style-type: none"> Inspection Review - 2/26/2013 OSI Letters - 12/5/2012 & 2/27/2013 (x2)
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>)	<ul style="list-style-type: none"> Filing Review - 8/13/2012 Approval - 3/20/2013 Memorandum for re-submission - 7/28/2014
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>)	<ul style="list-style-type: none"> Filing Review - 9/6/2012 Approval - 3/22/2013
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>)	<ul style="list-style-type: none"> Filing Review - 8/14/2012 Approval - 4/1/2013
❖ 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	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<ul style="list-style-type: none"> Filing Review - 8/15/2012 Approval - 2/15/2013
❖ 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	
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<ul style="list-style-type: none"> • Filing Review - 8/29/12 • Memorandum - 9/25/2012 • Product Quality (Biopharmaceutics): Approval - 3/21/13 • Product Quality (DS & DP): Pending an overall acceptable facilities recommendation - 3/21/13 • Product Quality (DS & DP): Addendum for disapproval - 4/26/13 • Memorandum for re-submission - 5/1/14 • Product Quality (DS & DP): Approval - 9/5/14
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <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 Product Quality Review (Page 77) - 3/21/2013
<input 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>	3/21/2013

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable - EER Summary Report included (EER Detailed Report included in Product Quality Review - 9/4/14) <input checked="" type="checkbox"/> Withhold recommendation (4/25/13) <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)
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
❖ 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 checked="" 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

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

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

/s/

MYUNG JOO P HONG
09/25/2014



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

DATE: September 9, 2014
NDA: 203093/Original Submission
TO: Christophe Beraud, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Gilead Science, Inc.
SUBJECT: PMR Comment

Please refer to your June 27, 2012 and April 4, 2014 submissions submitted to NDA 203093. The DAVP is proposing the following postmarketing requirement (PMR). Please provide your response to this request by **September 12, 2014**.

PREA PMR

Because Vitekta[®] represents the approval of a new formulation and a new dosing regimen, pediatric studies will be required under the provisions of the Pediatric Research Equity Act (PREA).

Evaluate the pediatric pharmacokinetics (PK), safety, and antiviral activity of once daily elvitegravir combined with a background regimen including a protease inhibitor coadministered with ritonavir in HIV-1 treatment-experienced pediatric subjects from 4 weeks to less than 18 years of age. Initial evaluation of elvitegravir exposure (when combined with a protease inhibitor and ritonavir) must be performed to allow dose selection to be agreed upon with the FDA. Evaluation of longer term treatment with elvitegravir, plus background regimen including protease inhibitor and ritonavir, must assess treatment response on the basis of HIV-1 RNA virologic response and conduct safety monitoring over at least 24 weeks of dosing.

Protocol Submission: submitted
Trial Completion: October 31, 2016
Final Report Submission: January 15, 2018

Please confirm your acceptance for the proposed timelines for the PREA PMR. 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. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** 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.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

MYUNG JOO P HONG
09/09/2014



NDA 203093

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Christophe Beraud, Ph.D.
Director, Regulatory Affairs

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated and received June 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir Tablets, 85 mg/150 mg.

We also refer to:

- Your correspondence dated September 13, 2012, received September 14, 2012, requesting review of the proposed proprietary name, "Vitekta"
- Our letter dated September 20, 2012, stating that your proposed proprietary name was conditionally acceptable
- Our Complete Response Action Letter dated April 26, 2013
- Your NDA Resubmission dated and received April 4, 2014

Finally, we refer to your correspondence dated and received April 9, 2014, requesting review of your proposed proprietary name, Vitekta. We have completed our review of the proposed proprietary name Vitekta, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your April 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact 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}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

AZEEM D CHAUDHRY
06/13/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
06/14/2014

From: Hong, Myung-Joo P.
To: [Prerna Menon \(Prerna.Menon@gilead.com\)](mailto:Prerna.Menon@gilead.com)
Subject: NDA 203093.EVG.Information Request
Date: Wednesday, April 30, 2014 1:16:00 PM

Dear Prerna, the clinical reviewer is reviewing the safety update report included in the March 26, 2014 submission and we have the following questions, comments and requests for additional information:

- Do the numbers in the “Original NDA” column in the Resubmission Safety Update document include the 120-day safety update information submitted in October 2012?
- Is there a mechanism to determine which narratives pertain to events that occurred since the original NDA submission, including the 120-day safety update? The narratives provided in module 5.3.5.3 appear to contain events to date, rather than those which occurred during the resubmission safety update period between the original NDA/120-day safety update and the resubmission. If no mechanism exists as submitted, please provide the patient ID numbers for the new deaths, treatment-emergent SAEs, and AEs leading to discontinuation not included in the original NDA or 120-day safety update in the ETV groups for Studies GS-US-183-0145 and GS-US-183-0130.

Please submit your response by May 14, 2014.

*Best Regards,
Pat*

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

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

/s/

MYUNG JOO P HONG
04/30/2014



NDA 203093

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Gilead Sciences, Incorporated
Attention: Perna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

We acknowledge receipt on April 4, 2014, of your April 4, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VITEKA[®] (elvitegravir) tablets, 85 and 150 mg.

We consider this a complete, class 2 response to our April 26, 2013 action letter. Therefore, the user fee goal date is October 4, 2014.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

MYUNG JOO P HONG
04/17/2014



NDA 203093

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Prerna Menon, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Menon:

Please refer to your New Drug Application (NDA) dated and received June 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir, Tablets, 150 mg/85 mg.

We also refer to:

- Your correspondence dated September 13, 2012, received September 14, 2012, requesting review of the proposed proprietary name, "Vitekta"
- Our Proprietary Name Conditionally Acceptable letter to Gilead Sciences, Inc. sent September 20, 2012
- Our Complete Response letter dated April 26, 2013
- Your NDA Resubmission dated and received April 4, 2014

Finally, we refer to your correspondence dated and received April 9, 2014, requesting a review of your proposed proprietary name, Vitekta. Upon preliminary review of your submission, we have determined that it is a complete submission as described in our Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

Therefore, the user fee goal date is July 8, 2014.

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

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

AZEEM D CHAUDHRY
04/14/2014

From: Hong, Myung-Joo P.
To: [Perna Menon \(Perna.Menon@gilead.com\)](mailto:Perna.Menon@gilead.com); "[Christophe Beraud](#)"
Subject: NDA 203093 & 203094.Advices
Date: Monday, March 24, 2014 12:05:00 PM

Dear Perna and Christophe, we have the following comment/request for EVG and COBI's Re-Submission:

"In NDA 205834 for Ledipasvir and Sofosbuvir tablets, where developmental methods were used in the batch analysis of ledipasvir drug substance, the specific methods were identified (Table 7 in S.4.4). Additionally, those methods and validation results were described in the NDA (S.7.3) together with bridging studies where appropriate. This approach could be very useful when the Cobicistat and Elvitegravir NDAs are resubmitted. It could also be useful to include in those resubmissions a summary of what was done as part of the supplemental validation listed for some methods in Gilead's February 21, 2014 letter."

Best Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA/CDER/OAP/DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
03/24/2014



NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

MEETING MINUTES

Gilead Sciences, Incorporated
Attention: Prerna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitekta[®] (elvitegravir) tablets, 85 and 150 mg, and Tybost[®] (cobicistat) tablets, 150 mg.

We also refer to the teleconference between representatives of your firm and the FDA on January 22, 2014. The purpose of the teleconference was to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta[®] (elvitegravir) tablets and Tybost[®] (cobicistat) tablets.

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 Myung-Joo Patricia Hong, Regulatory Project Manager at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Other

Meeting Date and Time: January 22, 2014, 1 – 2 PM
Meeting Location: Teleconference

Application Number: NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

Product Name: Vitekta[®] (elvitegravir) and Tybost[®] (cobicistat)

Indication: Vitekta[®] (elvitegravir) for the treatment of HIV-1 infection and Tybost[®] (cobicistat) as a CYP3A inhibitor to increase systemic exposures of the HIV-1 protease inhibitors atazanavir and darunavir

Sponsor/Applicant Name: Gilead Sciences, Inc.

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

FDA ATTENDEES

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Linda Lewis, M.D., Clinical Team Leader, Division of Antiviral Products
Kimberly Struble, PharmD, Clinical Team Leader, Division of Antiviral Products
Peter Miele, M.D., M.P.H., Clinical Reviewer, Division of Antiviral Products
Russell Fleischer, MPH, PA-C, Clinical Reviewer, Division of Antiviral Products
Sarita Boyd, Pharm.D., Clinical Reviewer, Division of Antiviral Product
Peyton Myers, Ph.D., Nonclinical Reviewer, Division of Antiviral Products
Takashi Komatsu, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
Shirley Seo, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4
Islam Younis, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
Rapti Madurawe, Ph.D., Product Branch Chief, DNDQA II
Stephen Miller, Ph.D., Product Team Leader, DNDQA II
Mahesh Ramanadham, Compliance Officer, OMPQ/DGMPA

Krishna Ghosh, Ph.D., Compliance Officer, OMPQ/DGMPA
Elizabeth Thompson, M.S., Chief Project Management Staff, Division of Antiviral Products
Karen Winestock, Chief Project Management Staff, Division of Antiviral Products
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager, Division of Antiviral Products

SPONSOR ATTENDEES

Reza Oliyai, Ph.D., VP, Formulation and Process Development
Taiyin Yang, Ph.D., SVP, Pharmaceutical Development and Manufacturing
Tammis Matzinger, VP, Quality Assurance
Gary Visor, Ph.D., VP, Analytical Operations
Javier Szwarcberg, M.D., MPH., Senior Director, Clinical Research
Joseph Custodio, Ph.D, Clinical Pharmacologist II, Clinical Pharmacology
Naomi Kautz, M.Sc., Sr. Manager, Regulatory Affairs

BACKGROUND

Gilead is developing Vitekta[®] (elvitegravir, EVG) tablets and Tybost[®] tablets (cobicistat, COBI). Vitekta[®] and Tybost[®] are part of Stribild[®] (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) single tablet regimen for the treatment of HIV-1 infection.

Vitekta[®] (EVG), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, coadministered with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Tybost[®] (COBI) is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir (Original 1) and darunavir (Original 2) in the treatment of HIV-1 infection in adults.

The New Drug Applications for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094) were received on June 27 and 28, 2012, respectively. On April 15, 2013, DAVP requested that the NDA 203094 be separated into NDA 203094/Original 1 (indication of Tybost[®] as a pharmacoenhancer of atazanavir) and NDA 203094/Original 2 (indication of Tybost[®] as a pharmacoenhancer of darunavir). On April 26, 2014, Complete Response Letters for both products were issued due to the results of facility inspection findings at Gilead Sciences, Inc. located in Foster City, CA.

This Type A meeting was scheduled to discuss Gilead's proposal to address the comments in the Complete Response letters for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094/Original 1 and Original 2). Gilead Sciences sought agreement on:

- Gilead's proposal to address the deficiencies identified in facility inspections of the Gilead Foster City facility.

- Adequacy of data submitted in the responses to San Francisco District Office to address the deficiencies identified for product quality for NDA 203093 and NDA 203094.
- Adequacy of the data provided to address the clinical pharmacology items in the Complete Response Letter for NDA 203094/Original 2.
- The indication for Tybost[®] (cobicistat) tablets can be expanded to include the use with darunavir in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined to NDA 203094.

The proposed resubmission for both products is targeted for March, 2014.

1.0 DISCUSSION

On January 16, 2014 the Division of Antiviral Products (DAVP) sent preliminary responses to questions the sponsor submitted in the meeting briefing package via electronic mail. After reviewing the Division's responses, Gilead decided to limit the meeting's discussion to Question 1 (Facility Inspections and Product Quality). Gilead provided slides in advance of the teleconference.

Gilead's questions are in **bold**, DAVP's preliminary responses are in *italicized font*; and the meeting discussions are in standard font.

1.1 Facility Inspections and Product Quality

Q 1: Gilead intends to include the method validation and bridging study reports for those analytical methods used during clinical development for release and stability testing of elvitegravir and cobicistat on (b) (4) drug substances and Vitekta and Tybost drug products in DMF 25187, DMF 25188, NDA 203093 and NDA 203094, respectively. Does the Agency agree that the integrity of the drug substance and drug product release and stability data has been demonstrated and that the Quality issues identified in the Complete Response letters have been addressed satisfactorily so that Gilead may proceed with resubmission of the NDAs for Vitekta Tablets and Tybost Tablets?

The integrity of the data associated with the analytical method validation and method comparability studies appears to be adequate; however, the final determination can only be made during the review of the application. The integrity of this data will also be assessed during an on-site inspection. The most recent inspection of the Gilead Foster City site remains under review and the final status will be communicated through the San Francisco district office.

Additionally, we refer to the teleconference held between CDER and Gilead on October 29, 2013 in which Gilead stated its intent to contract a third party expert to assist in the evaluation of the stability and testing program at Gilead Foster City. We request the current status of these efforts and clarification if the data used to support elvitegravir and cobicistat have undergone this evaluation.

Discussion: The discussion began with a presentation by Gilead.

Gilead presented the status of the third party (b) (4) expert evaluation of the stability and testing program and data at the Gilead Sciences, Foster City site. The main points from the presentation were: 1) Gilead has retained (b) (4) to assist in the evaluation of the 483 deficiencies and Gilead's corrective action plans to address issues identified by FDA during past inspections, as well as improvement plans for the stability and testing program at the Foster City site; 2) (b) (4) experts conducted independent audits of the analytical data generated at Gilead Foster City submitted in recent NDAs, including IDELA (idelalisib) (filed Sept 2013) and the upcoming NDA for sofosbuvir/ledipasvir (SOF /LDV) (1st Q2014 NDA filing planned) (see Attachment 1, slides 3 and 4 for (b) (4) assessment of the data submitted to support these two NDAs); and 3) the third party expert assessments will continue for future Gilead NDAs. Gilead plans to conduct similar audits for the analytical data that will support the resubmission of Vitekta and Tybost NDAs.

FDA inquired whether the Gilead Foster City site will be included as a testing site for resubmission of Vitekta and Tybost NDAs and whether the (b) (4) audit reports and certification will be provided for the analytical data sets generated at the site. Gilead stated that the most recent inspection was completed in October, 2013 and they plan to include data from the (b) (4) audit in the resubmission of the Vitekta and Tybost NDAs, along with updated stability data. The certificates of the integrity of the analytical data generated at the Gilead Foster City site have been drafted and will be included in the resubmission of the Vitekta and Tybost NDAs. FDA informed Gilead that an internal review of the October 2013 inspection is on-going.

FDA emphasized that for the resubmissions, clear delineation should be made between analytical data generated at the Gilead Foster City site and analytical data generated by third-party contract laboratories.

FDA inquired about development methods and final methods/commercial methods and asked if Gilead had conducted any bridging studies between methods. Gilead responded that they had conducted a bridging study and submitted the results in response to the 483 observations. FDA stated that Gilead should include a reference guide to the batch analysis data and the linkage to the different methods (development methods versus final methods/commercial methods) with supportive validation and bridging data. Gilead stated it will include certifications and assessment results in the resubmission of Vitekta and Tybost NDAs.

FDA stated that Gilead had submitted this information early in the sofosbuvir development process, which provided FDA with a reasonable depth of evaluation. It would be helpful for all three applications (EVG, COBI, and SOF/LDV) to submit information about data generated using developmental methods.

FDA asked Gilead to clarify the role of the Foster City site in the resubmission of the two NDAs. FDA noted that the initial data for Vitekta and Tybost were generated at the Foster City site and asked about data generated at other sites. Gilead stated the Foster City site is a key site for drug development methodology and that quality control (QC) release testing at the site had been re-qualified. For upcoming applications, Gilead plans to use alternative facilities for commercial testing. For IDELA, (b) (4) will be used as a commercial testing site and (b) (4) is a contract laboratory for other projects. Gilead offered to submit a list of contractors. Gilead noted that there are redundancies for commercial analytical testing facilities for all three NDAs (COBI, EVG, and SOS/LDV) and its general qualification strategy includes multiple manufacturing sites and multiple contract testing laboratories along with the Foster City site. FDA asked Gilead to submit any redundancies in testing facilities. Gilead agreed to submit the requested information with the upcoming NDA and resubmission of the Vitekta and Tybost NDAs.

1.2 Clinical Pharmacology for NDA 203094/Original 2 (Tybost)

Q2: Does the Agency agree that the clinical pharmacology information provided in the Meeting Information Package adequately addresses the 483 observations at the (b) (4) laboratories so that Gilead could proceed with resubmission of NDA 203094?

Plases see our response below for Q2 and Q3.

Q3: Does the Agency agree that the indication of COBI can be expanded to include increase in systemic exposure of darunavir (DRV) in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined into a single NDA 203094?

Overall, the clinical pharmacology information included in the meeting package to address the 483 observations from the inspections of the (b) (4) bioanalytical laboratories is sufficient to proceed with the resubmission of NDA 203094.

There is only one NDA for cobicistat, NDA 203094. However, the NDA has two original submissions. To reactivate the review clock for NDA 203094 Original 1 and Original 2, you will need to submit a resubmission to both. This can be accomplished by submitting all of the data to Original 2 and a cross reference letter, all required administrative forms, and SPL labeling to Original 1. The labeling (package insert and Patient

Information) for atazanavir/cobicistat and darunavir/cobicistat should be merged and submitted to both submissions.

Discussion: The sponsor accepted DAVP's response; no discussion occurred.

The following comments were included in our preliminary responses:

- 1. In the darunavir/ritonavir method validation report (Amendment 1), the retest date for the certificate of analysis for the cobicistat reference standard was (b) (4). However, the analytical experiments for Amendment 1 were conducted up through (b) (4). Please specify whether the cobicistat reference standard with a retest date of (b) (4) was recertified and, if the reference standard was recertified, please provide the updated certificate of analysis. If the reference standard was not recertified, please provide information to support the acceptability of the stability results for darunavir combined with cobicistat from runs 9 to 10 that were conducted after (b) (4).*
- 2. In Table 2 of the meeting package, please clarify how the data from run #22 for Subject 2029 was handled. Was the pre-dose concentration from Period 1 excluded or assigned a value of below the limit of quantification (BLQ)?*
- 3. Please provide further information regarding the storage conditions for the darunavir and ritonavir plasma samples at (b) (4). Specifically, were the plasma samples that were analyzed for darunavir and ritonavir concentrations stored at -20°C or at -70°C?*
- 4. Please specify whether QCs or calibration standards prepared on the day of the stability assessment (4 freeze thaw cycles or Day 54 for the long term stability assessments) were included as part of runs 9 and 10 that were conducted as part of the darunavir/ritonavir method validation (Amendment 1).*
- 5. As part of the resubmission for NDA 203094, please submit both the original and the revised pharmacokinetic datasets that were used in deriving Table 1 and Table 2 of the meeting package in SAS transport (.xpt) format and include information that outlines the differences between the two datasets.*
- 6. DAVP recommends that you conduct a relative bioavailability study to compare elvitegravir exposures following administration of elvitegravir and cobicistat as single entities versus administration of elvitegravir and cobicistat as components of the Stribild[®] fixed-dose combination tablet. The results of this study would support an indication for elvitegravir in combination with cobicistat as single entities plus two NRTIs in HIV-1 infected treatment-naïve patients and permit administration of elvitegravir to patients who are unable to take Stribild[®] (e.g., patients with creatinine clearance below 50 mL/min).*

Discussion: The sponsor accepted DAVP's comments; no discussion occurred.

2.0 ADDITIONAL POST-MEETING COMMENTS

- Comprehensive third party audit reports are not required in the resubmission of these NDAs. Copies of the third party audit reports can be communicated to the district office, who will then communicate with CDER as needed.
- FDA requests that Gilead confirm that the (b) (4) review of data relevant to the three applications will be completed before each application is submitted (SOF/LDV) or resubmitted (COBI or EVG).

3.0 ATTACHMENTS AND HANDOUTS

- Copy of Gilead's presentation slides

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

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

/s/

DEBRA B BIRNKRANT
02/11/2014



NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Incorporated
Attention: Perna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitekta[®] (elvitegravir) tablets, 85 and 150 mg and Tybost[®] (cobicistat) tablets, 150 mg.

We also refer to your December 13, 2013, correspondence requesting a meeting to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta[®] (elvitegravir) tablets and Tybost[®] (cobicistat) tablets.

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) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
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: Type A
Meeting Category: Other

Meeting Date and Time: January 22, 2014, 1 – 2 PM
Meeting Location: WO Bldg 22, Room 1315

Application Number: NDA 203-093
NDA 203-094/Original 1
NDA 203-094/Original 2

Product Name: Vitekta[®] (elvitegravir) and Tybost[®] (cobicistat)

Indication: Vitekta[®] (elvitegravir) for the treatment of HIV-1 infection and Tybost[®] (cobicistat) as a CYP3A inhibitor to increase systemic exposures of the HIV-1 protease inhibitors atazanavir and darunavir

Sponsor/Applicant Name: Gilead Science, 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 January 22, 2014, 1 - 2 PM, WO Bldg 22, Room 1315 between Gilead Sciences, Inc. and the Division of Antiviral Products (DAVP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gilead is developing Vitekta[®] (elvitegravir, EVG) tablets and Tybost[®] tablets (cobicistat, COBI). Vitekta[®] and Tybost[®] are part of Stribild[®] (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) single tablet regimen for the treatment of HIV-1 infection.

Vitekta[®] (EVG), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Tybost[®] (COBI) is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir (Original 1) and darunavir (Original 2) in the treatment of HIV-1 infection in adults.

The New Drug Applications for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094) were received on June 27 and 28, 2012, respectively. On April 15, 2013, DAVP requested that the NDA 203094 be separated into NDA 203094/Original 1 (indication of Tybost[®] as a pharmacoenhancer of atazanavir) and NDA 203094/Original 2 (indication of Tybost[®] as a pharmacoenhancer of darunavir). On April 26, 2014, Complete Response Letters for both products were issued due to the results of facility inspection findings in Gilead Sciences, Inc. located in Foster City, CA.

This Type A meeting was scheduled to present and discuss Gilead's proposal to address the comments in the Complete Response letters for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094/Original 1 and Original 2). Gilead Sciences seeks agreement on:

- Gilead's proposal to address the deficiencies identified in facility inspections of the Gilead Foster City facility.
- Adequacy of data submitted in the responses to San Francisco District Office to address the deficiencies identified for product quality for NDA 203093 and NDA 203094.
- Adequacy of the data provided to address the clinical pharmacology items in the Complete Response Letter for NDA 203094/Original 2.
- The indication for Tybost[®] (cobicistat) tablets can be expanded to include the use with darunavir in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined to NDA 203094.

2.0 DISCUSSION

Gilead's questions are in bold italics and DAVP comments are in standard font.

2.1 Facility Inspections and Product Quality

Q 1: Gilead intends to include the method validation and bridging study reports for those analytical methods used during clinical development for release and stability testing of elvitegravir and cobicistat on [REDACTED] (b) (4) drug substances and Vitekta and Tybost drug products in DMF 25187, DMF 25188, NDA 203093 and NDA 203094, respectively. Does the Agency agree that the integrity of the drug substance and drug product release and stability data has been demonstrated and that the Quality issues identified in the Complete Response letters have been addressed satisfactorily so that Gilead may proceed with resubmission of the NDAs for Vitekta Tablets and Tybost Tablets?

The integrity of the data associated with the analytical method validation and method comparability studies appears to be adequate; however, the final determination can only be made during the review of the application. The integrity of this data will also be assessed during an on-site inspection. The most recent inspection of the Gilead Foster City site remains under review and the final status will be communicated through the San Francisco district office.

Additionally, we refer to the teleconference held between CDER and Gilead on October 29th, 2013 in which Gilead stated its intent to contract a third party expert to assist in the evaluation of the stability and testing program at Gilead Foster City. We request the current status of these efforts and clarification if the data used to support elvitegravir and cobicistat have undergone this evaluation.

2.2 Clinical Pharmacology for NDA 203094/Original 2 (Tybost)

Q2: Does the Agency agree that the clinical pharmacology information provided in the Meeting Information Package adequately addresses the 483 observations at the [REDACTED] (b) (4) laboratories so that Gilead could proceed with resubmission of NDA 203094?

Please see our response below for Q2 and Q3.

Q3: Does the Agency agree that the indication of COBI can be expanded to include increase in systemic exposure of darunavir (DRV) in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined into a single NDA 203094?

Overall, the clinical pharmacology information included in the meeting package to address the 483 observations from the inspections of the (b) (4) and (b) (4) bioanalytical laboratories is sufficient to proceed with the resubmission of NDA 203094.

There is only one NDA for cobicistat, NDA 203094. However, the NDA has two original submissions. To reactivate the review clock for NDA 203094 Original 1 and Original 2, you will need to submit a resubmission to both. This can be accomplished by submitting all of the data to Original 2 and a cross reference letter, all required administrative forms, and SPL labeling to Original 1. The labeling (package insert and Patient information) for atazanavir/cobicistat and darunavir/cobicistat should be merged and submitted to both submissions.

We have the following additional comments:

1. In the darunavir/ritonavir method validation report (Amendment 1), the retest date for the certificate of analysis for the cobicistat reference standard was (b) (4). However, the analytical experiments for Amendment 1 were conducted up through (b) (4). Please specify whether the cobicistat reference standard with a retest date of (b) (4) was recertified and, if the reference standard was recertified, please provide the updated certificate of analysis. If the reference standard was not recertified, please provide information to support the acceptability of the stability results for darunavir combined with cobicistat from runs 9 to 10 that were conducted after (b) (4).
2. In Table 2 of the meeting package, please clarify how the data from run #22 for Subject 2029 was handled. Was the pre-dose concentration from Period 1 excluded or assigned a value of below the limit of quantification (BLQ)?
3. Please provide further information regarding the storage conditions for the darunavir and ritonavir plasma samples at (b) (4). Specifically, were the plasma samples that were analyzed for darunavir and ritonavir concentrations stored at -20°C or at -70°C?
4. Please specify whether QCs or calibration standards prepared on the day of the stability assessment (4 freeze thaw cycles or Day 54 for the long term stability assessments) were included as part of runs 9 and 10 that were conducted as part of the darunavir/ritonavir method validation (Amendment 1).
5. As part of the resubmission for NDA 203094, please submit both the original and the revised pharmacokinetic datasets that were used in deriving Table 1 and Table 2 of the meeting package in SAS transport (.xpt) format and include information that outlines the differences between the two datasets.
6. DAVP recommends that you conduct a relative bioavailability study to compare elvitegravir exposures following administration of elvitegravir and cobicistat as

single entities versus administration of elvitegravir and cobicistat as components of the Stribild[®] fixed-dose combination tablet. The results of this study would support an indication for elvitegravir in combination with cobicistat as single entities plus two NRTIs in HIV-1 infected treatment-naïve patients and permit administration of elvitegravir to patients who are unable to take Stribild[®] (e.g., patients with creatinine clearance below 50 mL/min).

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.

As your original Pediatric Plans for elvitegravir and cobicistat were submitted with the original NDAs, you may reference those plans in your resubmissions if no substantive changes are proposed. Please provide an update of any changes to the original Pediatric Plans including anticipated timelines.

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

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

/s/

MYUNG JOO P HONG
01/16/2014



NDA 203093

MEETING REQUEST GRANTED

Gilead Sciences, Incorporated
Attention: Perna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your New Drug Application (NDA) dated and received June 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitekta™ (elvitegravir) tablets, 85 and 150 mg.

We also refer to your December 13, 2013, correspondence requesting a meeting to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta™ tablets. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: January 22, 2014
Time: 1 - 2 PM Eastern Time
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Invited CDER participants:

Division of Antiviral Products

Debra Birnkrant, M.D., Division Director
Jeffrey Murray, M.D., Deputy Director
Kendall Marcus, M.D., Deputy Director for Safety
Linda Lewis, M.D., Clinical Team Leader
Kimberly Struble, Pharm.D., Clinical Team Leader
Russell Fleischer, M.P.H., PA-C., Clinical Reviewer
Peter Miele, M.D., Clinical Reviewer
Sarita Boyd, M.D., Clinical Reviewer

Julian O'Rear, Ph.D., Clinical Virology Team Leader
Sung Rhee, Ph.D., Clinical Virology Reviewer
Takashi Komatsu, Ph.D., Clinical Virology Reviewer
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Peyton Myers, Ph.D., Pharmacology/Toxicology Reviewer
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer
Beth Thompson, M.S., Chief Regulatory Project Management
Karen Winestock, Chief Regulatory Project Management
Myung-Joo Patricia Hong, M.S., Regulatory Project Management

Office of Clinical Pharmacology

Shirley Seo, Ph.D., Clinical Pharmacology Team Leader, Division of
Clinical Pharmacology 4
Islam Younis, Pharm.D., Clinical Pharmacology Team Leader,
Division of Clinical Pharmacology 4
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology 4
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology 4
Jeffrey Florian, Pharm.D., Pharmacometrics Team Leader, Division of
Clinical Pharmacology 4

Office of New Drug Quality Assessment

Rapti Madurawe, Ph.D., Product Branch Chief, DNDQA II
Stephen Miller, Ph.D., Product Team Leader, DNDQA II
Fugiang Liu, Ph.D., Product Reviewer, DNDQA II
Milton Sloan, Ph.D., Product Reviewer, DNDQA II
Karen Riviere, Ph.D., Biopharmaceutics Reviewer, DNDQA II
Deepika Arora Lakhani, Ph.D., Biopharmaceutics Reviewer, DNDQA III

Office of Compliance

Krishnakali Ghosh, Compliance Officer, OMPQ/DGMPA
Tara Gooen, Compliance Officer, OMPQ/DGMPA
Mahesh Ramanadham, Compliance Officer, OMPQ/DGMPA

Office of Biometrics

Greg Soon, Ph.D., Biometrics Team Leader, OB/DBIV
Yanming Yin, Ph.D., Biometrics Reviewer, OB/DBIV

Please e-mail me any updates to your attendees at myung-joo.hong@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-

U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Myung-Joo Patricia Hong at 301-796-0807; or Michael Stanfield at 301-796-1500.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	January 22, 2014: 1 PM
MEETING ENDING DATE AND TIME	January 22, 2014: 2 PM
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg 22, Room 1315
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Myung-Joo Patricia Hong Regulatory Project Manager WO Bldg 22, Room 6235 301-796-0807
ESCORT INFORMATION (If different from Hosting Official)	

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

/s/

MYUNG JOO P HONG
12/17/2013



MEMORANDUM OF FACSIMILE:

Date: September 17, 2013

NDA: 203094
203093

Drug: TYBOST (cobicistat)
VITEKTA (elvitegravir)

To: Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs
Perena Menon, Ph.D., Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Stacey Min, Pharm.D., Senior Regulatory Project Manager and
Pat Hong, M.S., Senior Regulatory Project Manager

Subject: NDA 203094 and NDA 203093 Comments on Proposed Safety
Update for Resubmission

Please refer to your NDA 203094 for TYBOST (cobicistat) and NDA 203093 for VITEKTA (elvitegravir). We also refer to your August 13, 2013 submission to both the NDAs requesting feedback on your proposed safety update for your resubmission for cobicistat and elvitegravir. We have reviewed your submission agree that your proposal is acceptable if you follow the same format as the original Safety Update, including a summary of new data since the original NDA submission. Please confirm that the trials being included are similar to those in the Safety Update for the original NDA submission.

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

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

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

/s/

STACEY MIN
09/17/2013



MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2013
TIME: 3:30 - 4 pm
LOCATION: White Oak Bldg 22, Room 6201
APPLICATION: NDA 203093 & 203094
DRUG NAME: Vitakta™ and Tybost™
TYPE OF MEETING: Informal Advice - Teleconference

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

FDA ATTENDEES:

Debra Birnkrant, M.D., Division Director, DAVP
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Linda Lewis, M.D., Clinical Team Leader, DAVP
Russ Fleischer, PA-C, MPH, Clinical Reviewer (via phone)
Kim Struble, Pharm.D., Clinical Team Leader (via phone)
Peter Miele, M.D., Clinical Reviewer (via phone)
Rapti Madurawe, Ph.D., CMC Branch Chief, ONDQA
Stephen Miller, Ph.D., CMC Team Leader, ONDQA
Celia Cruz, Ph.D., CMC Reviewer, ONDQA
Milton Sloan, Ph.D., CMC Reviewer, ONDQA (via phone)
Fugiang Liu, Ph.D., CMC Reviewer, ONDQA (via phone)
Kareen Rieviere, Ph.D., CMC Reviewer, ONDQA
Deepika Arora Lakhani, Ph.D., CMC Reviewer, ONDQA (via Phone)
Krishnakali Ghosh, Ph.D., Compliance Officer, GDMAB (via phone)
Tara Goen, Acting Branch Chief, NDMAB, Office of Compliance
Madesh Ramanadham, NDMAB, Office of Compliance
Karen Winestock, Chief Project Management Staff
Beth Thompson, M.S., Acting Chief Project Management Staff
Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager
Sammie Beam, Regulatory Project Manager
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES (Gilead's participants):

Andrew Cheng, M.D., Ph.D., Senior Vice President, Clinical Research
Javier Szwarcberg, M.D., Senior Director, Clinical Research
David Pizzuti, M.D., Vice President, Regulatory Affairs
Paul Tomkins, Ph.D., Senior Director, Regulatory Affairs
Christophe Beraud, Ph.D., Director, Regulatory Affairs
Taiyin Yang, Ph.D., Senior Vice President, Pharmaceutical Development and Manufacturing

Ron Branning, B.B.A., Vice President, Quality Assurance
Sujatha Narayan, M.S., Senior Director CMC, Regulatory Affairs

BACKGROUND:

Today, April 26, 2013, DAVP issued complete response letters for NDA 203093 (Vitekta™) and 203094 (Tybost™). A teleconference was scheduled to inform the applicant about the Division's action (Complete Response) and advise the applicant on how to resolve the issues identified during the inspection conducted at the Gilead Sciences (Foster City, CA) manufacturing facility site.

During the recent inspection of the Gilead Sciences (Foster City, CA) release and stability testing facility for these applications, FDA field investigators found significant deficiencies and discussed them with the firm management. FDA field investigators found significant concerns regarding the release and stability data presented in the NDAs and DMFs primarily due to lack of validation of the test methods used to obtain these data. The firm management acknowledged these deficiencies in their letter dated April 23, 2013. Satisfactory resolution of the significant deficiencies is required before this application may be approved.

DISCUSSION:

The Division of Antiviral Products (DAVP) initiated the discussion by acknowledging that this was a courtesy call related to the Complete Response Letters issued today. The DAVP commented that there were sufficient data from field inspection to issue a Complete Response letter. DAVP could not comment on all the deficiencies, as inspections were still ongoing, but noted that there was lack of validation of test methods used and the release/stability tests were not validated for both NDAs. Some deficiencies represented repeat observations noted as deficiencies during the previous STRIBILD application (NDA 203100). The DAVP and Office of Compliance recommended to Gilead Sciences the following:

1. Determine appropriate corrective actions to the Form FDA-483 issued to the firm and have the manufacturing facility submit a written response directly to the District Office.
2. Once Gilead has determined the extent/impact of the findings, submit detailed proposals to reconcile the analytical methods and resolve the deficiencies.
3. Request a Type A meeting (within 3 months) to discuss the impact of the findings on the data submitted in the application. The meeting request should be submitted to the review division.

The DAVP recommended that Gilead's follow-up action should be a priority and the firm should provide their responses as thoroughly as possible. The firm should provide adequate data to review and should submit a complete meeting package.

The DAVP reiterated that there are multiple deficiencies listed in the Form-483 and Gilead Sciences should consult the District Office to resolve the issues identified during inspection. The DAVP asked Gilead to determine how these findings will impact the new NDA (NDA 204671), which was submitted on April 8, 2013. Gilead Sciences committed to follow-up on this issue.

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

/s/

MYUNG JOO P HONG
04/30/2013



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

DATE: April 5, 2013
NDA: 203-093/Original Submission
TO: Prerna Menon, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Gilead Science, Inc.
SUBJECT: PMR/PMC Comments

Please refer to your June 27, 2012 submission submitted to NDA 203-093. The DAVP is proposing the following postmarketing commitment (PMC) and requirement (PMR). Please provide your responses to these requests by **April 11, 2013**.

PREA PMR

Because Vitekta™ represents the approval of a new formulation and a new dosing regimen, pediatric studies will be required under the provisions of the Pediatric Research Equity Act (PREA).

1. Evaluate the pediatric pharmacokinetics, safety, and antiviral activity of once daily elvitegravir combined with a background regimen including a protease inhibitor coadministered with ritonavir in HIV-1 treatment-experienced pediatric subjects from 4 weeks to less than 18 years of age. Using doses selected based on the PK evaluation and agreed upon with the FDA, conduct a longer-term evaluation of pediatric safety and treatment of elvitegravir, plus background regimen including protease inhibitor/ritonavir, assessing treatment response on the basis of HIV-1 RNA virologic response and conducting safety monitoring over at least 24 weeks of dosing.

Protocol Submission: [Gilead, please provide protocol submission date]
Trial Completion: October 31, 2016
Final Report Submission: May 31, 2017

Clinical Pharmacology PMC

(b) (4)

Please confirm your acceptance for the proposed timelines for the PREA PMR and provide a date for protocol submission. Please propose your timeline for clinical pharmacology PMC.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** 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.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

MYUNG JOO P HONG
04/05/2013

From: Hong, Myung-Joo P.
To: ["Prerna Menon"](#)
Cc: [Regulatory Archives](#)
Subject: RE: Clarifications regarding comments in the EVG label proposal NDA 203093
Date: Tuesday, March 19, 2013 3:51:00 PM
Attachments: [Virology response to Q1.doc](#)

Dear Prerna, requested clinical virology response is attached.

Thanks,
Pat

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

From: Prerna Menon [mailto:Prerna.Menon@gilead.com]
Sent: Tuesday, March 19, 2013 1:39 PM
To: Hong, Myung-Joo P.
Cc: Regulatory Archives
Subject: Clarifications regarding comments in the EVG label proposal NDA 203093

Hi Pat,

We are working on the label proposal for elvitegravir tablets and the Gilead team had the following questions:

1. In Section 12.4 Microbiology under section 'Treatment-Experienced HIV-1 infected Subjects' for the statement included 'For the change in subject number Week 96, evidence of emerging primary elvitegravir resistance-associated substitutions T66A/I, E92G/Q, T97A, Q146R, S147G, Q148R or N155H was observed in (b) (4) of the 74 subjects with evaluable genotypic data in Study 145', Could the Agency please provide the subject identification numbers for the (b) (4) and 74 subjects with evaluable genotypic data in Study 145.
2. In Patient Information Section, How to store Vitakta section, the Agency's comment in this section was to see comment in Section 16 but there is no comment included in Section 16 of the label. Could you please clarify the request so that Gilead can address the comment.

Thanks
Prerna
Prerna Menon, Ph.D.
Manager, Regulatory Affairs

- Subject IDs for 74 subjects
- Subjects with primary EVG resistance-associated substitutions are highlighted in green.

GS-US-183-0145-0031-3075
 GS-US-183-0145-0031-3253
 GS-US-183-0145-0031-3267
 GS-US-183-0145-0031-3283
 GS-US-183-0145-0031-3328
 GS-US-183-0145-0031-3350
 GS-US-183-0145-0031-3367
 GS-US-183-0145-0089-3015
 GS-US-183-0145-0128-3241
 GS-US-183-0145-0255-3275

GS-US-183-0145-1537-3420
 GS-US-183-0145-1543-3404
 GS-US-183-0145-1622-4106
 GS-US-183-0145-1622-4158
 GS-US-183-0145-1668-3061
 GS-US-183-0145-1668-3304
 GS-US-183-0145-1729-3183
 GS-US-183-0145-1808-3124
 GS-US-183-0145-1808-3168
 GS-US-183-0145-1808-3180

GS-US-183-0145-0302-3052
 GS-US-183-0145-0302-3222
 GS-US-183-0145-0310-3062
 GS-US-183-0145-0310-3465
 GS-US-183-0145-0433-3021
 GS-US-183-0145-0444-3346
 GS-US-183-0145-0444-3398
 GS-US-183-0145-0550-3030
 GS-US-183-0145-0550-3266
 GS-US-183-0145-0559-4042

GS-US-183-0145-1950-3231
 GS-US-183-0145-1950-3422
 GS-US-183-0145-1960-3172
 GS-US-183-0145-1960-3296
 GS-US-183-0145-2003-3245
 GS-US-183-0145-2003-3292
 GS-US-183-0145-2003-3417
 GS-US-183-0145-2003-3463
 GS-US-183-0145-2058-3269
 GS-US-183-0145-2058-3282

GS-US-183-0145-0566-3094
 GS-US-183-0145-0566-3134
 GS-US-183-0145-0574-4181
 GS-US-183-0145-0595-4125
 GS-US-183-0145-0595-4154
 GS-US-183-0145-0652-3179
 GS-US-183-0145-0661-3085
 GS-US-183-0145-0661-3342
 GS-US-183-0145-0729-3381
 GS-US-183-0145-0744-3313

GS-US-183-0145-2152-3093
 GS-US-183-0145-2475-3203
 GS-US-183-0145-2704-3256
 GS-US-183-0145-2825-3181
 GS-US-183-0145-2843-3038
 GS-US-183-0145-3671-4069
 GS-US-183-0145-3673-4020
 GS-US-183-0145-3712-4235
 GS-US-183-0145-3714-4112
 GS-US-183-0145-3714-4204

GS-US-183-0145-0828-3479
 GS-US-183-0145-0959-4027
 GS-US-183-0145-0959-4156
 GS-US-183-0145-0991-3060
 GS-US-183-0145-0991-3318
 GS-US-183-0145-1015-4176
 GS-US-183-0145-1407-3037
 GS-US-183-0145-1534-3056
 GS-US-183-0145-1534-3297
 GS-US-183-0145-1537-3198

GS-US-183-0145-4114-4173
 GS-US-183-0145-4838-3473
 GS-US-183-0145-5007-3441
 GS-US-183-0145-5007-3471

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

/s/

MYUNG JOO P HONG
03/19/2013



NDA 203093

LABELING PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Prerna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your June 27, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VITEKTA (elvitegravir), 85 and 150 mg Tablets.

We also refer to our September 6, 2012, letter in which we notified you of our target date of March 30, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On June 27, 2012, we received your original proposed labeling submission to this application which was revised and resubmitted on October 18, 2012. Our proposed revisions are included as an enclosure. In addition, we are providing the following comments. Please review the label and provide a response no later than **March 29, 2013**.

Indication

1. Upon further review, the Division determined that there was insufficient evidence to support the proposed indication for the use of elvitegravir in combination with cobicistat and 2 NRTIs in HIV-1 infected treatment-naïve patients due to the absence of comparative pharmacokinetic and clinical data evaluating elvitegravir and cobicistat as single entities relative to Stribild.

Container Label

2. Please revise the color of the shaded box behind the strengths, 85 mg and 150 mg, to two different colors to provide adequate strength differentiation between the two strengths.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Labeling

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

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

/s/

MYUNG JOO P HONG
03/15/2013

From: Hong, Myung-Joo P.
To: ["Prerna Menon"](#)
Subject: NDA 202093.Information Request
Date: Wednesday, February 27, 2013 12:27:00 PM

Dear Prerna, we have the following request from clinical pharmacology review team.

- Please provide long-term stability data at -70 degrees C to cover plasma sample storage time periods of 815 days (Study GS-US-183-0145) and 665 days (Study GS-US-183-0152). Please submit your response ASAP.

Thanks,
Pat

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

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

/s/

MYUNG JOO P HONG
02/27/2013

From: Hong, Myung-Joo P.
To: ["Prerna Menon"](#)
Subject: NDA 203093.CMC.Information Request
Date: Tuesday, February 26, 2013 12:38:00 PM

Dear Prerna, we have the following request from CMC review team.

"Please provide a stability update, including available stability data, for the ACCESS image batches AJ1101F1 and AJ1101H1." Please submit your response by March 8, 2013.

Thanks,
Pat

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

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

/s/

MYUNG JOO P HONG
02/26/2013

From: Hong, Myung-Joo P.
To: "[Prerna Menon](#)"
Subject: NDA 203093.Information Request
Date: Wednesday, February 13, 2013 10:59:00 AM

Hello Prerna, I have the following requests from CMC review team:

We find your proposed specification for tablet (b) (4) of NMT (b) (4) % justified. However, based on the equilibrium (b) (4) measured for tablets stored at open dish conditions, we expect that packaged tablets could reach a (b) (4) value of (b) (4) at shelf life. A (b) (4) value of (b) (4) is considered a threshold value for which microbiological purity should be verified. Please update both stability protocols as follows:

- Include microbiological purity testing at t =0 and at shelf life.
- Include (b) (4) monitoring at t=0 and at least annually.

Please provide your response by Feb. 15, 2013. If you agree, I only need your commitment to correct as recommended above.

Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
' 301-796-0807
' 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
02/13/2013

From: Hong, Myung-Joo P.
To: ["Prerna Menon"](#)
Subject: NDA 203093.Information Request
Date: Thursday, February 07, 2013 10:53:00 AM

Dear Prerna, we have the following request:

In your recent submission dated on Feb 1, 2103, you stated "54 subjects were classified as having rebound before Week 96 using the TLOVR algorithm, but resuppressed at Week 96 and therefore were classified as responder using the snapshot algorithm." These 54 subjects account for more than 7% of subjects in the ITT population, which is a percentage higher than we have observed in other studies. Please provide your assessment of what accounted for you claiming that each of these rebounds that were re-suppressed as responders and not as treatment failures.

Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
' 301-796-0807
' 301-796-9883 (fax)
* myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
02/07/2013

From: Hong, Myung-Joo P.
To: ["Prerna Menon"](#)
Subject: NDA 203903 - Clarification Request
Date: Monday, February 04, 2013 4:33:00 PM

Hi Prerna, would you clarify the following point? In your January 15, 2013 submission, you stated that "Bracket provided a new randomization file containing randomization date and time upon request from Gilead.... Gilead can match the treatment received by all subjects with the treatment original randomization file provided by Bracket (sent by Gilead via FedEx, on June 27, 2012)"

Which of the following files is the Bracket randomization file containing the randomization date and time?

Gilead GS-US-183-0145 - Randomization Certificate.pdf; GS144rand.xls;
gs-us-183-0144-dummy-randomization-list-approval-v1-0-signed.pdf;
gs-us-183-0144-final-randlist-ver-2-2.csv;
gs-us-183-0144-list-based-randomization-req-v2-2-signed.pdf;
gs-us-183-0145-dummy-randomization-list-approval-v1-0-signed.pdf;
gs-us-183-0145-final-randlist-ver-1-0.csv;
gs-us-183-0145-list-based-randomization-req-v1-0-signed.pdf; .Rand0145.xpt

Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
' 301-796-0807
' 301-796-9883 (fax)
* myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
02/04/2013

Cuff, Althea

From: Prerna Menon [Prerna.Menon@gilead.com]
Sent: Tuesday, January 22, 2013 2:43 PM
To: Cuff, Althea
Cc: Christophe Beraud; Regulatory Archives
Subject: RE: NDA 203093 - Information Request

Dear Althea,

I confirm receipt of this information request.

Kind Regards,

Prerna

Prerna Menon, Ph.D.
Manager, Regulatory Affairs
650-522-4754

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Tuesday, January 22, 2013 11:21 AM
To: Prerna Menon
Cc: Christophe Beraud
Subject: NDA 203093 - Information Request

Dear Prerna,

In reviewing the Chemistry, Manufacturing and Control section of the NDA, we have the following Information Request:

 (b) (4) Please update

Section P.3.3. accordingly.

We request a response by Tuesday, January 29, 2013. Please confirm receipt of this e-mail.

Thanks,

Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061

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

/s/

ALTHEA CUFF
01/22/2013



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

DATE: January 18, 2013

NDA: 203-093/OS

TO: Prerna Menon, Ph.D., Manger, Regulatory Affairs

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

THROUGH: Lei Nie, Ph.D., Statistical Reviewer

CONCUR: Greg Soon, Ph.D., Statistical Team Leader

SUBJECT: Advice/Information Request

Please refer to an amendment received on January 16, 2012 (SDN #17) which contains responses to our correspondence dated December 13, 2012. We have the following comments from the review team:

1. In your earlier response, you provided the updated snapshot results based on the standard analysis windows proposed in the "FDA snapshot guidance." We expect the updated snapshot results to be used in the label if the NDA is approved. We noticed that you still use your original snapshot results in the analysis of heterogeneity. Please repeat the analysis using the updated snapshot results. We acknowledge the differences could be very small.
2. Your revised snapshot results confirm that heterogeneity occurs in gender (e.g., p-value=0.063; considered significant as < 20% of the population are female) and race (e.g., p-value=0.037). Please provide an explanation for the observed heterogeneities. We note that your analyses based on TLOVR do not reveal these heterogeneities. Please provide an explanation for the differences in your conclusions based on different algorithms. In our experience, conclusions based on either snapshot or TLOVR algorithms have been consistent.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** 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.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

MYUNG JOO P HONG
01/18/2013



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

DATE: December 13, 2012

NDA: 203-093/OS

TO: Christophe Beraud, Ph.D., Associate Director, Regulatory Affairs

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

THROUGH: Lei Nie, Ph.D., Statistical Reviewer

CONCUR: Greg Soon, Ph.D., Statistical Team Leader

SUBJECT: Advice/Information Request

Please refer to your June 27, 2012 NDA submission submitted to NDA 203093. We have the following comments from the review team:

1. The heterogeneity of treatment effect of EVG relative to RAL, expressed in the primary endpoint (virologic response, <50 copies/ml) and/or the important secondary endpoint (virologic failures, >50 copies/ml), has been found in gender, in race, and in region (USA versus non-USA). It is our current view that the heterogeneity is beyond random errors. If you disagree with our current view, please provide evidence we may have missed and the supporting statistical analyses (including programming SAS code).
2. The attached SAS file below illustrates some potential inconsistent results: 1) between the IVRS randomization file (RAND0145.xpt you sent via FedEx, on June 27, 2012) and the subject level analysis dataset file (~\m5\datasets\gs-us-1830145\analysis\adam\datasets\96-wk\ADSL.xpt) in the levels of stratifications factors; and 2) between the actual treatment received and the treatment original randomization code would assign. We acknowledge that the inconsistency could be the result of the reviewer's misunderstanding of some factors, e.g., the complexity caused by unification of two trials. Please provide an explanation for these findings.
3. Please clarify whether a number of subjects had viral load <50 copies/ml at baseline. We understand the baseline viral loads could be different than the screening viral loads, but we are unclear why these subjects' viral loads reached such a low level before the start of investigational drugs.

4. It appears that the rate of discontinuation due to reasons other than adverse event, death, lack of efficacy, pregnancy in 0145 is remarkably higher than the same rate in Benchmark trials. Please comment on the differences and elaborate whether imperfect blinding due to different shapes (triangle versus pentagon) might contribute to the higher discontinuation rate.

The SAS Code referred in comment # 2.

(b) (4)

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

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** 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.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

MYUNG JOO P HONG
12/13/2012



NDA 203093

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir, 85 and 150 mg Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by January 7, 2013, in order to continue our evaluation of your NDA.

Biopharmaceutics

1. Provide dissolution data for the long term stability batches tested with the proposed dissolution method.
2. We recommend the following dissolution acceptance criterion: $Q = \text{(b) (4)}\%$ at 45 minutes. This recommendation is based on the mean in-vitro dissolution profiles for all strengths at release. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product. Note that dissolution data from the long term stability studies were not factored in the selection of the dissolution acceptance criterion because the long term stability batches were not tested with the proposed dissolution method.
3. There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following data:
 - a. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figure 7 demonstrating that the proposed drug product manufactured with the (b) (4) at the proposed

- ranges have similar dissolution rate compared to batches manufactured at the target parameter values.
- b. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figure 10 demonstrating that the proposed drug product manufactured with the (b) (4) at the proposed ranges have similar dissolution rate compared to batches manufactured at target parameter values.
 - c. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figures 12 and 13 demonstrating that the proposed drug product manufactured with the (b) (4) at the proposed ranges have similar dissolution rate compared to batches manufactured at target (b) (4).
 - d. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figure 14 demonstrating that the proposed drug product manufactured with the (b) (4) at the proposed ranges have similar dissolution rate compared to batches manufactured at the target (b) (4).

Drug Product

4. Regarding the control strategy for tablet (b) (4), address the following:
 - a. Based on the descriptions of the proposed 60-ml bottle configuration in P.7.1 and in the primary stability batches in P.8.1 and P.8.2, it appears that there is no (b) (4) in the bottle. However, you have provided a Letter of Authorization from (b) (4) and a description of a (b) (4) step in the packaging manufacturing description in P.3.3. Clarify if and how much (b) (4) was used in the development or stability batches. Please align and update the NDA sections appropriately.
 - b. There is a discrepancy between the stated (b) (4) limit for (b) (4) in the justification of no specification for (b) (4) (P.5.6) and that of the manufacturing process description in (P.3.3) and the proposed in-process controls (P.3.4). Clarify if the intended (b) (4) control is NMT than (b) (4) % or NMT (b) (4) %, and update the sections accordingly.
 - c. Clarify if, after film coating of tablets, any in process testing of tablet (b) (4) will be conducted as part of normal commercial operation.
 - d. Propose a (b) (4) specification for tablets, considering the (b) (4)
5. You have proposed both an HPLC and a UPLC method for dissolution determination under TM-168 and have provided adequate validation data for each. Clarify how selection of UPLC or HPLC will be decided and whether selection of method will be documented accordingly. Also, clarify if a sample that fails with one method can be

retested with the other method. Otherwise, provide independent method numbers and determination of primary and alternative method.

6. Update the batch formulas for US and Access tablets to reflect the amount of (b) (4) addition of microcrystalline cellulose and croscarmellose sodium, or include proportions in the manufacturing process descriptions.
7. Regarding the manufacturing process description in P.3.3, address the following:

- a.
- b.
- c.
- d.
- e.



If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

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

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

/s/

RAPTI D MADURAWA
12/12/2012

From: Hong, Myung-Joo P.
To: ["Christophe Beraud"](#)
Subject: NDA 209093 - Information Request
Date: Thursday, November 29, 2012 3:03:00 PM

Dear Christophe, would you provide narratives for all subjects who discontinued Study 0145 due to consent withdrawal, investigator/sponsor decision, lost to follow-up, non-compliance, or other reasons?

Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
' 301-796-0807
' 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
11/29/2012

From: Hong, Myung-Joo P.
To: "[Christophe Beraud](#)"
Subject: NDA 203093.IR
Date: Monday, November 05, 2012 1:56:00 PM

Dear Christophe, we have the following request for NDA 203093. Please provide the following information:

1. Output tables for final POPPK model (run 116: sdtab116, patab116, cotab116, and catab116)
2. A table of Study ID, Subject ID and derived exposure metrics (AUC and Ctau) for each individual included in the POPPK analysis.

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

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

Please submit the requested information by November 9, 2011.

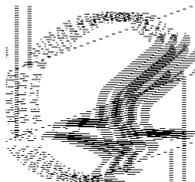
Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
' 301-796-0807
' 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
11/05/2012

**MEMORANDUM OF FACSIMILE:**

Date: October 10, 2012
NDA: 203093
Drug: Elvitegravir
To: Christophe Beraud, Ph.D., Senior Manager, Regulatory Affairs
Sponsor: Gilead Sciences, Inc.
From: Stacey Min, Pharm.D., Regulatory Project Manager
Subject: NDA 203093

Please refer to your NDA 203093, elvitegravir 85 and 150 mg tablets submitted on June 27, 2012, to be used in combination with ritonavir boosted protease inhibitor and other antiretroviral (ARV) agents for the treatment of HIV-1 infection in ARV treatment-experienced adults. In your submission dated Oct 4, 2012 (SDN-6), you stated the windows used for the Week 48 and 96 snapshot analyses were: 1) Week 48 analysis window was between Study Day 309 and Study Day 364, inclusive; 2) Week 96 analysis window was between Study Day 645 and Study Day 700, inclusive.

These analysis windows are different than the standard windows defined in the snapshot guidance (see the attached snapshot guidance), which are:

Visit	Window (through end of Study Week) (express in days for non-overlap)	Window (Days)
24	18-30	126-209
48	42-54	294-377
96	90-102	630-713

To facilitate the review of your NDA and to maintain consistency across labels for new HIV treatments,

1. Please clarify whether the analysis windows you used were prespecified. If they are, please identify the source document(s) that detailed these prespecifications. In addition, please provide a justification for your selection of visit windows.

2. Please reanalyze the efficacy data for Study 0145 in the NDA based on the standard visit windows as shown in the table above and the snapshot guidance document.

We are attaching a copy of the latest snapshot document for your reference.

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

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

The TLOVR analysis previously used in labeling by the DAVP has often led to multiple queries for the applicant. DAVP statistical and clinical reviewers recently completed a project titled, “Handling uncertainty in endpoint selection and other endpoint issues.” The goal of the project was to determine if simplified or more powerful endpoints could be used for traditional approval at Week 48. The team evaluated 18 trials from seven NDAs with 8046 patients. CDISC datasets for HIV RNA, demographics, CD4 cell counts, and discontinuation were created. Results obtained using the TLOVR algorithm, which utilized data from every visit to consider the pattern of HIV responses, were compared to a less complicated “snapshot” approach which only utilized HIV RNA data at the visit of interest. A high concordance between the TLOVR algorithm and snapshot results was observed. Using the TLOVR algorithm, 61% of the 8046 patients remained in the study for 48 weeks and were virologic responders compared to 61% of the subjects using the snapshot approach; 18% were virologic non-responders using the TLVOR algorithm compared to 17% using the snapshot approach and approximately 20% discontinued prior to Week 48 using both approaches. The likelihood of clinically significant differences between the two methodologies for evaluating efficacy is minimal.

Based on the findings from the project and the ease of the snapshot method, pending sNDAs and future NDAs will include virologic outcome results based on snapshot approach in the product labeling. Included below are the principles and procedures for calculating virologic outcome for labeling.

Snapshot Approach

Proposed windows

- Window size is ½ the duration of time between study visits
- Windows may be smaller at earlier time points and can possibly be asymmetric, particularly at earlier time points
- If your trial-defined windows differ from the proposed windows below, please discuss with the Division. In most cases the protocol-defined windows for completed trials are acceptable; however, for future trials we encourage standardization and request you use the following:

Visit	Window (through end of Study Week) <i>(express in days for non-overlap)</i>	Window (Days)
24	18-30	126-209
48	42-54	294-377
96	90-102	630-713

Example of efficacy presentation in labeling

Virologic Outcome at 96 week window (Window 90 – 102 weeks)

	Drug A	Drug B
Virologic Success HIV RNA ≤ 50 copies/mL	60%	50%
Virologic Failure#	20%	30%
No Virologic Data at 96 Window		
Reasons		
Discontinued study/study drug due to AE or Death*	10%	8%
Discontinued study/study drug for Other Reasons**	6%	6%
Missing data during window but on study	4%	6%

#Includes patients who changed OBT to new class or changed OBT not permitted per protocol or due to lack of efficacy prior to Week 96, subjects who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96 week window

*Includes patients who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

**Other includes: withdrew consent, loss to follow-up, moved etc.

Principles of snapshot analysis

- The primary efficacy endpoint is intended to be primarily a virologic endpoint and not a clinical endpoint. This method follows a “Virology First” hierarchy.
- Percentages not included in “virologic success or failure” rows are meant to describe reasons for no data at a specified analysis time window in an ITT analysis. These percentages are not meant to represent comprehensive safety or clinical efficacy analyses.
- Given this is primarily a virologic endpoint, the hierarchy for assessing row and column percentages is “Virologic Success” or “Failure” first for any given time window followed by reasons for “No Virologic Data in the Window”.

Procedures for calculating virologic outcome

Data in the window

- Virologic Success or Failure will be determined by the last available measurement while the subject is on- treatment and continued on-trial within the time window (see windows table below).
 - Examples: HIV RNA = 580 at Day 336, HIV-RNA < 50 on Day 350. This is a success.
 - In the rare example that someone would have HIV RNA < 50 at Day 336 and then ≥ 50 at Day 350, this would still be called a failure (we believe

this will be rare, because undetectable patients would not be likely to have a second lab result in a window).

No data in the window

- If there are no data in a time window, then tally percentages for each category of missing data.
- There are 3 reasons for no data in the window:
 - Discontinued Study due to Adverse Events or Death.

Any subject who discontinues due to an adverse event or death **prior to** the window should be classified as “Discontinued due to AE” or “Death” (as appropriate), regardless of the HIV RNA result, even if the HIV RNA <50 at the time of discontinuation. [Note: there will not be a separate category for Death. We believe a separate category for Death is misleading, because it does not account for all Deaths. Instead, in text we can report all AIDS defining events and Deaths.] However, if a subject has an HIV RNA value in the time window and also discontinues **in the time window**, we use the viral load data. This is the “Virology First” hierarchy. Example: HIV-RNA < 50 at Day 336 and discontinues due to AE or even dies on Day 360---this person is a virologic success. Likewise if HIV-RNA is 552 on Day 336 and subject discontinues on Day 360, subject is a virologic failure. **Bottom line:** if there are any virologic data in the window **while on-treatment**—use this first to assess the endpoint.
 - Discontinued Study due to Other Reasons.

Same examples above, apply to this category. If someone discontinues study before the window due to “lack of efficacy” then they should be included in the virologic failure row and not in the “Discontinue for Other Reasons” row. To further clarify, subjects who “Discontinue for Other Reasons”, it is essential to realize that in the “Virology First” hierarchy only subjects who have achieved virologic suppression may be counted as “Discontinued due to Other Reasons.” Subjects who do not have their last viral load < 50 copies/mL, must be categorized as virologic failure. For example, if a subject discontinues due to “subject withdrew consent” and their HIV-1 RNA result at the time of discontinuation was ≥ 50 copies/mL, then they must be counted as a virologic failure and NOT as “Discontinue for Other Reasons.” However, if a subject discontinued due to “Lost to Follow-up” and the last HIV RNA result was 49 copies/mL, then the subject may be categorized as “Discontinue for Other Reasons.”

 - Likewise, if subjects changed background treatment—*not permitted by protocol*—they should be considered an efficacy failure and captured in the virologic failure row.
 - On Study but Missing Data.

Only data in the window may be used for subjects remaining on study. If there is no data in the window, you may not look past the window and use

the next value. For example, if there are no data during Days 294-377, but there is an HIV-RNA < 50 on Day 380, this subject is considered "On Study but Missing Data." This subject may count as a success at subsequent analysis points (e.g., 96 weeks), if they remain undetectable at the subsequent analysis window (e.g., 96 weeks). Conversely, if there are no data during Days 294-377, but there is an HIV-RNA \geq 50 on Day 280, this subject is also considered "On Study but Missing Data".

OBT substitutions

Typically trials have permitted one in class substitution of an OBT drug for documented toxicity reasons. As more drugs are available, across class substitutions were permitted in some trials; however, this can impact long term durability of a regimen particularly if the OBT change occurred later in the trial. OBT substitutions (in class or across class) permitted per protocol for documented toxicity reasons are permitted on or before the first trial visit without penalty.

We have received requests from sponsors to amend the algorithm such that only across-class switches are classified as primary endpoint failures because not allowing within class OBT substitutions may create disincentives. Such disincentives cited are investigators may be de-incentivized to ensure long-term follow-up after an OBT switch because those subjects are deemed as analysis failures or may result in unnecessary increase in early switches to avoid classifying subjects as failures in the primary efficacy analysis.

We decided not to amend the algorithm for the following reasons:

- All in-classes switches are not the same. With the expanded number of drugs in each class and the approval of second generation drugs within the same class, switching therapy after knowledge of viral load changes may confound the results. One would then have to decide which switches are appropriate for the population being studied.
- We attempted to make the snapshot as concise and stringent as possible to reduce the amount of end-of-FDA-review negotiations over single cases. Having to decide which in-class switches are appropriate for specific populations (naïve, experienced, etc.) would complicate the algorithm. Example: in what population is a switch from atazanavir to darunavir considered acceptable.
- We believe that the unwanted scenarios mentioned above can be minimized. Both types of analyses can be conducted, perhaps allowing cross-class switches in analyses presented in publications, etc. However, for FDA labeling purposes, the snapshot should be used. Therefore investigators could be informed that not all analyses results in their particular subject counting as a failure if they switch and that follow-up should be maintained.
- We do not believe that there is one "correct" analysis. All analyses only approximate truth. We are only striving for efficiency and consistency across multiple applications. This should not prohibit the presentation of slightly

different analyses at meetings or publications. Differences can be described in footnotes.

Datasets for snapshot approach

For submission with multiple trials, each trial should have its own dataset for the snapshot analysis. The datasets should contain, at minimum, the following information:

- study ID
- patient study ID
- study day and date of last double-blind treatment
- virologic outcome at Week 96 based on the snapshot approach (i.e., virologic success, virologic failure, discontinued due to AE or death, discontinued due to other reasons, missing data during window but on study)
- the HIV RNA measurement and the corresponding study day and date used to determine the above virologic outcome if the measurement was not missing
- study day and date when the patient switched to open-label treatment due to virologic failure if applicable
- discontinuation study day and date, reason and last on-double-blind-treatment measurement before discontinuation for the patients who discontinued drug
- treatment phase in dataset should be defined and only include 3 categories as follows: screening (or baseline), treatment, and follow-up

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

/s/

STACEY MIN
10/10/2012

From: Hong, Myung-Joo P.
Sent: Thursday, September 27, 2012 4:41 PM
To: 'Christophe Beraud'
Cc: Regulatory Archives
Subject: NDA 203093.Information Request
Signed By: myung-joo.hong@fda.hhs.gov

Dear Christophe, we are reviewing the subjects who discontinued from Studies 0105 and 0145 due to adverse events and would like to have Gilead provide some additional information as requested below:

1. [Study 0105](#)

For subjects 0436-2230 and 1682-2284, please explain how their events were classified as being related to study medications.

2. [Study 0145](#)

For subjects 0688-4077, 1925-3259, 2493-3065, 3672-4022, 0310-3047, 0433-3102, 0661-3173, 1021-4031, 1536-3031, 1603-3363, 1950-3252, 3991-4023 and 5007-3451, please explain how their events were classified as being related to study medications.

3. In section 11.6.2.1 of the CSR for Study 0145, you mention 5 subjects with increased creatinine levels, 1 with decreased GFR, 4 with decreased serum phosphate/hypophosphatemia, and 5 with proteinuria/urine protein present. Please provide a narrative for each subject. In the narrative please describe if the subject had more than one of the abnormalities listed and if the subject was receiving TDF (and for how long) at the time of their laboratory abnormalities.

Thanks,
Pat

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Health Project Manager
FDA/OAP/DAVP
☎ 301-796-0807
☎ 301-796-9883 (fax)
✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
09/27/2012



IND 072177
NDA 203093

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Beraud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) and to your New Drug Application (NDA) dated and received June 27, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir Tablets, 85 mg, and 150 mg.

We also refer to:

- Your initial proprietary name submission dated and received March 28, 2012, submitted under the IND requesting review of your proposed proprietary name, Vitekta; and
- Your proprietary name amendment dated and received April 2, 2012, submitted under the IND clarifying the dose of this product; and
- Your subsequent proprietary name submission dated September 13, 2012, and received September 14, 2012, submitted under the NDA requesting review of your proposed proprietary name, Vitekta.

We have completed our review of the proposed proprietary name Vitekta, and have concluded that it is acceptable. The proposed proprietary name, Vitekta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

Additionally, if **any** of the proposed product characteristics as stated in your September 13, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

IND 072177
NDA 203093
Page 2

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 Patricia Hong at 301-796-0807.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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

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

/s/

AZEEM D CHAUDHRY
09/20/2012

CAROL A HOLQUIST
09/20/2012



NDA 203093

FILING COMMUNICATION

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated and received June 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for elvitegravir, 85 and 150 mg tablets.

We also refer to your amendments dated July 3, 2012, August 6, 2012, and August 27, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 27, 2013.

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, midcycle, 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 March 30, 2013.

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

We request that you submit the following information by October 5, 2012:

Chemistry, Manufacturing and Controls

1. We note that you have presented Proven Acceptable Ranges (PAR) for process parameters in section P.2.3 that were determined on the basis of multivariate studies. However, section P.3.3 includes only Normal Operating Ranges (NOR) or set points for the parameters, where the NOR are a subset of the PAR. Please clarify how you intend to handle movements outside the NOR (as listed in section P.3.3) but within the PAR (as provided in section P.2.3).
2. Please provide the following clarification regarding intended commercial batch size, which is stated to be from (b) (4) kg to (b) (4) kg, based on uncoated tablet weight. Please include in your response:
 - a. A summary table indicating the intended batch size for the (b) (4) and film coating unit operations to accommodate the proposed batch size range. If different scale equipment is used to accommodate varying batch sizes, please include in your response.
 - b. A description of when parts are combined or batches are split for further processing.
 - c. An updated Table 2 in section P.3.4 to clearly indicate the scale (b) (4) used for the batches indicated.
3. Please include microbiological purity testing for the Elvitegravir (EVG) tablets in the stability protocol for the first three commercial batches and annual commitment batches at initial time point and at shelf life.
4. Please include reporting of t =0 in the stability protocols for first three commercial batches and annual commitment batches. Please update Tables 1 and 2 in section P.8.2, accordingly.
5. Because EVG tablets may be used in all climatic zones world-wide, revise all post-approval stability protocols for both the US and Access tablets to show the long term condition as “30°C/75%RH (optionally, additional studies may be conducted at 25°C/60%RH).” Tables and text in section P.8.3 should be revised.
6. Please submit a sample of EVG tablets, 85 and 150 mg, packaged in the proposed 30’s count bottle configuration.

Statistical

7. Please explain how your analysis deals with the HIV viral load data which were measured by two (or actually three) assays. We note that, at some time points, HIV viral load was measured by only one of following three HIV RNA assays: 1) Amplicor/standard; 2) Amplicor/ultra sensitive; and 3) Taqman.

8. Please provide information to identify which subjects are originally from Study 144.
9. The randomization code does not indicate whether subjects were randomized using the randomization code for Study 0144 or 0145. Please provide the original randomization (Rand0144 and Rand0145) for Studies 0144 and 0145 and provide source information demonstrating how they were merged into the new Study 145.
10. Please clarify the reasons why the information from L:\m5\datasets\gs-us-183-0145\tabulations\sdtm\96-wk\ds.xpt does not match your Figure 8-1, in the Study 0145 report. For example, the data show 725 subjects were randomized, but your figure says 724. The data show 11 deaths but your figure shows 10. There are many other examples of inconsistencies between the data and the figures.
11. Please explain how you define the week 48 and week 96 window for the snapshot analysis. Our preliminary assessment of your snapshot classification reveals some inconsistency between your classifications and ours, which could be related to a different window definition. For example, we consider subject 2475-3203 to be a failure rather than “not missing data but on study.” This subject stopped treatment on 2011-2-24, when the viral load was 33,700 on day 700.

Clinical

12. The analysis datasets submitted for clinical studies GS-US-183-0145 are inconsistent with respect to the formatting used for reported dates. Some date variables appear to use a SAS code. Since this formatting issue is noted within and across multiple datasets, please resubmit the analysis datasets using a consistent standard date format. In every dataset, all dates must be formatted as ISO date format. In addition, please include treatment and demographic variables, including treatment start and stop dates, to all analysis datasets.
13. In light of the recent Stribild® approval, the Division requests you modify the proposed indications for the individual drugs cobicistat (COBI) and elvitegravir (EVG) to include treatment of HIV-1 infection in treatment-naïve adults in combination with two nucleos(t)ide reverse transcriptase inhibitors. We are not aware of any data to suggest that the combination of EVG/COBI or EVG/r should not be used with other NRTI/NtRTI combinations besides FTC/TDF as part of an antiretroviral regimen. The basis of dose selection for EVG/COBI in Stribild® was identification of an antiviral effect with EVG/r and matching that EVG exposure with EVG/COBI. As such, an indication for EVG/COBI or EVG/r in treatment-naïve patients may increase treatment options for patients in whom TDF, for example, is not advised. Thus, for elvitegravir, the indication in treatment-naïve patients should include use with cobicistat or ritonavir in combination with two NRTIs. Please submit a revised label for each NDA that takes into account the above indications.

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

Under Highlights

14. The route of administration should follow after the dosage form.

[TRADENAME] (elvitegravir) tablets, **for oral use**

15. Please delete the following information from the “Use in Specific Populations” section:



Under Full Prescribing Information

16. Several sub-subsection headings are bolded under subsection 12.3 and 12.4. Please remove the bold.

We request that you resubmit labeling that addresses these issues and requested information above by **October 5, 2012**. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies (birth to < 4 weeks) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

DEBRA B BIRNKRANT
09/06/2012



NDA 203093

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

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

Name of Drug Product: Elvitegravir, 85 and 150 mg Tablets

Date of Application: June 27, 2012

Date of Receipt: June 27, 2012

Our Reference Number: NDA 203093

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 August 26, 2012, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

MYUNG JOO P HONG
07/03/2012

From: [David, Jeannie C](#)
To: ["Linda McBride"](#)
Cc: ["christophe.beraud@gilead.com"](mailto:christophe.beraud@gilead.com); [Hong, Myung-Joo P.](#)
Subject: NDA 203093
Date: Wednesday, June 27, 2012 3:59:00 PM

Dear Linda,

We refer to Gilead's NDA 203093, submitted on June 27, 2012. We have the following CMC requests for information regarding the establishment information:

1. Clarify the drug product "packaging and labeling" responsibilities that occur at ^{(b) (4)}
 Gilead Sciences Limited (Cork, Ireland), and Gilead Sciences Inc. (San Dimas, CA).
2. Clarify the drug product "release" responsibilities that occur at Gilead Sciences Limited (Cork, Ireland), Gilead Sciences Inc. (San Dimas, CA), and Gilead Sciences Inc. (Foster City, CA).

We request that you provide Gilead's response as an amendment to the NDA. Please confirm receipt of this email.

Best regards,

Jeannie

Jeannie David, M.S.
CMC Regulatory Health Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
Phone: (301) 796-4247

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

/s/

JEANNIE C DAVID
06/27/2012



IND 72177

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

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

We also refer to your December 22, 2011, correspondence, received December 23, 2011, requesting a pre-NDA meeting to discuss the content and format of the elvitegravir NDA targeted for submission in second quarter of 2012.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 5, 2012, 2:30 PM to 4:00 PM, EST between Gilead Sciences, Inc. and the Division of Antiviral Products (DAVP). 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. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Question 1

Gilead will be seeking an indication for elvitegravir in combination with a ritonavir-boosted protease inhibitor and other antiretrovirals for the treatment of HIV-1 infection in treatment-experienced adults. Refer to the Target Product Profile (Section 1 – Indication and Usage) provided in Attachment 2.

The proposed indication is based on the pivotal Phase 3 Study GS-US-183-0145 in treatment-experienced, HIV-1 infected adults. This indication will be further supported by two Phase 2 studies of elvitegravir in treatment-experienced adults (GS-US-183-0105 and GS-US-183-0130). Furthermore, the Phase 2 and 3 studies with the EVG/COBI/FTC/TDF STR in treatment-naive, HIV-1 infected adults will provide additional evidence of the contribution of EVG to the safety of an EVG-containing antiretroviral regimen. Gilead anticipates submitting the NDA for EVG in Q2 2012.

A summary of the 96-week safety and efficacy data from the pivotal Phase 3 Study GS-US-183-0145 in support of the proposed indication for EVG tablets is provided in Attachment 3. Gilead does not intend to seek an indication for the EVG tablet in combination with the cobicistat tablet and other antiretroviral agents (b) (4)



A tabular presentation of the studies to be included in the application in support of the proposed indication for EVG tablets is provided in Table 1 below. Also refer to the approach for the presentation of the safety and efficacy data in the Target Product Profile (Section 14 – Clinical Studies and Section 6 – Adverse Reactions; Attachment 2).

Does the Agency agree that the proposed indication for EVG tablets is adequately supported by the pivotal and supportive studies listed in Table 1 and the proposed approach to presentation of the safety and efficacy data in the Target Product Profile?

In general, the proposed indication appears reasonable; the final wording will be contingent upon review of the data. Pivotal Study 0145 and supportive Studies 101 and 105 appear sufficient to support submission of an NDA for EVG Tablets. It is unclear if data from Studies GS-US-236-102, 103 and 104 will be helpful or necessary to support approval of EVG/r. As such, it is not necessary for you to resubmit all the study data to the EVG Tablet NDA. Instead, please provide a cross reference to relevant information from NDA 203100 in the EVG Tablet NDA.

Question 2

A Target Product Profile for EVG tablets is provided in Attachment 2. Included in the Target Product Profile is a draft of the proposed drug interaction-related sections of the product label, together with the rationale and list of studies supporting the proposed text, as shown in Table 2 below.

Does the Agency have any comments regarding the proposed draft of the drug interaction-related sections of the EVG Target Product Profile?

Although a detailed examination of the EVG Target Product Profile has not been conducted, the general approach taken with respect to the drug interaction information included appears to be acceptable. Upon preliminary inspection, we recommend that Section 5.1 of the Target Product Profile be edited for length and conciseness; for an example, please refer to the approved PREZISTA® (darunavir) labeling. Further comments regarding the drug interaction-related sections of the label will be forwarded during the review of the NDA.

Question 3

Integrated (pooled) analyses of the efficacy and safety data from the Phase 2 and 3 studies of EVG tablets in treatment-experienced, HIV-1 infected subjects (GS-US-183-0145, GS-US-183-0105, and GS-US-183-0130) will not be conducted due to the different design of these three studies. Gilead plans, however, to include an integrated analysis of the Phase 2 and 3 studies with EVG/COBI/FTC/TDF STR within the Summary of Clinical Safety (m2.7.4), with statistical outputs and electronic datasets provided in m5.3.5.3. The integrated analysis of safety is the same as that submitted in the EVG/COBI/FTC/TDF STR Original NDA 203-100, Sequence 0000.

Does the Agency agree with the proposed approach for provision of the integrated analysis of safety in the EVG tablet NDA?

The proposed approach for provision of the integrated analysis of safety in the EVG Tablet NDA appears reasonable. Please do not resubmit an integrated analysis of the Phase 2 and 3 studies with EVG/COBI/FTC/TDF STR within the Summary of Clinical Safety (m2.7.4), with statistical outputs and electronic datasets provided in m5.3.5.3 in the EVG Tablet NDA. Rather, please provide a cross-reference to these data in NDA 203100.

Question 4

As part of the EVG/COBI/FTC/TDF STR NDA 203-100 Safety Update, Gilead will submit updated safety information (deaths, SAEs, discontinuations due to AEs, AEs of interest) for a number of ongoing EVG and EVG/COBI/FTC/TDF STR studies. In order to supplement the body of data existing in the clinical study reports included in the EVG NDA, Gilead plans to include the data from the NDA 203-100 Safety Update in the EVG NDA as shown in Table 3 below. A copy of the EVG/COBI/FTC/TDF STR Safety Update together with statistical outputs will be provided in Module 5.3.5.3.

Does the Agency agree with Gilead's plan to include data from the EVG/COBI/FTC/TDF STR NDA 203-100 Safety Update in the NDA for EVG tablets?

DAVP agrees with the proposal for the EVG Tablet NDA Safety Update. Please do not resubmit data from the EVG/COBI/FTC/TDF STR studies to the EVG Tablet NDA. Rather, please provide a cross-reference to these data when submitted to NDA 203100. In addition, please include an

update on deaths from trials conducted with the STR for NDA 203100 and any other EVG-containing trials.

Question 5

The draft Table of Contents for the EVG NDA is provided in Attachment 4. Please note that the list of bioanalytical and analytical methods and validation reports are not included in m5.3.1.4 and m4.2.2.1 of this draft Table of Contents but will be included in the EVG NDA submission.

Does the Agency have any comments regarding the list of nonclinical and clinical studies to be included in the EVG NDA?

Please include 2 additional virology study reports in Section 5.3.5.4 Other Study Reports and Related Information: (1) A Virology Study Report for Study GS-US-183-0130 and (2) A Virology Study Report for an integrated EVG resistance analysis (with a resistance dataset for subjects included in this analysis) on pooled genotypic/phenotypic data from all EVG-exposed virologic failure subjects in 6 studies GS-US-183-0105, -0130, and -0145, and GS-US-236-0102, -0103, and -0104.

Please do not resubmit all nonclinical study reports listed in module 4 that were submitted to NDA 203100, but rather only include new information that has not been previously submitted.

Question 6

Gilead plans to follow the approach agreed upon with the Agency and used for NDA 203-100 for EVG/COBI/FTC/TDF STR as shown in Table 4 below.

Does the Agency agree with the proposals detailed in above for the content and structure of the application?

In module m5, please include CRFs for subjects who discontinued due to “other” reasons.

Question 7

Gilead proposes to include in the EVG NDA m1 documentation for investigator financial disclosure, source documents for treatment allocation codes, statement of availability of HIV-1 RNA and CD4 cell count, disclosure of financial agreement with vendors used to manage treatment allocation codes, and investigator contact information, as detailed in Table 5 below.

Gilead does not intend to provide this information for the Phase 2 and 3 studies with EVG/COBI/FTC/TDF STR, as this information has already been submitted to NDA 203-100.

Does this Agency agree with the proposal for provision of the m1 documentation described in Table 5?

Yes, we concur.

Question 8

Per 21CFR314.50(d)(5)(vi)(b), Gilead plans to submit a Safety Update 120 days following the submission of the EVG NDA for ongoing clinical studies listed in Table 6 below. The Safety Update will include cumulative deaths, serious adverse events, discontinuations due to adverse events, and adverse events of interest. The data cut-off dates for the Safety Updates are provided in Table 6.

Does the Agency agree with the proposal for the scope of the EVG NDA Safety Update?

DAVP agrees with the proposal for the EVG Tablet NDA Safety Update. Please do not submit data from the EVG/COBI/FTC/TDF STR studies to the EVG Tablet NDA. Rather, please provide a cross-reference link to these data when submitted to NDA 203100.

Question 9

In response to the submission of a Proposed Pediatric Study Request (PPSR) for EVG (b)(4) Gilead received correspondence from the Agency dated 02 December 2011 (Attachment 5) requesting that a description of the pediatric investigational plans for EVG, (b)(4) be presented considering the (b)(4) nature of the development plans for (b)(4) products and emphasizing that the Agency does not favor switch studies in pediatric patients.

(b)(4)

Does the Agency have any comments on the proposed EVG, (b)(4) pediatric development plan?

(b)(4)

Upon review of the proposed pediatric plan for EVG Tablets, it is not clear if pharmacokinetic sampling will be performed during Part B of Study (b)(4). Please clarify whether or not blood samples will be collected for measurement of EVG plasma concentrations. The availability of pharmacokinetic data will facilitate the analysis of EVG exposure-response relationships that are observed during the study.

Additional Biometrics Comments:

1. Please submit the screening dataset and raw dataset following the data submission guidelines (see attachment A).

2. Please submit an efficacy analysis dataset and SAS (or other software) programs that were used to derive the dataset. Please follow the efficacy data submission guidance (see attachment B) to prepare your efficacy analysis dataset. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets.
3. We recommend you analyze the efficacy data using a snapshot algorithm following the snapshot algorithm guidance (see attachment C) and that you provide a program that implements the snapshot algorithm which generates the primary endpoint. The program should ideally be self-sufficient, meaning that it does not invoke other macros and only uses raw datasets that are necessary. We are requesting this information because based on our experience, the snapshot algorithm results generated by sponsors and the Agency may differ due to program complexity. A program that is easy to run and check helps us to reach agreement earlier in the review process by reducing unnecessary communications.

Additional Clinical Pharmacology Comments:

4. Please provide an update on your plans to evaluate potential EVG drug interactions with boceprevir and telaprevir. The results of such studies would inform EVG dosing guidelines in the HIV/HCV-coinfected patient population.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests 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.				

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.
 Regulatory Project Manager
 Division of Antiviral Products
 Office of Antimicrobial Products
 Center for Drug Evaluation and Research

Enclosures: Attachments A, B and C

Anti-viral Datasets Submission Guidance

1. Screening dataset

The screening information on all subjects screened would assist our better understanding of the study population and entry criteria. *However, the raw datasets submitted in the FDA/EDR do not provide this information.* Please submit a screening dataset that contains the information of all screened subjects from screening to randomization in the randomized trials or from screening to enrollment in the nonrandomized trials.

The variables should include a subject's demographics, disease characteristics, inclusion and exclusion criteria, status of randomization, reasons for not being randomized in the randomized trials or reasons for not being enrolled in the nonrandomized studies, major violation of entry criteria, and any other information collected before or at randomization or enrollment. The variables should directly come from the CRFs or other original source documents. The annotated CRFs or other source documents should be provided with the variables in the dataset linked to these documents.

2. Description of Datasets

To facilitate the use of the datasets, we have the following two recommendations.

1) Within each folder for the datasets for one study, there should be a PDF file, preferably as part of the "define" file, briefly describing the study, including the key elements of the planned design and any significant deviations from the design. Anything that requires more explanation than provided by the variable descriptions or footnotes can be further explained in this document. For example, if a key derived variable was based on variables from several raw dataset and involves intermediately derived variables, and requires lengthy explanation which does not fit into the variable explanation or footnotes, then it should be included in this document. Make sure links between the target variable and the explanation are provided. Please also provide a master description of the study dataset, in a format similar to the table below:

Study ID (Dataset included in this submission)	Study Design	Treatment Arms (Number of Randomized Subjects)	Key Results
Study No (make it a link to the dataset) Date of the first patient enrolled Date of database lock	Briefly describe the study design and the primary endpoint.		

It is recommended to have an introductory paragraph for each submitted dataset to describe the purpose and structure of the dataset along with the detailed explanation of all derived variables in the document. For derived categorical variables, please list all possible values and their meanings in details. Here are a few examples.

Example 1: This dataset has one record per subject with fields for demographic and baseline characteristics.

Example 2: This dataset has one record per subject's visit with fields for laboratory identification and laboratory measurements, including name, character value, and numeric value, and unit, the upper and lower ranges of normal. In addition, the dataset also includes fields X, Y, and Z for subject level covariates. Lab parameters X, Y and Z have two different units of measurement depending on which lab conducted the measurement. X is either measured in IU/ml or mg/dl; Y is measured in either y1 or y2; Z is measured in either z1 or z2. A measurement with a value outside the limits of quantitation is recorded as missing values for the numeric value field and '<50', or '>75,000'.

Example 3: This dataset has one record per subject's visit with fields for the date of visit, day since the start of the first drug, and primary efficacy variable.

2) For each submission that includes the dataset, please provide a description for the purpose of this dataset submission. For example, it should be clearly stated that if the original submitted dataset contains errors and the new dataset is its replacement.

The information requested above may be present in other sections of the submission. However, following the above recommendations will make it easier for FDA reviewers to retrieve the basic information to understand the study before using the dataset.

3. Consistent variable naming

The names for the variables should be consistent across the studies and be compliant with the CDISC and ADaM naming conventions whenever applicable.

4. Raw datasets

Raw datasets refer to the dataset created directly based on the CRF or other original source documentation without any modifications. If exceptions are made, then clear explanation should be provided. Preferably raw datasets should be separated from the derived datasets, either by placing them in different folders (Raw Data and Derived Data), or by a clearly self-explained naming convention. If raw variables and derived variables are in the same dataset, appropriate flags should be created to indicate the raw vs. derived status. All variables from raw datasets should directly link to the CRFs and a hyperlink is desirable.

5. Programs for derived dataset and key efficacy analysis

The SAS or other programs such as R that were used to derive the key efficacy variables should be submitted together with the description of the algorithm. Similarly the programs for key efficacy analyses that can be used easily to reproduce the results in the study report should be provided. This could be part of description of dataset document mentioned in section 2. The current computing platform in FDA is Windows XP, please make sure your programs and datasets submitted will work on this platform.

6. Dataset for deaths and disease progression

1. Please make sure all deaths and new disease progression information is captured in a separate dataset.
2. In addition to the follow-up information for the patients who were in the primary efficacy analysis population, reasons for not participating in the study should be collected. We expect complete information on survival for all subjects randomized.

7. Dataset Source documentation, Source documentation, randomization code and standard operating procedures (SOPs)

- 1) Please clarify if the copies of the laboratory source documents of key measurements such as viral loads and CD4⁺ cell counts measurements for submitted trials are available at the sites. If such documents are not available please describe:
 - a. How this information was communicated to the investigators and the sponsor.
 - b. How and where these original source documents are maintained.
- 2) Please provide the address and phone number of the central laboratory used.
- 3) If external vendors were used to generate the treatment allocation codes for trials, please provide their addresses and telephone numbers. In addition, please disclose to

FDA any financial or partnering agreements between the sponsor and the external vendors.

4) For all submitted randomized trials, please send the original source documents related to the treatment randomization schedules generation to FDA directly. These in general includes:

1. The full treatment allocation (randomization) codes and information on when the vendors received/generated the original codes.
2. The program code that generated the treatment allocation codes.
3. The randomization log file in the IVRS system.
4. Certification that the documents are the original source documents and that the treatment allocation codes were generated and received on the date mentioned in part a (above) prior to study initiation.

If external vendors were used to generate or manage the treatment allocation codes, please have the external vendors do the following:

1. Submit the above requested information to the drug applicant to be included as part of the official submission.
2. Submit a copy to the FDA program manager directly. Alternatively, the vendor has the option to send the documents to the drug applicant in a tamper-proof envelope and the drug applicant then forwards the documents to the FDA program manager.

5) For all submitted randomized trials, please submit all other source documents of treatment allocation codes (e.g., from your Clinical Pharmaceutical Operations or drug packaging group).

6) For all submitted randomized trials, please provide your SOPs for randomization treatment code generation, unblinding and release of randomization codes, along with corresponding flow charts. Please specify how the randomization was done and how does the treatment allocation code link to the corresponding patient so that it is possible to verify whether each subject receives the correct treatment. In addition, please add one variable specifying the randomization code in the demographic dataset and provide a hyperlink between this variable and CRF.

8. Pilot dataset

To facilitate regulatory review the NDA, we recommend sponsors submit mock datasets, in the same format that will be used for the final submission, along with the define.pdf or define.xml and the description of dataset document prior to the final submission for review.

9. CDER data standards

CDER strongly encourages sponsors/applicants to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Efficacy Data Submission in ADaM Conversion for HIV Drugs

Introduction

The document provides detailed information about the clinical trial efficacy data submission in SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) conversion, additional to the regular clinical trial data submission, for HIV drug development. These datasets should strive to be “One Statistical Procedure Away” from the statistical results wherever possible. This approach eliminates or greatly reduces the amount of programming required by the statistical reviewers. Sponsors must submit seven data tabulation datasets as following:

1. Efficacy outcomes and related covariates
2. Raw HIV viral load and immunology data

The efficacy outcomes and related covariate dataset shall have one record only per subject and need to include at least following information:

1. Demographic variables
2. Baseline characteristics (including Baseline Genotypic and Phenotypic Data, stratification factors, etc.)
3. Exposure variables (first and last dosing date, etc.)
4. Population flags (ITT, PP, etc.)
5. Efficacy outcomes (primary, secondary, etc.)
6. Covariates and subgroup variables
7. Subject disposition variables.
8. AE. If there are one or more AEs leading to discontinuation of treatment or discontinuation of study, please record the most serious one. Otherwise, please record the most serious AE the subject experienced prior to discontinuation.

The raw HIV viral load data shall include all HIV RNA measures during the course of the trial for all subjects. It should have multiple records per subject and includes the derived window variables, which are defined in the protocol or statistical analysis plan (SAP) for each scheduled visit. Deviations from the plan should be identified and clearly documented.

- Five safety datasets are also required, one for CD4, one for lipids, one for liver (ALT, AST, bilirubin, albumin, total protein, PT/INR), one for hematology (e.g., WBC, RBC, neutrophils), one for renal events (BUN, creatinine, creatinine clearance, Glucose), and one for electrolytes (Sodium, potassium, bicarbonate).

The following section provides detailed variable list for each dataset and related information.

- Efficacy Outcomes and Related Covariates (**if any of the following variables are not consistent with the CDISC SDTM formats, please feel free to change them to CDISC SDTM formats**)

Variable Name (max=8)	Variable Label	Type	Codes (example)	Origin	Comments
1. Demog (DM)					
STUDYID	Study Identifier	Char			Unique identifier for a study.
USUBJID	Unique Subject identifier	Char			Unique among all patients submitted for the product.
SUBJID	Subject ID for the study	Char			Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.
SITEID	study site identifier				
SITEGRP	Pooled Site Group	Char			Character description of the grouping of clinical sites for analysis purposes if permissible.
INVID	Investigator identifier	char			
INVNAM	investigator Name	char			
RANDDT	Subject randomization date	Num (Date9.)	DDMMMYYYY		Date the subject is randomized
RFSTDTC	Subject Reference	char			Reference Start Date/time for the subject in ISO 8601 character format. Usually equivalent to date/time when subject was first exposed to study treatment. Required

	Start Date/Time				for all randomized subjects; will be null for all subjects who did not meet the milestone the date requires, such as screen failures or unassigned subjects.
RFSTDT	subject reference start date	Num (Date9.)	DDMMMYYYY		Numeric date of reference start date
RFENDTC	Subject Reference End Date/Time	char			Reference End Date/time for the subject in ISO 8601 character format. Usually equivalent to the date/time when subject was determined to have ended the trial, and often equivalent to date/time of last exposure to study treatment. Required for all randomized subjects; null for screen failures or unassigned subjects.
RFENDT	subject reference end date	Num (Date9.)	DDMMMYYYY		Numeric date of reference end date
BRTHDTC	Date/Time of Birth	char			Date/time of birth of the subject in ISO 8601 character format.
DOB	Date of Birth	Num (Date9.)	DDMMMYYYY		Numeric Date of Birth of the subject
AGE	Age	Num			Age expressed in AGEU. May be derived as (RFSTDT- BRTHDTC), but BRTHDTC may not be available in all cases (due to subject privacy concerns).
AGEU	Age Units	char			Unites associated with Age. Should be the same across studies when appropriate
SEX	Sex	char			Sex of the subject.
SEXCD	Sex code	Num	1=MALE, 2=FEMALE		Optional
RACE	Race	char	White, Black, Asian, Other		
RACECD	Race Code	Num	1=White, 2=Black, 3=Asian, 4=Other		Optional
ETHNIC	Ethnicity	char	Hispanic and non-hispanic		
ARMCD	Planned Arm Code	char			ARMCD is limited to 20 characters and does not have special character restrictions.
ARM	Description of	Char			Name of the Arm to which the subject was assigned (randomized).

	Planned Arm				
COUNTRY	Country	char			
...					
2. Baseline Characteristics					
WEIGHT	Weight measure at BL	Num			Optional
HEIGHT	Height measure at BL	Num			Optional
HIP	Hip measure at BL	Num			Optional
WAIST	Waist measure at BL	Num			Optional
REGION	Region	char			
VLOADBLC	Baseline HIV viral load category	char			Category used to stratify the randomization. For example, $<10^5$ at screening visit or $\geq 10^5$ at screening visit. Optional
VLOADBLN	Baseline HIV viral load value	Num			Numeric value of HIV RNA load at Baseline. Sometime this is the average of viral load of several visits before dosing. Optional
CD4BLN	Baseline CD4 count	Num			Numeric value of CD4 at Baseline. Use LOCF if missing at randomization
STR_CD4	CD4+ count category	Char			
STR_ART	Antiviral treatment category	Char			
Additional BL variables					Create as needed according to the protocol
HAPLOF	CCR5 promoter Haplotype	char			This is an example. You may change accordingly.

Additional stratification factors					Create as needed according to the protocol
REGION	Region	char			This is an example. You may change accordingly.
HCV_BSL	Hepatitis B virus infection status at Baseline	Char	YES or NO		
HBV_BSL	Hepatitis C virus infection status at Baseline	Char	YES or NO		
VIRUSBSL	Other virus infection at Baseline	Char			Value will be the name of the viruses detected at the Baseline. Like HSV INFLUENZA RSV, etc
TRTHIST	Treatment experience at entry of study	Char \$20	Naïve, NRTI Experienced PI Experienced INIST Experienced ...		Naïve, NRTI experienced, PI-Experienced, etc.
PR_VF	Whether the subject had experience prior virologic failure?	Char	YES or NO		
2.1 Baseline Genotypic and Phenotypic Data					
T_PI	Total number of PIs in the baseline	Num			

	background regimen				
T_NRTI	Total number of NRTIs in the baseline background regimen	Num			
T_NNRTI	Total number of NNRTIs in the baseline background regimen	Num			
T_FI	Total number of FI in the baseline background regimen	Num			
T_II	Total number of Integrase Inhibitor in the baseline background regimen	Num			
T_CCR5	Total number of CCR5 Inhibitor in the baseline background regimen	Num			
T_Total	Total number of inhibitors	Num			
P_PI	PSS for PI	Num			Phenotypic sensitivity score for protease inhibitor including darunavir

P_NRTI	PSS for NRTI	Num			Phenotypic sensitivity score for nucleoside reverse transcriptase inhibitor
P_NNRTI	PSS for NNRTI	Num			Phenotypic sensitivity score for non-nucleoside reverse transcriptase inhibitor
P_FI	PSS for FI	Num			Phenotypic sensitivity score for fusion inhibitor including enfuvirtide
P_II	PSS for Integrase Inhibitor	Num			Phenotypic sensitivity score for integrase inhibitor
P_CCR5	PSS for CCR5 Inhibitor	Num			Phenotypic sensitivity score for CCR5 inhibitor
P_TOTAL	Total PSS score	Num			Total phenotypic sensitivity score
G_PI	GSS for PI	Num			Genotypic sensitivity score for protease inhibitor including darunavir
G_NRTI	GSS for NRTI	Num			Genotypic sensitivity score for nucleoside reverse transcriptase inhibitor
G_NNRTI	GSS for NNRTI	Num			Genotypic sensitivity score for non-nucleoside reverse transcriptase inhibitor
G_FI	GSS for FI	Num			Genotypic sensitivity score for fusion inhibitor including enfuvirtide
G_II	GSS for Integrase inhibitor	Num			Genotypic sensitivity score for integrase inhibitor
G_CCR5	GSS for CCR5 inhibitor	Num			Genotypic sensitivity score for CCR5 inhibitor
G_TOTAL	Total GSS score	Num			Total genotypic sensitivity score
2.2 Resistance data					

3. Exposure (EX)					
TRTA	Treatment actual received	char			Treatment arm name received in the trial.
TRTP	Planned treatment	char			The planned treatment for the subject.
TRTSEQP	Planned Treatment Sequence	char			
TRTSEQA	Actual Treatment Sequence	char			
EXSTDY	Study day of start of treatment	Num			Study day of start of treatment relative to the sponsor-defined RFSTDTC.
EXENDY	Study day of end of Treatment	Num			Study day of end of treatment relative to the sponsor-defined RFSTDTC.
EXDUR	Duration of Treatment	Num			Total duration of the treatment.
BG_TRT	Background regimen at the entry	Char \$40			1. List all the background drugs' trade names, use “;” between the drug; 2. List the trade name of each drug for the combination drug; e.g., “tenofovir, emtricitabine” for truvada.
	3.1 HIV drug change				
ANYCHGDY	Study Days of first change of any drug, either study drug or background drug	Num			study days from RFSTDTC of first change of any drug.
ANYCHGDT	Date of first	Num (Date9.)	DDMMYYYY		

	change of any drug either study drug or background drug				
ANYCHGRS	Reason for the change	char			
ANYCHGAE	Any ongoing AE when discontinued?	char	YES, NO		
ANYCHAEG	Grade level of the ongoing AE	char	I, II, III, IV		
	3.2 Study drug change				
DGCHGDY	Study Days of changing the study drug	Num			
DGCHGDT	Date of first change of the study drug	Num (Date9.)	DDMMMYYYY		
DGCHGRS	Reason for the change	char			
DGCHGAE	Any ongoing AE when discontinued?	char	YES, NO		
DGCHAEG	Grade level of the ongoing AE	char	I, II, III, IV		
	3.3 Background drug changes				
STNDT	Subject reference start date/time for adding a new	Num (Date9.)	DDMMMYYYY		Some change of background drug or temporary dose modification during the trial may be permitted by the protocol and will not be considered adding a new drug

	drug				
STADT	Subject reference start date/time for adding a new drug	Num (Date9.)	DDMMMYYYY		Similar to STNDT except protocol-specified changes are also recorded
BGCHG1DY	Study Days add a new background drug	Num			Some predefined changes should be excluded
BGCHG1DT	Date of first change of the background drug	Num (Date9.)	DDMMMYYYY		
BGCHG1RS	Reason for the change	char			
BGCHG1OD	1 st Drug removed from background drug	Char \$20			Use the trade name
BGCHG1N	1 st Drug used to replace the removed old drug in background drug, or drug adding in the background therapy	Char \$20			Use the trade name
BGCHG1AE	Any ongoing AE when discontinued?	char	YES, NO		

BGCH1AEG	Grade level of the ongoing AE	char	I, II, III, IV		
BGCHG2DY	Study Day of 2 nd time add a new background drug	Num			
BGCHG2DT	Date of 2 nd change of new background drug	Num (Date9.)	DDMMYY		
BGCHG2RS	Reason for the change	char			
BGCHG2OD	2 nd Drug removed from background drug	Char \$20			Use the trade name
BGCHG2N	2 nd Drug used to replace the removed old drug in background drug, or drug adding in the background therapy	Char \$20			Use the trade name
BGCHG2AE	Any ongoing AE when discontinued?	char	YES, NO		
BGCH2AEG	Grade level of the ongoing	char	I, II, III, IV		

	AE				
4. POPULATION FLAG					
ITTFL	Intent-to-treat population flag	char	N, Y		ADaM character Indicator for the ITT population
ITTFLN	Intent-to-treat population flag, Num	Num	0, 1		ADaM numeric Indicator for the ITT population
PPROTFL	Per-protocol population flag	char	N, Y		ADaM. Indicator for the per-protocol population
PPROTFLN	Per-protocol population flag, Num	Num	0, 1		
FASFL	Full analysis set population flag	char	N, Y		ADaM. Indicator for the Full Analysis Set population
FASFLN	Full analysis set population flag, Num	Num	0, 1		
SAFFL	Safety population flag	char	N, Y		ADaM. Indicator for the Safety population
SAFFLN	Safety population flag, Num	Num	0, 1		
COMPCT	Compliance to the study drug	%			Average compliance percentage before discontinuation of study drug
...					
5. EFFICACY OUTCOMES					

5.1 TLOVR outcomes (cutoff=50 and 400 copies/mL) at Weeks 24, 48, and 96					
V24_T400	TLOVR outcome <400 copies/ML at week 24 flag	char	N, Y		
V24_T40C	Category of TLOVR outcome <400 copies/ML at week 24	Char	1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96) 4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
V24_T50	TLOVR outcome <50 copies/ML at week 24 flag	char	N, Y		
V24_T5C	Category of TLOVR outcome <50 copies/ML at week 24	Char	1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96) 4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
V48_T400	TLOVR outcome <400 copies/ML at week 48 flag	char	N, Y		
V48_T40C	Category of TLOVR outcome <400		1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96)		

	copies/ML at week 48		4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
V48_T50	TLOVR outcome <50 copies/ML at week 48 flag	char	N, Y		
V48_T5C	Category of TLOVR outcome <50 copies/ML at week 48	Char	1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96) 4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
V96_T400	TLOVR outcome <400 copies/ML at week 96 flag	char	N, Y		
V96_T40C	Category of TLOVR outcome <400 copies/ML at week 96	Char	1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96) 4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
V96_T50	TLOVR outcome <50 copies/ML at	char	N, Y		

	week 96 flag				
V96_T5C	Category of TLOVR outcome <50 copies/mL at week 96	Char	1=Responder 2=Virologic Failure 3=Never Suppressed through week xx (48 or 96) 4=Rebound 5=Discontinuation due to AE 6=Discontinuation due to Subject Default 7=Discontinuation due to Death 8=Discontinuation due to Other		
5.2 Snapshot outcomes (cutoff=50 and 400 copies/mL) at Weeks 24, 48, and 96, and related variables					
V24_S50	Snapshot outcome <50 copies/mL at Week 24	char	1 = Virologic success (HIV RNA <50 copies/mL); 2 = Virologic failure; 2a=HIV RNA ≥50 copies/mL; 2b=Discontinued due to virologic failure 2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was ≥ 50 copies/mL, 2d)=OBT changed 3. No Virologic Data 3a= Discontinued due to AE or death; 3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <50 copies/mL 3c = missing data during the window but on study.		
V24_S5C	Category of Snapshot outcome <50 copies/mL at week 24	Char			

V24_S400	Snapshot outcome <400 copies/mL at Week 24	char	<p>1 = Virologic success (HIV RNA <400 copies/mL);</p> <p>2 = Virologic failure;</p> <p>2a=HIV RNA ≥400 copies/mL;</p> <p>2b=Discontinued due to virologic failure</p> <p>2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL,</p> <p>2d)=OBT changed</p> <p>3. No Virologic Data</p> <p>3a= Discontinued due to AE or death;</p> <p>3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <400 copies/mL</p> <p>3c = missing data during the window but on study.</p>		
V24_S40C	Category of Snapshot outcome <400 copies/ML at week 24	Char			
V24_VL	HIV RNA level used to determine the snapshot outcome at Week 24	Num			
V24_VLDY	study day when the HIV RNA level was assessed and used to	Num			

	determine the snapshot outcome at Week 24				
V24_VLDT	date when the HIV RNA level was assessed and used to determine the snapshot outcome at Week 24	Num			
V48_S50	Snapshot outcome <50 copies/mL at Week 48	char	<p>1 = Virologic success (HIV RNA <50 copies/mL); 2 = Virologic failure; 2a=HIV RNA ≥50 copies/mL; 2b=Discontinued due to virologic failure 2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was ≥ 50 copies/mL, 2d)=OBT changed 3. No Virologic Data 3a= Discontinued due to AE or death; 3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <50 copies/mL 3c = missing data during the window but on study.</p>		
V48_S5C	Category of Snapshot outcome <50	Char			

	copies/ML at week 48				
V48_S400	Snapshot outcome <400 copies/mL at Week 48	char	<p>1 = Virologic success (HIV RNA <400 copies/mL);</p> <p>2 = Virologic failure;</p> <p>2a=HIV RNA ≥400 copies/mL;</p> <p>2b=Discontinued due to virologic failure</p> <p>2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL,</p> <p>2d)=OBT changed</p> <p>3. No Virologic Data</p> <p>3a= Discontinued due to AE or death;</p> <p>3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <400 copies/mL</p> <p>3c = missing data during the window but on study.</p>		
V48_S40C	Category of Snapshot outcome <400 copies/ML at week 48	Char			
V48_VL	HIV RNA level used to determine the snapshot outcome at Week 48	Num			
V48_VLDY	study day when the HIV RNA level	Num			

	was assessed and used to determine the snapshot outcome at Week 48				
V48_VLDT	date when the HIV RNA level was assessed and used to determine the snapshot outcome at Week 48	Num			
V96_S50	Snapshot outcome <50 copies/mL at Week 96	char	<p>1 = Virologic success (HIV RNA <50 copies/mL);</p> <p>2 = Virologic failure;</p> <p>2a=HIV RNA \geq50 copies/mL;</p> <p>2b=Discontinued due to virologic failure</p> <p>2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was \geq 50 copies/mL,</p> <p>2d)=OBT changed</p> <p>3. No Virologic Data</p> <p>3a= Discontinued due to AE or death;</p> <p>3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <50 copies/mL</p> <p>3c = missing data during the window but on study.</p>		
V96_S5C	Category of	Char			

	Snapshot outcome <50 copies/ML at week 96				
V96_S400	Snapshot outcome <400 copies/mL at Week 96	char	<p>1 = Virologic success (HIV RNA <400 copies/mL);</p> <p>2 = Virologic failure;</p> <p>2a=HIV RNA ≥400 copies/mL;</p> <p>2b=Discontinued due to virologic failure</p> <p>2c=Discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL,</p> <p>2d)=OBT changed</p> <p>3. No Virologic Data</p> <p>3a= Discontinued due to AE or death;</p> <p>3b = discontinued due to other reasons and HIV-1 RNA at the time of discontinuation was <400 copies/mL</p> <p>3c = missing data during the window but on study.</p>		
V96_S40C	Category of Snapshot outcome <400 copies/ML at week 96	Char			
V96_VL	HIV RNA level used to determine the snapshot outcome at Week 96	Num			
V96_VLDY	study day	Num			

	when the HIV RNA level was assessed and used to determine the snapshot outcome at Week 96				
V96_VLDT	date when the HIV RNA level was assessed and used to determine the snapshot outcome at Week 96	Num			
5.3 other efficacy outcomes					
TAD	Time averaged difference	Num			
V48_TAD	TAD of Viral Load at Week 48	Num			LVCf (censored at last available visit)
V48_TADB	TAD of Viral Load at Week 48	Num			BLCF
V48_CB	Week 48 VL Change from baseline	Num			
V24_CB	Week 24 VL Change from	Num			1) If there were multiple measurements within a visit window, then the last one was used.

	baseline				<p>2) If the subject withdrew from the study or discontinued the assigned study before Week 24, then the subject was considered as no change from baseline, i.e., baseline observation carried forwards (BOCF).</p> <p>3) Otherwise, if the measurement at Week 24 was missing but the one at next visit was available, then the one at the next visit was used; and if the one at next visit was missing as well, then the one at the previous visit, was carried forwards to Week 24.</p>
V96_CB	Week 96 VL Change from baseline	Num			
CD4_48	CD4 cell counts at week 48	Num			
CD4CB_48	Change in CD4 cell counts from Baseline to week 48	Num			
CD4_96	CD4 cell counts at week 96	Num			
CD4CB_96	Change in CD4 cell counts from Baseline to week 96	Num			
CD8_48	CD8 cell counts at week 48	Num			
CD8CB_48	Change in CD8 cell	Num			

	counts from Baseline to week 48				
CD8_96	CD8 cell counts at week 96	Num			
CD8CB_96	Change in CD8 cell counts from Baseline to week 96	Num			
VF400_TS	Time of confirmed response <400 copies/mL	Num			If never then set the day to 100000
VF400_TF	Time of first rebound				
VF400_T2	Time to confirmed re-suppression				Re-suppression after confirmed rebound
VF50_TS	Time of confirmed response <50 copies/mL	Num			
VF50_TF	Time of first rebound				
VF50_T2	Time to confirmed re-suppression				
VFNDR_T	Time first reached nadir				
VFNDR_TF	Time of				Use 1 log above nadir with confirmation. May be a

	rebound from nadir				better indicator for viral resistance
Add other variables when appropriate					
6. Covariates / Subgroup					
DrugCat	HIV Drug Classes for the experimental drug	Char			NRTI, NNRTI, PI, FI, CCR5, etc.. If the experimental drug is more than 1 and from more than 1 drug class, MIX may be used
DrugID	Experimental drug generic name	Char	Lamivudine, tipranavir, ...		ADaM, may be used by sponsor for ISE, or for reviewers for drug class analysis
APV	Is Amprenavir (APV) in the randomized background regimen?	Num	0=No 1=Yes		Create variables only for the drugs used
ATV	Is Atazanavir (ATV) in the randomized background regimen?	Num	0=No 1=Yes		Create variables only for the drugs used
DRV	Is Darunavir (DRV) in the randomized background regimen?	Num	0=No 1=Yes		
FAPV	Is Fosamprenavir	Num	0=No 1=Yes		

	(FAPV) in the randomized background regimen?				
IDV	Is Indinavir (IDV) in the randomized background regimen?	Num	0=No 1=Yes		
LPVr	Is Lopinavir/Ritonavir (LPVr) in the randomized background regimen?	Num	0=No 1=Yes		
NFV	Is Nelfinavir (NFV) in the randomized background regimen?	Num	0=No 1=Yes		
RTV	Is Ritonavir (RTV) in the randomized background regimen?	Num	0=No 1=Yes		
SQV	Is Saquinavir (SQV) in the randomized background regimen?	Num	0=No 1=Yes		
TPV	Is Tipranavir (TPV) in the	Num	0=No 1=Yes		

	randomized background regimen?				
ABC	Is Abacavir (ABC) in the randomized background regimen?	Num	0=No 1=Yes		
DDI	Is Didanosine (DDI) in the randomized background regimen?	Num	0=No 1=Yes		
FTC	Is Emtriciabine (FTC) in the randomized background regimen?	Num	0=No 1=Yes		
3TC	Is Lamivudine (3TC) in the randomized background regimen?	Num	0=No 1=Yes		
D4T	Is Stavudine (D4T) in the randomized background regimen?	Num	0=No 1=Yes		
TDF	Is Tenofovir (TDF) in the randomized background regimen?	Num	0=No 1=Yes		

FTC	Is Zalcitabine (FTC) in the randomized background regimen?	Num	0=No 1=Yes		
ZDV	Is Zidovudine (DV) in the randomized background regimen?	Num	0=No 1=Yes		
DLV	Is Delavirdine (DLV) in the randomized background regimen?	Num	0=No 1=Yes		
EFV	Is Efavirenz (EFV) in the randomized background regimen?	Num	0=No 1=Yes		
ETV	Is Etravirine (ETV) in the randomized background regimen?	Num	0=No 1=Yes		
NVP	Is Nevirapine (NVP) in the randomized background regimen?	Num	0=No 1=Yes		
T20	Is Enfuvirtide (T20) in the randomized	Num	0=No 1=Yes		

	background regimen?				
RAL	Is Raltegravir (RAL) in the randomized background regimen?	Num	0=No 1=Yes		
MVC	Is Maraviroc (MVC) in the randomized background regimen?	Num	0=No 1=Yes		
7. Disposition (DS)					
DSCAT	category for disposition event	char		From CRF	
DSSCAT	Subcategory for disposition event	char			A further categorization of disposition event
DSDTC	Date/Time of Collection	char	ISO 8601		
DSDT	Date of Collection	Num (Date9.)	DDMMMYYYY		
DSSTDTC	Start Date/Time of Disposition Event	Char	ISO 8601		
DSSTDT	Start Date of Disposition Event	Num (Date9.)	DDMMMYYYY		
DSSTDY	Study Day of	Num			

	Start of Disposition Event				
DSCNRSN	Investigator classification				For reasons of discontinuation
DSCNRSN1	Additional reasons				
DSCNRSN2	Additional reasons				
DSCNCMT	Comments for discontinuation				Describe posthoc efforts to adjudicate the reasons
DSCNVL	Viral load at discontinuation				In log10 copies/mL
DSCNCD4	CD4 counts at discontinuation				
DSCNAE	Any ongoing AE when discontinued?				
DSCNAEG	Grade level of the ongoing AE				Highest grade level with 14? days
CDCDy	Study day of the first new CDC Class C event				
DeathDy	Study day for death				
8. Adverse Events (AE)	AE includes: GI, rash, reno toxicity, cardiovascular, malignancy, neurological AE, neuropathy, lipid lowering events, kidney stone.				

--	--	--	--	--	--

3. Raw Viral Load Data one for HIV, one for CD4, one for lipids, one for liver (ALT, AST, bilirubin, albumin, total protein, PT/INR), one for hematology (eg, WBC, RBC, neutrophils), one for renal events (BUN, creatinine, creatinine clearance, Glucose), and one for electrolytes (Sodium, potassium, bicarbonate). **If any of the following variables are not consistent with the CDISC SDTM formats, please feel free to change them to CDISC SDTM formats.**

Variable Name (max=8)	Variable Label	Type	Codes (example)	Origin	Comments
USUBJID	Unique Subject identifier	Char			Unique among all patients submitted for the product.
SUBJID	Subject ID for the study	Char			Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.
VISITNUM	Visit Number	Num			
VISITDY	Study Day	Num			
VISIT	Visit name	Char			
<i>ANAWEEK</i>	Analysis Week	Char	Screening Baseline Week 2 Week 4 ...		
ANAWEEKN	Analysis week	Num	-1=Screening 0=Baseline 2=week 2 4=week 4 ... 48=week 48 .. 96=week 96		

			... 999=unscheduled visit ...		
LBANALFL					indicates which value in the analysis week was used if there are multiple values in a window
LBACTDT	Actual Date of specimen collection				
LBACTDY	Actual Study Day of Specimen Collection				
LBTEST	Lab test name		Need input of test codes		
LBSTRESN	Result				
LBSTUNIT	Standard unit				
LBTESTL					Lower limit for the normal range of the lab measure
LBTESTU					Upper limit for the normal range of the lab measure
LBFLAG	Lab flag for fasted sample				
TOXCLASS					lab toxicity grade assigned
PHASE			0=screening 1=on randomized treatment 2=on randomized treatment with non-protocol-specified change in the		Phase=1 as long as the patient is on the original randomized treatment even if that is beyond the planned duration of the study and being called follow-up. Protocol-specified changes of background do not count as changes of original treatment. Phase=99 only if patient has changed the original randomized treatment. Protocols

			background regimen 99=follow-up period		may allow treatment interruptions without any rescue medication being given in place of randomized treatment, Phase=1 during such protocol-specified interruptions.

References

1. CDISC – SDTM V1.2 and SDTM IG V3.1.2
2. CDISC – ADaM 2.1 and ADaMIG 1.0 Draft

Dates: The year should be in 4 digits like 1983, 2003 etc.

The TLOVR analysis previously used in labeling by the DAVP has often led to multiple queries for the applicant. DAVP statistical and clinical reviewers recently completed a project titled, “Handling uncertainty in endpoint selection and other endpoint issues.” The goal of the project was to determine if simplified or more powerful endpoints could be used for traditional approval at Week 48. The team evaluated 18 trials from seven NDAs with 8046 patients. CDISC datasets for HIV RNA, demographics, CD4 cell counts, and discontinuation were created. Results obtained using the TLOVR algorithm, which utilized data from every visit to consider the pattern of HIV responses, were compared to a less complicated “snapshot” approach which only utilized HIV RNA data at the visit of interest. A high concordance between the TLOVR algorithm and snapshot results was observed. Using the TLOVR algorithm, 61% of the 8046 patients remained in the study for 48 weeks and were virologic responders compared to 61% of the subjects using the snapshot approach; 18% were virologic non-responders using the TLVOR algorithm compared to 17% using the snapshot approach and approximately 20% discontinued prior to Week 48 using both approaches. The likelihood of clinically significant differences between the two methodologies for evaluating efficacy is minimal.

Based on the findings from the project and the ease of the snapshot method, pending sNDAs and future NDAs will include virologic outcome results based on snapshot approach in the product labeling. Included below are the principles and procedures for calculating virologic outcome for labeling.

Snapshot Approach

Proposed windows

- Window size is ½ the duration of time between study visits
- Windows may be smaller at earlier time points and can possibly be asymmetric, particularly at earlier time points
- If your trial-defined windows differ from the proposed windows below, please discuss with the Division. In most cases the protocol-defined windows for completed trials are acceptable; however, for future trials we encourage standardization and request you use the following:

Visit	Window (through end of Study Week) <i>(express in days for non-overlap)</i>	Window (Days)
24	18-30	126-209
48	42-54	294-377
96	90-102	630-713

Example of efficacy presentation in labeling

Virologic Outcome at 96 week window (Window 90 – 102 weeks)

	Drug A	Drug B
Virologic Success HIV RNA ≤ 50 copies/mL	60%	50%
Virologic Failure#	20%	30%
No Virologic Data at 96 Window		
Reasons		
Discontinued study/study drug due to AE or Death*	10%	8%
Discontinued study/study drug for Other Reasons**	6%	6%
Missing data during window but on study	4%	6%

#Includes patients who changed OBT to new class or changed OBT not permitted per protocol or due to lack of efficacy prior to Week 96, subjects who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96 week window

*Includes patients who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

**Other includes: withdrew consent, loss to follow-up, moved etc.

Principles of snapshot analysis

- The primary efficacy endpoint is intended to be primarily a virologic endpoint and not a clinical endpoint. This method follows a “Virology First” hierarchy.
- Percentages not included in “virologic success or failure” rows are meant to describe reasons for no data at a specified analysis time window in an ITT analysis. These percentages are not meant to represent comprehensive safety or clinical efficacy analyses.
- Given this is primarily a virologic endpoint, the hierarchy for assessing row and column percentages is “Virologic Success” or “Failure” first for any given time window followed by reasons for “No Virologic Data in the Window”.

Procedures for calculating virologic outcome

Data in the window

- Virologic Success or Failure will be determined by the last available measurement while the subject is on- treatment and continued on-trial within the time window (see windows table below).
 - Examples: HIV RNA = 580 at Day 336, HIV-RNA < 50 on Day 350. This is a success.
 - In the rare example that someone would have HIV RNA < 50 at Day 336 and then ≥ 50 at Day 350, this would still be called a failure (we believe

this will be rare, because undetectable patients would not be likely to have a second lab result in a window).

No data in the window

- If there are no data in a time window, then tally percentages for each category of missing data.
- There are 3 reasons for no data in the window:
 - Discontinued Study due to Adverse Events or Death.

Any subject who discontinues due to an adverse event or death **prior to** the window should be classified as “Discontinued due to AE” or “Death” (as appropriate), regardless of the HIV RNA result, even if the HIV RNA <50 at the time of discontinuation. [Note: there will not be a separate category for Death. We believe a separate category for Death is misleading, because it does not account for all Deaths. Instead, in text we can report all AIDS defining events and Deaths.] However, if a subject has an HIV RNA value in the time window and also discontinues **in the time window**, we use the viral load data. This is the “Virology First” hierarchy. Example: HIV-RNA < 50 at Day 336 and discontinues due to AE or even dies on Day 360---this person is a virologic success. Likewise if HIV-RNA is 552 on Day 336 and subject discontinues on Day 360, subject is a virologic failure. **Bottom line:** if there are any virologic data in the window **while on-treatment**—use this first to assess the endpoint.
 - Discontinued Study due to Other Reasons.

Same examples above, apply to this category. If someone discontinues study before the window due to “lack of efficacy” then they should be included in the virologic failure row and not in the “Discontinue for Other Reasons” row. To further clarify, subjects who “Discontinue for Other Reasons”, it is essential to realize that in the “Virology First” hierarchy only subjects who have achieved virologic suppression may be counted as “Discontinued due to Other Reasons.” Subjects who do not have their last viral load < 50 copies/mL, must be categorized as virologic failure. For example, if a subject discontinues due to “subject withdrew consent” and their HIV-1 RNA result at the time of discontinuation was ≥ 50 copies/mL, then they must be counted as a virologic failure and NOT as “Discontinue for Other Reasons.” However, if a subject discontinued due to “Lost to Follow-up” and the last HIV RNA result was 49 copies/mL, then the subject may be categorized as “Discontinue for Other Reasons.”

 - Likewise, if subjects changed background treatment—*not permitted by protocol*—they should be considered an efficacy failure and captured in the virologic failure row.
 - On Study but Missing Data.

Only data in the window may be used for subjects remaining on study. If there is no data in the window, you may not look past the window and use

the next value. For example, if there are no data during Days 294-377, but there is an HIV-RNA < 50 on Day 380, this subject is considered "On Study but Missing Data." This subject may count as a success at subsequent analysis points (e.g., 96 weeks), if they remain undetectable at the subsequent analysis window (e.g., 96 weeks). Conversely, if there are no data during Days 294-377, but there is an HIV-RNA \geq 50 on Day 280, this subject is also considered "On Study but Missing Data".

OBT substitutions

Typically trials have permitted one in class substitution of an OBT drug for documented toxicity reasons. As more drugs are available, across class substitutions were permitted in some trials; however, this can impact long term durability of a regimen particularly if the OBT change occurred later in the trial. OBT substitutions (in class or across class) permitted per protocol for documented toxicity reasons are permitted on or before the first trial visit without penalty. If OBT substitutions for toxicity reasons occur after the first trial visit, then patients are considered virologic failures if they have HIV RNA > 50 copies/mL at the time of switch.

We have received requests from sponsors to amend the algorithm such that only across-class switches are classified as primary endpoint failures because not allowing within class OBT substitutions may create disincentives. Such disincentives cited are investigators may be de-incentivized to ensure long-term follow-up after an OBT switch because those subjects are deemed as analysis failures or may result in unnecessary increase in early switches to avoid classifying subjects as failures in the primary efficacy analysis.

We decided not to amend the algorithm for the following reasons:

- All in-classes switches are not the same. With the expanded number of drugs in each class and the approval of second generation drugs within the same class, switching therapy after knowledge of viral load changes may confound the results. One would then have to decide which switches are appropriate for the population being studied.
- We attempted to make the snapshot as concise and stringent as possible to reduce the amount of end-of-FDA-review negotiations over single cases. Having to decide which in-class switches are appropriate for specific populations (naïve, experienced, etc.) would complicate the algorithm. Example: in what population is a switch from atazanavir to darunavir considered acceptable.
- We believe that the unwanted scenarios mentioned above can be minimized. Both types of analyses can be conducted, perhaps allowing cross-class switches in analyses presented in publications, etc. However, for FDA labeling purposes, the snapshot should be used. Therefore investigators could be informed that not all analyses results in their particular subject counting as a failure if they switch and that follow-up should be maintained.

- We do not believe that there is one “correct” analysis. All analyses only approximate truth. We are only striving for efficiency and consistency across multiple applications. This should not prohibit the presentation of slightly different analyses at meetings or publications. Differences can be described in footnotes.

Datasets for snapshot approach

For submission with multiple trials, each trial should have its own dataset for the snapshot analysis. The datasets should contain, at minimum, the following information:

- study ID
- patient study ID
- study day and date of last double-blind treatment
- virologic outcome at Week 96 based on the snapshot approach (i.e., virologic success, virologic failure, discontinued due to AE or death, discontinued due to other reasons, missing data during window but on study)
- the HIV RNA measurement and the corresponding study day and date used to determine the above virologic outcome if the measurement was not missing
- study day and date when the patient switched to open-label treatment due to virologic failure if applicable
- discontinuation study day and date, reason and last on-double-blind-treatment measurement before discontinuation for the patients who discontinued drug
- treatment phase in dataset should be defined and only include 3 categories as follows: screening (or baseline), treatment, and follow-up

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

/s/

STACEY MIN
03/01/2012



IND 101,283

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GS-9350.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2010. The purpose of the Type B, End of Phase 2 meeting was to review the nonclinical, Phase 1 and Phase 2 clinical data and to provide comments on the design of the Phase 3 studies of GS-9350. We also discussed the key aspects of the development plan for GS-9350, including the data required to support an indication to boost antiretrovirals including elvitegravir (EVG), atazanavir (ATV), and darunavir (DRV).

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

If you have any questions, call Stacey Min, Pharm.D., Regulatory Project Manager at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 12, 2010

TIME: 1:00 – 2:30 PM

LOCATION: White Oak, CSU, E-2046

APPLICATION: IND 101,283

DRUG NAME: GS-9350

TYPE OF MEETING: Type B Meeting

MEETING RECORDER: Stacey Min, Pharm.D., Regulatory Project Manager

FDA ATTENDEES:

Debra Birnkrant, M.D.	Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH	Deputy Director, DAVP
Linda Lewis, M.D.	Medical Team Leader, DAVP
Peter Miele, M.D.	Medical Officer, DAVP
Kellie Reynolds, Pharm.D.	Deputy Director, Division of Clinical Pharmacology 4 (OCP/DCP4)
Sarah Robertson, Pharm.D.	Clinical Pharmacology Team Leader, (OCP/DCP4)
Vikram Arya, Ph.D.	Clinical Pharmacology Reviewer, (OCP/DCP4)
Peyton Myers, Ph.D.	Pharmacology/Toxicology Acting Team Leader, DAVP
Greg Soon, Ph.D.	Biometrics Team Leader, DAVP
Wen Zeng, Ph.D.	Biometrics Reviewer, DAVP
Julian O'Rear, Ph.D.	Clinical Virology Team Leader, DAVP
Takashi Komatsu Ph.D.	Clinical Virology Reviewer, DAVP
Mark Seggel, Ph.D.	Product Quality Acting Team Leader, Office of New Drug Quality Assessment IV (ONDQA IV)

Kimberly Struble, Pharm.D.
Victoria Tyson
Vanessa Perry, M.S.
Camille Bossard
Stacey Min, Pharm.D.

Medical Team Leader, DAVP
Chief, Project Management Staff, DAVP
Regulatory Project Manager, DAVP
Student Intern
Regulatory Project Manager, DAVP

EXTERNAL CONSTITUENT ATTENDEES:

Gilead Sciences, Inc:

Roy Bannister, Ph.D., DABT
Christophe Beraud, Ph.D.
Brian Kearney, Pharm.D

Steven Chuck, M.D.
Paul Tomkins, Ph.D.

Director, Drug Safety Evaluation
Senior Manager, Regulatory Affairs
Senior Director, Clinical Research and
Clinical Pharmacology, Project Leader
Vice-President, Clinical Research
Senior Director, Regulatory Affairs

1. BACKGROUND

Gilead Sciences Inc. is developing a new chemical entity, GS-9350 under IND 101,283 as a pharmacoenhancer to increase the systemic levels of coadministered antiretroviral agents metabolized by CYP3A enzymes, including elvitegravir (EVG), atazanavir (ATV) and darunavir (DRV).

Gilead has conducted Phase 1 and 2 studies to study the effects of GS-9350 as a pharmacoenhancer for once daily EVG, ATV, or DRV. GS-9350 is also under development as a fixed-dose combination (FDC) tablet consisting of EVG/FTC/TDF/GS-9350 under IND 103,093.

Gilead requested this Type B, End-of-Phase 2 meeting to discuss the nonclinical, Phase 1 and Phase 2 clinical data with GS-9350 and the FDC tablet and to seek agreement on key aspects of the development plan for GS-9350, including data required to support an indication to boost antiretrovirals including EVG, ATV and DRV.

2. DISCUSSION

Question 1

Does the Agency agree that Phase 3 clinical studies of GS-9350 as the stand-alone tablet or as part of the EVG/FTC/TDF/GS-9350 FDC tablet can proceed?

We agree that Phase 3 clinical studies of GS-9350 may proceed. See, however, comments below regarding GS-9350's boosting effect of darunavir and further protease inhibitor (PI) boosting studies.

Discussion: No further discussion.

Question 2a

Does the Agency have any comments regarding the Phase 3 study of GS-9350-boosted ATV versus RTV-boosted ATV both in combination with Truvada (FTC/TDF) in treatment-naïve, HIV-1 infected subjects (Study GS-US-216-0114), as the pivotal study to support the approval of GS-9350 as a booster of ATV?

- We agree with the trial design, study population and endpoints of GS-US-216-0114. The 12% of non-inferiority margin used for ART-naïve subjects is acceptable for planning purposes and study design but will be assessed further during the review.*

Discussion: No further discussion.

- *We note that you intend to use the TLOVR algorithm. The Division has recently switched to the snapshot methodology. A document containing recommendations on conducting the snapshot analysis will be made available to you in the near future. Please change the primary efficacy endpoint to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. The TLOVR algorithm for HIV-1 RNA <50 copies/mL through Week 48 should be used for one of your secondary efficacy endpoints.*

Discussion:

The Agency informed Gilead that TLOVR method of analyses will no longer be used for the primary endpoint but has been replaced with the snapshot methodology. The snapshot analyses will be implemented for all studies moving forward. The Agency will finalize documents on conducting the snapshot analyses and will send recommendations to Gilead next week. Gilead asked the Agency about subjects who switch therapy. The Agency responded that if a new antiretroviral (ARV) is added to a subject's regimen, the subject will be classified as failure whether or not the viral load is greater than 50 copies/mL in the window. Switches for documented toxicity reasons are permitted on or before the first trial visit without penalty. If the switch occurs after the first trial visit, patients are considered failures if they have HIV-1 RNA > 50 copies/mL at time of the switch. The Agency asked Gilead to define acceptable therapeutic switches. The Agency agreed that the TLOVR analysis need not be a prespecified secondary endpoint, but acknowledged that having the TLOVR analysis would be useful as the Agency plans to compare both analyses. Gilead agreed to make the TLOVR secondary analyses available.

- *We also note that the control arms for GS-US-216-0114 and GS-US-236-0103 are identical, namely ritonavir-boosted atazanavir plus FTC/TDF. The Division suggests you consider combining the two studies into a single study with one comparator arm in order to conserve study subject populations.*

Discussion:

Gilead thanked the Agency for the suggestion, but indicated that it would be logistically difficult to combine the two trials into a single, 3-arm trial due to issues of blinding. Subjects would be required to take more pills and the duration of the trial would have to be extended. Gilead will conduct the two separate trials, GS-US-216-0114 and GS-US-236-0103, as originally planned. Gilead plans to start the trials soon and will incorporate the snapshot methodology in the statistical analysis plan (SAP). The Agency agreed.

Question 2b

Does the Agency agree that the proposed development plan will support the registration of GS-9350 tablet as a pharmacoenhancer of EVG tablets and DRV?

The proposed development plan seems appropriate. Please be aware of the following:

- *When co-administered with GS-9350 (either once daily or twice daily), if PI exposures are determined to be lower than the PI exposures when co-administered with ritonavir (RTV) at the approved PI/RTV dose, supporting efficacy data will be needed. If PI/GS-9350 exposures are higher than PI/RTV exposures, then supporting safety data will be needed. If supporting efficacy or safety data cannot be provided to support the lower or higher PI exposures observed with GS-9350, additional evaluation in HIV-infected patients will be necessary to determine the clinical relevance of the increased or decreased pharmacokinetic (PK) parameters of the PI.*

Discussion:

Gilead agreed that strict bioequivalence of PI exposure when co-administered with RTV or GS-9350 is ideal and asked the Agency about the clinical data that would be required if strict bioequivalence is not demonstrated. In the case of DRV, Gilead noted that C_{tau} was not bioequivalent between RTV and GS-9350 boosting but C_0 was bioequivalent, and that C_0 is reflected in the DRV label. The Agency informed Gilead they have not seen the full study report for the PK study performed with DRV + GS-9350. Gilead indicated they would provide supporting data obtained from literature, the DRV label and from Tibotec to support the efficacy of DRV when boosted with GS-9350. The Agency asked if Gilead had any arrangement with Tibotec. Gilead indicated there was no formal arrangement, but that they have been in communication with Tibotec regarding the use of DRV with GS-9350. The Agency informed Gilead that a Right of Reference would be required to use any of the previously submitted DRV data in an NDA for GS-9350. The Agency stated that in the event the PK parameters are matched for a given PI boosted with GS-9350, the need for further clinical data in HIV patients will be evaluated on a case-by-case basis and will depend on the outcome of ongoing trials of atazanavir/GS-9350 and other PK data.

Question 3

Does the Agency agree with the possible staggered filing of the GS-9350 tablet NDA relative to the NDAs for EVG tablets and EVG/FTC/TDF/GS-9350 FDC tablet?

We agree with the possible staggered filing of the GS-9350 tablet NDA relative to the NDAs for EVG tablets and the FDC tablet. The content and format of the NDAs will require further discussion at the Pre-NDA meetings. Please be aware, if you submit the EVG and FDC tablet NDAs prior to the GS-9350 NDA, you will be eligible for three years of exclusivity, rather than five years of exclusivity, for a new chemical entity.

Discussion:

Gilead acknowledged that they will only be eligible for three years of exclusivity if the GS-9350 NDA is submitted after the NDAs for EVG and the FDC tablet. The Agency

inquired about the reason for the delay in filing the NDA for GS-9350 compared to the two other NDAs. Gilead stated that logistically it would be difficult to submit three NDAs simultaneously. Gilead will submit the product quality information for GS-9350 with the NDA for the FDC tablet.

Question 4a

Does the Agency agree that the proposed plan to study drug interactions between GS-9350 and other PIs, including those administered twice-daily is sufficient to support registration of GS-9350 and to provide appropriate drug interaction labeling information for these agents?

The proposed plan seems appropriate. Please address the following:

- *Will dosing recommendations pertaining to the concomitant use of all of the PIs (used once or twice daily) and GS-9350 be available at the time of submitting the registration application for GS-9350 as pharmacoenhancer for ATV and DRV?*

Discussion:

Gilead indicated that following an evaluation of GS-9350 with EVG, atazanavir (ATV) and DRV, (b) (4) will be evaluated. In addition, the feasibility of twice-daily dosing with GS-9350 will be addressed (b) (4). The Agency agreed that the proposal seems appropriate and expressed that determination of an appropriate dose may not be feasible or necessary for every PI. The need for additional studies with other PIs will be determined by the results of ongoing and planned PK studies. The Agency, however, encouraged Gilead to obtain as much data as possible for all of the approved PI regimens, such that an appropriate dose or recommendation for use can be clearly stated in the GS-9350 label for each PI in order to prevent off-label use. Gilead stated that a study to evaluate the PK and safety of GS-9350 twice daily and additional studies including GS-9350 plus twice daily DRV will be provided in the original NDA.

Question 4b

Does the Agency agree that the plan to evaluate the drug interaction potential of GS-9350 with key concomitant medications and to study GS-9350 in special populations is sufficient to support registration of GS-9350?

The need for additional drug-drug interaction studies (in addition to the studies outlined in the meeting package) will be determined by the results of ongoing and planned drug-drug interaction studies. For example, the results from the planned “cocktail” study will help determine the need for evaluating the drug-drug interaction potential of GS-9350 with other antiretroviral and non-antiretroviral drugs.

Please address the following:

- a) *How will drug-drug interaction information be extrapolated from a “PI/RTV/co-administered drug” combination to “PI/GS-9350/co-administered drug” combination?*

Discussion:

Gilead acknowledged that the cocktail study and planned drug interaction studies with (b) (4) will provide additional information to help determine the need for additional drug interaction studies. Gilead stated that they intend to systematically address each of the established DDIs for a given PI and will determine the need for data with GS-9350 + the PI + coadministered drug on a case-by-case basis. The Agency stated that there are many factors and pathways involved in PI/RTV interactions with other drugs and a rationale will need to be provided for each combination.

- b) *Has GS-9350 been evaluated as a potential substrate, inducer, or inhibitor for transporters OATP1B1, OATP1B3 and BCRP? Since ritonavir is an inhibitor of OATP1B1 and OATP1B3, the extrapolation of certain drug-drug interactions for a particular PI/RTV combination will require knowledge of GS-9350 specificity for these transport proteins.*

Discussion:

Gilead stated that they have developed assays for these transporters and will be conducting these in vitro studies soon.

- c) *Given that the observed increase in serum creatinine with GS-9350 is being described as consistent with inhibition of active tubular secretion of creatinine, similar to that observed with cimetidine, please comment on plans to evaluate the specificity or inhibition potential of GS-9350 for OCT transporters.*

Discussion:

The Agency reviewed the draft Phase 3 protocol for GS-9350 and asked Gilead to consider lowering the screening CrCL criterion to > 50 mL/min in order to evaluate the effect of GS-9350 in subjects with renal impairment. Alternatively, Gilead could conduct additional studies in subjects who fail to meet the CrCL criterion for the Phase 3 trial. Gilead clarified that CrCL > 70 mL/min will remain the screening criterion for the Phase 3 trial. Given the observed renal toxicities with tenofovir, the Agency inquired how Gilead plans to monitor for early signs of renal toxicity during the course of the trial. Gilead will provide investigators with CrCL calculations and estimated creatinine clearance on a regular basis.

Gilead plans to conduct a renal impairment study of GS-9350 in healthy subjects to determine the effect on safety (SCr and GFR) and PK. The Agency informed Gilead that longer duration data in HIV-infected subjects is desired. This may be accomplished by lowering the screening CrCL criterion to 50 mL/min in the Phase 3 trial or conducting separate studies. The Agency asked Gilead to include data on subjects with renal impairment with the NDA submission. Otherwise, this issue may generate a postmarketing commitment (PMC).

Question 5

Does the Agency have any comments regarding the timing and scope of the proposed pediatric development plan?

A more detailed discussion of your pediatric development plan may be needed in the near future. We recommend that you provide a more detailed plan with draft protocols or synopses as soon as they are available and urge you to begin pediatric PK, safety and activity studies simultaneously with the adult Phase 3 studies unless you identify a safety issue of specific concern in pediatric patients. We also recommend you submit copies of any communications you have had with the EMA regarding pediatric drug development. In the absence of significant safety issues, it is not necessary to stagger studies of different pediatric age groups (i.e., adolescents, then school age children, then younger children and infants) as this tends to delay collection of important pediatric data.

DAVP plans to issue a Written Request (WR) for Pediatric Studies for both EVG and GS-9350. The WR for EVG will closely parallel those for other antiretroviral drugs (see example/template posted on FDA's Pediatric website). The WR for GS-9350 is likely to be similar in scope, but internal discussion may be needed to determine how much pediatric PK and safety data are needed across age groups for a new PK enhancer. In addition, under the Pediatric Research Equity Act, all submitted NDAs, including those for fixed-dose combination products, may be subject to post-marketing requirements to evaluate new products in pediatric patients if they are likely to provide a public health benefit. All NDAs must contain a pediatric assessment and requests for waivers or deferrals of pediatric studies must be justified at the time of NDA submission.

We also question the feasibility of switch studies as a means to evaluate GS-9350 in adolescents, as we have recent examples that this type of study may be prone to failure.

Discussion:

Gilead indicated plans to submit pediatric investigational plans to all three INDs by end of May, 2010. The Agency explained that it is very likely that a pediatric assessment deferral or waiver with justification will be required for any NDA submission, including the EVG stand-alone NDA. The Agency informed Gilead of recent feedback from the Pediatric Review Committee (PeRC) that tablets of particular size or fixed-dose formulations might not be granted a waiver for pediatric studies if the FDC tablet provides a public health benefit. Therefore, it is possible that pediatric studies may still be

required for the FDC tablet in younger patients. The Agency advised Gilead to consider developing a scored or smaller size tablet. Gilead has discussed internally the pediatric studies for the FDC tablet and stated it may be a challenge to develop a lower-dose FDC tablet if each of the four components needs to be adjusted differently. Gilead is also not sure if the weight bands for tenofovir dosing can be collapsed. The Agency referred to data for the tenofovir 75 mg tablet and PEPFAR products that are available for pediatric populations. The Agency stated pediatric studies will likely require further discussion.

The Agency inquired about Gilead's plans to use switch studies to evaluate GS-9350 in adolescents as the Agency's experience with switch studies has shown them to be prone to failure. Gilead plans to evaluate a switch from RTV to GS-9350 only. The Agency advised Gilead to consider other study designs because tolerability and adherence issues following a switch in one or more drugs can result in poorer outcomes.

Gilead asked if the Agency would permit extrapolation of safety and efficacy data from adult studies. The Agency responded that it is possible to extrapolate from adult data to pediatrics and the Agency acknowledges the difficulty of enrolling comparative studies in children due to the small number of subjects. Single-arm pediatric studies are often acceptable. The Agency will consider extrapolation of adult data but adequate safety data will be needed. The Agency informed Gilead that the primary outcomes for pediatric studies should be PK and safety, with efficacy extrapolated mainly from adult studies; virologic outcomes are evaluated as secondary endpoints. Gilead inquired whether 24 weeks of pediatric trial data will be suitable to demonstrate efficacy. The Agency noted that 24 weeks is a little short but will make a determination based on a review of the data.

Additional discussion:

The Agency reiterated the renal toxicity issue with GS-9350 and also inquired about the effect on PR prolongation and bilirubin levels. Gilead responded that they have not seen an effect on PR prolongation in Phase 2 studies with GS-9350. Increases in bilirubin increases were similar in the ATV/RTV and ATV/GS-9350 arms of the study. No increases in bilirubin, liver enzymes or PR prolongation were observed with the FDC tablet in Phase 2 trials.

In the thorough QTc study conducted with GS-9350, PR prolongation was observed in the supratherapeutic range. However this study is still under review by the Agency's IRT. The Agency re-emphasized a comment sent to Gilead regarding the EVG single-drug TQTc study which questioned whether the supratherapeutic dose was high enough. The Agency stated they would re-send the comment.

Question 6

Does the Agency have any comments on the completed and planned nonclinical toxicology package for GS-9350 and its adequacy to support registration?

The nonclinical package appears adequate.

Discussion: No further discussion.

Question 7

Does the Agency agree with our proposal for submission of study analysis datasets, CRFs, or laboratory data in the NDA for GS-9350, but also the associated NDAs for EVG/FTC/TDF/GS-9350 and EVG?

The proposal for submission of study analysis datasets is acceptable. Please submit the SAS programs for generating the analysis datasets and primary efficacy endpoint analyses. In addition to submission of these data, other efficacy datasets may be requested for the NDA submission. The specification of these other datasets will be provided at a later date and further discussion regarding dataset formats may be held at the pre-NDA meeting.

Discussion:

Gilead requested clarification on whether SDTM (Study Data Tabulation Model) data format will become mandatory. The Agency stated that SDTM data format is recommended but not mandatory but asked Gilead to submit the data in this format as it would help in the review process.

3. ISSUES REQUIRING FURTHER DISCUSSION

- The Agency asked Gilead to submit the final protocol for Study GS-US-216-0114 to IND 101,283 prior to initiating the study and to include the SAP.
- The Agency informed Gilead that if any proprietary data from other approved drugs is submitted with the NDA, the application will be classified as a 505(b)(2). The Agency advised Gilead to not use the RTV label as a guide for the GS-9350 NDA as RTV does not have an approved indication as a pharmacoenhancer.
- The Agency informed Gilead that PK data in HIV-infected patients will be required for DRV if the DRV PK parameters in the presence of GS-9350 do not match the DRV PK parameters in the presence of RTV in healthy subjects. If the target PK parameters are met, the need for further studies will depend on the results of ongoing and long-term data. Therefore, the Agency informed Gilead that this issue may require further discussion.
- Additional discussion is required regarding the pediatric investigational plans.

4. ACTION ITEMS

- The Agency will provide comments on studies the Phase 3 protocols GS-US-216-0102 and GS-US-236-0103, submitted to IND 103,093
- The Agency will provide recommendations for implementation and conduct of the snapshot methodology for the efficacy primary endpoint
- The Agency will provide comments on the GS-9350 QTc study report.
- The Agency will re-send the comment from IRT regarding the elvitegravir QTc study and suprathereapeutic dose (see below).
- Gilead will submit Proposed Pediatric Study Request for EVG, GS-9350 and FDC tablet
- Gilead will submit the study report for the DRV/GS-9350 drug interaction study
- Gilead will submit copies of any communications between Gilead and EMA regarding pediatric drug development

ATTACHMENTS AND HANDOUTS

As a reference, the following comment was previously sent to Gilead in comment 5 of the June 4, 2007 meeting minutes.

QUESTION POSED BY SPONSOR (December 7, 2006/ SN 090):

Does the Agency agree that the results from the Thorough QTc Study confirm the lack of effect of GS-9137 on the QT/QTc interval, and that no further evaluation is warranted in the phase 3 clinical trials?

IRT QT Response (June 4, 2007):

Yes, if you can provide data that confirm that the drug concentrations achieved in this study are higher than those that can be reasonably expected after administration of the highest therapeutic dose. The suprathereapeutic dose provides only a 60% increase in mean Cmax. There may be intrinsic (e.g., hepatic impairment) or extrinsic (e.g., drug-interactions) factors that increase concentrations higher than 3663 ng/mL that have not been considered. The adequacy of the exposures achieved in this study will be a review issue when more clinical studies have been submitted for review.

Follow-up Elvitegravir QTc Comments:

The results of the thorough QT study indicate that the suprathereapeutic dose of GS-9137 results in a mean increase of 60 % in Cmax. In order to determine whether this increase in Cmax

adequately encompasses the maximum concentrations GS-9137 that may be observed clinically, please provide a table which compares the C_{max} of GS-9137 observed in all the pharmacokinetic and clinical studies conducted so far with the C_{max} observed at the supratherapeutic dose in the QT study.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-101283

GI-1

GILEAD SCIENCES
INC

GS-9350

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

04/09/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

INDs 72,177, 101,283, 103,093

Gilead Sciences
Attention: Christophe Beraud, Ph.D.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for elvitegravir (IND 72,177), GS-9350 (IND 101,283) and elvitegravir (EVG), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF) and GS-9350 in a fixed-dose combination tablet (IND 103,093).

We also refer to your October 30, 2008, correspondence, requesting a meeting to discuss the integrated development and registration plans for elvitegravir, GS-9350, and EVG/FTC/TDF/GS-9350 fixed-dose combination tablets.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 14, 2009 between Gilead Sciences 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. Sponsor should provide a hardcopy or electronic version of any materials (e.g. slides, or handouts) to be presented and/or discussed at the meeting to the RPM to be appended to the meeting minutes.

Below please find our preliminary comments. Sponsor questions are in **bold** followed by FDA response in *italics*.

BACKGROUND:

Gilead is evaluating elvitegravir (GS-9137) under IND 72,177, in two ongoing identical Phase 3 clinical studies in treatment-experienced adults with HIV-1 infection (Studies GS-US-183-0144 and GS-US-183-0145). Gilead plans to conduct a development program that includes one Phase 2 and two Phase 3 studies with EVG/FTC/TDF/GS-9350 fixed-dose combination tablets in treatment-naïve HIV subjects under IND 103,093. Therefore, Gilead proposes to combine these two ongoing Phase 3 studies with elvitegravir in treatment-experience HIV adults into a single Phase 3 study (GS-US-183-0145) to enroll a total of 700 subjects. In this revised development and registration plan for elvitegravir, 48-week data from two Phase 3 studies in treatment-naïve adults evaluating EVG/FTC/TDF/GS-9350 fixed-dose combination tablets and one Phase 3 study of ritonavir-boosted EVG in treatment experienced adults will form the basis for simultaneous registration of EVG/FTC/TDF/GS-9350 tablets and EVG tablets.

Gilead determined in Study GS-US-916-0101 the ability of GS-9350 to inhibit CYP3A-mediated metabolism is similar to that of ritonavir and provided an overview of the proposed clinical studies to support the use of GS-9350 as a pharmacoenhancer for the HIV-1 protease inhibitor atazanavir. The clinical development program for GS-9350 which includes separate Phase 2 and Phase 3 studies, is outlined below:

- A Phase 2 study of GS-9350 vs. ritonavir each in combination with atazanavir + Truvada (FTC/TDF) in treatment-naïve adults with HIV-1 infection (GS-US-216-0105)
- A Phase 3 study of GS-9350 vs. ritonavir each in combination with atazanavir + Truvada (FTC/TDF) in treatment-naïve adults with HIV-1 infection (GS-US-216-0114)

Gilead plans to evaluate the pharmacokinetics and pharmacoenhancement of atazanavir with GS-9350 in early first quarter of 2009 (GS-US-216-0110). Additional clinical pharmacology studies are also planned to characterize GS-9350 and thereby support the proposed Phase 3 program including a thorough QTc study, hepatic impairment study, and drug interaction studies including a hormonal (oral) contraceptive study.

Gilead is proposing to conduct one Phase 2 and two Phase 3 studies with EVG/FTC/TDF/GS-9350 fixed-dose combination tablet vs. current standard of care in antiretroviral-naïve adults with HIV-1 infection:

- A Phase 2 study of EVG/FTC/TDF/GS-9350 fixed-dose combination tablet vs. Atripla (EFV/FTC/TDF) in antiretroviral-naïve adults with HIV-1 infection (GS-US-236-0104)
- A Phase 3 study of EVG/FTC/TDF/GS-9350 fixed-dose combination tablet vs. Atripla (EFV/FTC/TDF) in antiretroviral-naïve adults with HIV-1 infection (GS-US-236-0102)

- A Phase 3 study of EVG/FTC/TDF/GS-9350 fixed-dose combination tablet vs. a comparator protease inhibitor with Truvada in antiretroviral-naïve adults with HIV-1 infection (GS-US-236-0103).

DISCUSSION POINTS:

The proposed development plans depend on the final review of Study GS-US-236-0101 and demonstration of bioequivalence of the fixed-dose combination tablet relative to the individual components (boosted with ritonavir for elvitegravir). As preliminary data from Study GS-US-236-0101 suggest slightly higher tenofovir C_{max} and C_{tau} levels with administration of the fixed-dose combination tablet, the safety monitoring plan for these trials should take into account potential increases in tenofovir toxicity.

Question 1:

Preliminary data from Study GS-US-236-0101 have demonstrated that elvitegravir, emtricitabine and tenofovir exposures are similar following administration of EVG/FTC/TDF/GS-9350 fixed dose combination tablet compared to administration of either elvitegravir tablet with ritonavir, or emtricitabine capsule (Emtriva) and tenofovir DF tablet (Viread) in healthy subjects. Gilead plans to conduct one Phase 2 and two Phase 3 studies with the EVG/FTC/TDF/GS-9350 fixed-dose combination tablets in HIV-1-infected treatment-naïve adults to support the registration of this product for use in this patient population. Forty-eight week safety and efficacy data from the Phase 3 studies and longer-term data from the Phase 2 study will be included in the initial NDA submission for the fixed-dose combination tablets. Additional support for this indication would be safety and efficacy data of ritonavir-boosted elvitegravir tablets in the treatment-experienced subjects (including the Phase 3 study in treatment experienced adults, PK/PD, and general pharmacology data).

1a. Does the Agency agree that the proposed development plan supports registration of EVG/FTC/TDF/GS-9350 fixed-dose combination tablets as a complete regimen for the treatment of antiretroviral-naïve, HIV-1-infected adults?

The Division concurs with the proposed development plan for the fixed-dose combination tablets as outlined. The fixed-dose combination tablet has the most straightforward of the development plans.

Registration of elvitegravir tablets for the treatment of HIV-1 infection in adults will be supported by 48-week efficacy and safety data from one Phase 3 study with ritonavir-boosted elvitegravir in treatment-experienced subjects (GS-US-183-0145), long-term safety and efficacy data from a rollover study comprised of subjects from the Phase 2 of elvitegravir (GS-US-183-0130), and data from the above-mentioned Phase 2 and 3 studies with the fixed-dose combination product in treatment-naïve adults. The approach for this development program is consistent with the traditional development path for new medicinal products for the treatment of HIV-1 infection, specifically two Phase 3 studies in treatment-experienced subjects and one Phase 3 study in treatment-naïve subjects. In our case, two Phase 3 studies with EVG/FTC/TDF/GS-9350

fixed-dose combination tablets in naive subjects and one Phase 3 study with elvitegravir tablets in experienced subjects will be conducted.

1b. Does the Agency agree that the proposed development plan supports the registration of elvitegravir tablets for the treatment of HIV-1 infection?

If the elvitegravir exposure is confirmed to be similar after administration of the fixed-dose combination tablet or the single drug product (boosted with ritonavir), the fixed-dose combination tablet clinical trials are expected to be acceptable to support registration of elvitegravir tablets. Registration of elvitegravir tablets for a treatment-naïve indication will require two adequately-powered, Phase 3 clinical trials with data covering at least 48 weeks of dosing. Also, you will be required to provide 96 weeks safety and efficacy data for treatment-naïve subjects as a post-marketing commitment. For a treatment-experienced indication, 48-week efficacy and safety data from the single proposed Phase 3 trial will be considered acceptable in combination with supportive safety and efficacy data from your rollover study and the Phase 2 studies in experienced subjects. Based on your background information, we expect that these studies will be submitted as a single application and not as separate submissions.

Question 2:

Gilead plans to develop and register the GS-9350 tablets initially as a pharmacoenhancer for atazanavir. Consequently, the clinical development program for GS-9350 has been designed to focus on studies with this agent. Specifically, Gilead plans to conduct one Phase 2 study and one Phase 3 study comparing GS-9350 vs. ritonavir as a pharmacoenhancer for atazanavir in combination with Truvada (FTC/TDF) in treatment-naive adults with HIV-1 infection. Registration of GS-9350 tablets will be sought based on the 48-week efficacy and safety data from these studies and also be supported by the established safety and efficacy data of ritonavir-boosted atazanavir, bridging clinical pharmacokinetic data demonstrating appropriate atazanavir boosting by GS-9350, and 48-week safety data from the Phase 3 studies of EVG/FTC/TDF/GS-9350 fixed-dose combination tablets.

Does the Agency agree that GS-9350 tablets could be initially registered as a booster for atazanavir capsules based on the proposed development plan?

The GS-9350 development plan is the least straightforward. Our experience with ritonavir as a PK enhancer indicates that not all protease inhibitors respond similarly to ritonavir and different doses have been used with different protease inhibitors. The Division agrees, in principle, with the proposed indication of GS-9350 as a pharmacoenhancer for atazanavir and with the development plan as laid out. However, we strongly encourage pharmacokinetic studies with GS-9350 and as many other protease inhibitors as possible. We expect the potential for off-label use of GS-9350 with protease inhibitors other than atazanavir will be considerable and may constitute a significant safety issue if other drug-drug interactions have not been explored. These studies should be conducted early in the drug development process. In addition, we recommend pharmacokinetic studies with GS-9350 in a treatment-experienced

population. As an example, a comparative study of GS-9350 and ritonavir in HIV-infected patients successfully suppressed on a ritonavir-boosted protease inhibitor regimen might be informative.

Question 3:

	EVG Exposure 1 year or greater	EVG Total Exposure (including short-term exposure ¹)
Elvitegravir tablets	535	1420
EVG/FTC/TDF/GS-9350 tablets	550	714
Total	1085	2134

¹ At least 1 dose

The safety database for GS-9350 (including the fixed-dose combination product) will consist of:

	GS-9350 Exposure 1 year or greater	GS-9350 Total Exposure (including short-term exposure ¹)
GS-9350 tablets	300	468
EVG/FTC/TDF/GS-9350 tablets	550	714
Total	850	1182

¹ At least 1 dose

The safety database for EVG/FTC/TDF/GS-9350 fixed-dose combination product will consist of approximately 550 subjects exposed to this fixed-dose combination product for 1 year or greater, with a total exposure (including short-term exposure (at least one dose) of approximately 714 subjects. The above safety databases for elvitegravir, GS-9350 and the EVG/FTC/TDF/GS-9350 fixed-dose combination product meet in full the ICH E1 requirements for population exposure to assess the clinical safety of new drugs for long-term treatment (i.e., 300-600 patients for six months and 100 patients for 12 months). The total population exposure to elvitegravir, including short-term exposure also exceeds the ICH E1 requirement (n = 1500). It is anticipated that a total of 1182 subjects will have been exposed to GS-9350, including short-term exposure, by the time of the NDA submission. Given that a significant amount of long-term safety information (48 weeks or greater; approximately 850 subjects) is planned for inclusion in the NDA, and given the serious and life threatening nature of HIV-1 infection, Gilead believes that the overall exposure to GS-9350 is adequate to establish the overall safety profile of GS-9350.

During the Pre-IND Consultation for GS-9350 (IND 101,283), the Agency agreed that a safety database of approximately 700 patients should be robust enough to support the submission of an NDA for GS-9350 (letter dated 06 February 2008). Does the Agency concur with Gilead that the above-mentioned exposure to EVG/FTC/TDF/GS-9350 fixed-dose combination tablets and GS-9350 tablets would support NDAs for both of these products?

The Division concurs that the above mentioned exposures would support NDAs for both the fixed-dose combination tablet and GS-9350. Because GS-9350 is being evaluated only in combination with elvitegravir or atazanavir, it may be somewhat more difficult to determine its contribution to the safety/toxicity profile. The boosted atazanavir study will allow direct comparison of GS-9350 to ritonavir to assess safety but the fixed-dose combination tablet studies will not allow isolation of the safety profile of GS-9350.

Additional Comments:

Clinical Pharmacology:

1. Additional drug interaction studies may be necessary for EVG/FTC/TDF/GS-9350 fixed-dose tablets and GS-9350-boosted atazanavir, depending on the results of the GS-9350 probe substrate study. In addition, please comment on your study plans for evaluating the effect of a proton pump inhibitor and antacids on GS-9350-boosted atazanavir and the fixed-dose tablet.
2. Please clarify the overall development plan for GS-9350 with respect to its role as a pharmacoenhancer, including additional protease inhibitors and populations in which it might be evaluated. Given its potential utility in boosting protease inhibitors other than atazanavir, you are encouraged to perform PK studies with additional PIs early in the development process.

Clinical Microbiology Comments for IND 103,093

3. Please identify the assay that will be used for quantifying viral load.
4. Please provide a plan to monitor the development of resistance in the proposed study.

Quality Comments:

5. Once the clinical development plans for elvitegravir, GS-9350, and the EVG/FTC/TDF/GS-9350 fixed-dose combination product are established, please summarize how any required blinding of products will be carried out.

We request that at the end of the meeting, your designated representative provides a summary of the key discussion points, agreements and action items to ensure that all attendees are in accord on the meeting outcomes.

If you have any questions, call Stacey Min, Pharm.D., Regulatory Project Manager, at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

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

Linked Applications

Sponsor Name

Drug Name / Subject

IND 101283

GILEAD SCIENCES

GS-9350

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

/s/

JEFFREY S MURRAY

01/13/2009