

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203100Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203100

SUPPL # 0

HFD # 530

Trade Name Stribild

Generic Name elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) Fixed-dose combination 150 mg/150 mg/200 mg

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known



(b) (5)

6 Page(s) has been Withheld in Full immediately  
following this page as B5

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Name of person completing form: Stacey Min  
Title: Regulatory Project Manager  
Date: August 2, 2012

Name of Office/Division Director signing form: Debra Birnkrant  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STACEY MIN  
08/21/2012

DEBRA B BIRNKRANT  
08/21/2012

### **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 203-100, EVG/COBI/FTC/TDF fixed-dose combination tablets).

*[See appended electronic signature]*

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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	2011-09-20 11:01

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203100 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Stribild Established/Proper Name: elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate Dosage Form: 150 mg/150 mg/200 mg/300 mg tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Stacey Min		Division: Division of Antiviral Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>August 27, 2012</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> 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).

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</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</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>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 type="checkbox"/> REMS not required</p> <p>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 <input type="checkbox"/></p> <p>Comments:</p>	
<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)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other FDA Press Release and Information Advisory

<sup>3</sup> 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.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	August 27, 2012
<b>Officer/Employee List</b>	
❖ 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
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) August 27, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	August 27, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	October 26, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	n/a

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<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
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	October 26, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	n/a
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Acceptable: Letter- June 20, 2012 Review- June 12, 2012
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM n/a (NME) <input checked="" type="checkbox"/> DMEPA June 29, 2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) August 3, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) August 2, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM Filing Review: January 17, 2012 Filing Letter: December 23, 2011  <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>June 27, 2012</u>                If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	Included
❖ Internal memoranda, telecons, etc.	July 16, 2012 Tcon minutes
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg Pre-NDA meeting preliminary comments (7/8/11)
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg EOP2 meeting minutes submitted to IND <sup>(b) (4)</sup> (4/9/10)
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	Type C meeting to discuss integrated development plan (1/13/2009)
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	May 11, 2012
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	Included
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 27, 2012
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 6, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None July 16, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 11 PMRs
<b>Clinical Information<sup>6</sup></b>	
❖ 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>	July 2, 2012, December 16, 2011 (Filing Review)
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Included in clinical review (page 15)
❖ 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"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested July 17, 2012 March 8, 2012
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 2, 2012, December 16, 2011 (Filing Review)
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 29, 2012, July 19, 2012 (addendum), December 21, 2011 (Filing Review)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 2, 2012, August 21, 2012 (addendum), December 23, 2011 (Filing Review)
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 25, 2012
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 29, 2012
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 29, 2012, December 19, 2011 (Filing Review)
❖ 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 type="checkbox"/> No carc February 29, 2012
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page: February 10, 2012
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	August 26, 2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	February 17, 2012
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	July 2, 2012, February 16, 2012, January 3, 2012, August 24, 2012 (addendum)
❖ 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 type="checkbox"/> None	Biopharmaceutics Review: June 28, 2012
❖ 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>	May 3, 2012	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	May 3, 2012	
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: August 21, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable	
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (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 type="checkbox"/> Not needed (per review)	

<sup>7</sup> 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.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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STACEY MIN  
08/27/2012



Naumann Chaudry, PharmD  
Director, Regulatory Affairs Advertising and Promotions  
Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

**RE: NDA 203100**  
STRIBILD™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)  
Tablets, for oral use  
MA #1

Dear Dr. Chaudry:

This letter responds to Gilead Sciences, Inc.'s (Gilead) August 16, 2012, request to the Office of Prescription Drug Promotion, Division of Prescription Drug Promotion (DPDP) for comments on a proposed press release for STRIBILD™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Tablets, for oral use (Stribild).

DPDP has reviewed the proposed press release and we offer the following comments that should be applied to this submission and to all current and future promotional materials for Stribild that contain the same or similar claims or presentations. These comments are based on the draft labeling for Stribild submitted to DPDP by Gilead, dated August 10, 2012. We remind you that the press release should be updated to reflect the final approved labeling (PI).

### General Comments

The term "new" should only be used in your promotional material for six months from the time Stribild is initially marketed. After six months, this term should be revised or deleted.

We note that the press release makes references to Atripla®, Truvada®, and Complera® for use in HIV. This presentation misleadingly broadens the indication and omits all risk information for these products. We recommend revising this promotional press release to include the approved indications and important risk information for these products or deleting the references to these products from the press release.

### Misleading Presentations

Paragraph 1 on the first page claims, [REDACTED] This  
claim misleadingly implies [REDACTED] (b) (4)

(b) (4) when these are not the case. Therefore, we recommend deleting this claim.

Paragraph 2 on the first page claims, "Today's approval of [TRADENAME] will provide physicians and their patients (b) (4)

(emphasis added). This claim is misleading (b) (4)

(b) (4) Therefore, we recommend deleting claims that imply that Stribild is

### Unsubstantiated (b) (4) Claims

The press release claims that cobicistat is a "boosting" agent. This claim is misleading because it suggests that Stribild has improved efficacy compared to other antiretroviral drug regimens because it contains this "boosting" agent, when this is not the case. Stribild has not been proven to be more efficacious than other HIV-1 drug regimens. In addition, the Highlights section of the PI describes cobicistat as a "pharmacokinetic enhancer." We recommend deleting "boosting" and revising this claim to be consistent with the PI.

Paragraph 6 on the second page claims, "(b) (4) integrase inhibitors interfere with HIV replication by blocking the ability of the virus to integrate into the genetic material of human cells" (emphasis added). This claim misleadingly implies (b) (4) when this is not supported by substantial evidence or substantial clinical experience. The Clinical Studies section of the PI indicates that Stribild has demonstrated non-inferiority to comparator regimens (b) (4). Therefore, we recommend revising this claim (b) (4)

### Omission of Material Fact

Paragraph 3 on the first page claims, "The approval of [TRADENAME] is supported by the 48-week data from two pivotal Phase 3 studies in which the single tablet regimen met its primary objective of non-inferiority compared to Atripla® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) (Study 102) and to a regimen containing ritonavir-boosted atazanavir plus Truvada® (emtricitabine/tenofovir disoproxil fumarate) (Study 103)." This claim misleadingly lacks important information related to the clinical studies and which endpoints Stribild was found to be non-inferior to the comparators. Specifically, this claim fails to provide the strength of ritonavir, atazanavir, emtricitabine, and tenofovir disoproxil fumarate used in Study 103, the number of patients in each treatment group, baseline characteristics, description of the endpoints, and the efficacy results. We recommend including this important information.

The second bullet point on page 3 claims that the coadministration of Stribild and the listed drugs is contraindicated because of the “(b) (4) loss of virologic response and possible resistance to [TRADENAME].” This presentation misleadingly fails to reveal the mechanism of these drug interactions. According to the Highlights section of the PI, the coadministration of Stribild is contraindicated with drugs that are “highly dependant on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events” or “strongly induce CYP3A which may lead to lower exposure of one or more components and loss of efficacy of STRIBILD which may result in loss of virologic response and possible resistance.” We note that CYP3A interactions are included under the Drug Interactions section at the bottom of page 3. However, it is not clear that this is the mechanism for the contraindications. Therefore, we recommend revising the presentation of the contraindications to include this important information.

Page 4 claims, “Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. An Antiretroviral Pregnancy Registry has been established.” This presentation misleadingly fails to include important information. According to the Highlights section of the PI, “Use (b) (4) pregnancy only if the potential benefit justifies the potential risk.” We recommend including this important information.

### Overstatement of Efficacy

Paragraph 4 on the first page claims, “(b) (4) that address the individual needs of patients are critical to enhancing adherence and **increasing the potential for (b) (4) treatment success.** . . .” (emphasis added). This claim misleadingly overstates the efficacy of Stribild, by implying that Stribild has demonstrated (b) (4). As indicated in the Clinical Studies section of the PI, the efficacy of Stribild has only been analyzed through 48 weeks. (b) (4)

Therefore, we recommend deleting this claim.

### (b) (4) Indication

Paragraph 1 on the second page claims, (b) (4)

This claim misleadingly implies (b) (4)

(b) (4) when this is not the case. According to the Indications and Usage section of the PI, “Stribild is indicated as a complete regimen for the treatment of HIV-1 infection in **adults** who are **antiretroviral treatment-naïve**” (emphasis added). We note that the indication appears on pages 1 and 2 of the press release; however, this does not mitigate this misleading claim. Similarly, this claim misleadingly implies (b) (4)

(b) (4) when this is not the case. Therefore, we recommend deleting this claim.

### Omission/Minimization of Risk

The press release misleadingly fails to state that Stribild should not be administered with other antiretroviral products for treatment of HIV-1 infection. As indicated in the Warnings and Precautions and Drug Interactions sections of the PI, Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral products. We recommend revising the press release to prominently include this important information.

Paragraph 2 on the first page claims, "Today's approval of [TRADENAME] will provide physicians and their patients (b) (4)

(b) (4) " (emphasis added). In addition, the last paragraph on the first page claims, (b) (4)

(b) (4) These claims misleadingly (b) (4)  
when this is not the case. (b) (4)

(b) (4) Therefore, we recommend deleting claims that Stribild is (b) (4)

Page 3 of the press release includes a bullet for "New onset or worsening renal impairment." This presentation misleadingly omits an important monitoring recommendation. According to the Warnings and Precautions section of the PI, "Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety." We recommend including this important information.

The press release is misleading because it minimizes the risks associated with Stribild by failing to present important risk information relating to the boxed warnings, contraindications, warnings and precautions, and adverse events with a prominence and readability reasonably comparable with the presentation of the information relating to the effectiveness of the drug. Specifically, it fails to present the boxed warnings, contraindications, and warnings and precautions in conjunction with the efficacy claims for Stribild. Instead, this information does not appear until the bottom of page 2. The only risk information presented prior to this appears at the bottom of the first page: (b) (4)

(b) (4) This (b) (4)  
presentation misleadingly implies (b) (4)  
(b) (4) when this is not the case, and minimizes the risk of the serious adverse reactions associated with this drug. Therefore, we recommend revising the press release to convey the risk information in a manner consistent with the order of severity presented in the PI and with a prominence reasonably comparable to the efficacy claims for the drug, such as in conjunction with the first presentation of claims for the product. This presentation can be a concise summary of the most serious and common risks, if it is presented prominently (such as near the beginning of the press release) and is supplemented by a prominent reference to the location in the press release of the complete discussion of the risks associated with Stribild.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP), and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #1 in addition to the NDA number in all future correspondence relating to this particular matter. DPDP reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Jessica M. Fox, PharmD  
Regulatory Review Officer  
Division of Professional Drug Promotion  
Office of Prescription Drug Promotion

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/s/  
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JESSICA M FOX

08/22/2012

**Min, Stacey**

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**From:** Min, Stacey  
**Sent:** Monday, August 20, 2012 11:03 AM  
**To:** 'Christophe Beraud'  
**Subject:** FW: NDA 203100 Postmarketing Requirements

Hello Christophe:

In addition to the changes below, we are also adding MRP2 to the list of transporters for PMR #5.

PMR #5 should read as follows:

Evaluate inhibition by the components of Stribild of the renal transporters OCT2, MATE1, OAT1, OAT3, **MRP2** and MRP4 and evaluate transport of the renally eliminated components of Stribild (FTC and TDF) by renal transporters OCT2, OAT1, OAT3 and **MRP2**.

Thank you,  
Stacey

---

**From:** Min, Stacey  
**Sent:** Thursday, August 16, 2012 4:00 PM  
**To:** 'Christophe Beraud'  
**Subject:** RE: NDA 203100 Postmarketing Requirements

Dear Christophe:

We have reviewed your response to the PMRs for Stribild and agree with your proposed changes to PMR 4 and PMR 5 as listed below:

4. Evaluate inhibition by the components of Stribild of the hepatic transporters OATP1B1, OATP1B3, OCT1, and BSEP and evaluate transport of the hepatically eliminated components of Stribild (EVG and COBI) by the hepatic transporters OATP1B1, OATP1B3, and OCT1.

5. Evaluate inhibition by the components of Stribild of the renal transporters OCT2, MATE1, OAT1, OAT3 and MRP4 and evaluate transport of the renally eliminated components of Stribild (FTC and TDF) by the renal transporters OCT2, OAT1, and OAT3.

In addition, we propose the following change to PMR 3 as follows:

3. Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, renal phosphate threshold (TmP/GFR), urine protein and urine glucose. The trial

will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.

Please let me know if you have any follow-up questions.

Many thanks,  
Stacey

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**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Tuesday, August 14, 2012 5:24 PM  
**To:** Min, Stacey  
**Cc:** Regulatory Archives; Christophe Beraud  
**Subject:** RE: NDA 203100 Postmarketing Requirements

Dear Stacey:

I wanted to let you know that we have submitted our response to the Agency's proposed PMRs/PMCs today.

Please let me know if you have any questions.

Kind regards,

Christophe

---

**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

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**From:** Christophe Beraud  
**Sent:** Friday, August 10, 2012 2:04 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100 Postmarketing Requirements

Dear Stacey:

I hereby confirm the receipt of the Agency's correspondence.

Have a great weekend.

Christophe

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**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

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**From:** Min, Stacey [mailto:Stacey.Min@fda.hhs.gov]  
**Sent:** Friday, August 10, 2012 1:36 PM  
**To:** Christophe Beraud  
**Subject:** NDA 203100 Postmarketing Requirements

Dear Christophe:

Attached are the postmarketing studies for NDA 203100, Stribild. Please review the revised PMRs and the timelines and provide a response no later than August 15, 2012.

Many thanks,  
Stacey

Stacey Min, Pharm.D.  
Senior Regulatory Project Manager  
FDA\CDER\OND\Division of Antiviral Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Building 22, Room 6315  
Phone: 301-796-4253  
Fax: 301-796-9883  
stacey.min@fda.hhs.gov

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/s/  
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STACEY MIN  
08/20/2012

**Min, Stacey**


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**From:** Min, Stacey  
**Sent:** Tuesday, August 21, 2012 2:37 PM  
**To:** 'Christophe Beraud'  
**Subject:** RE: NDA 203100 Postmarketing Requirements

Hello Christophe:

The change you propose below is acceptable.

Thank you,  
 Stacey

---

**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Monday, August 20, 2012 3:12 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100 Postmarketing Requirements

Dear Stacey:

Thank you for your email regarding an additional change to the list of transporters for PMR #5.

Tenofovir has been shown in a number of experimental systems to not be a substrate or inhibitor of MRP2 (Report No. AD-104-2001; Ray et al. Antimicrob Agents Chemother 2006; Imaoka et al. Mol Pharmacol 2007). Cobicistat has been found to be a weak inhibitor of MRP2 ( $IC_{50} = 71 \mu M$ ) (Report No. AD-216-2030; Lepist et al. 51st ICAAC, 2011). To complete studies related to MRP2 requested by the Agency, we will further assess EVG and FTC as inhibitors and FTC as a substrate for MRP2.

We would like to make a minor change to the wording of the PMR to clarify that what is being analyzed is tenofovir (TFV) and not the product tenofovir disoproxil fumarate (TDF); see proposed edit in red below).

Evaluate inhibition by the components of Stribild of the renal transporters OCT2, MATE1, OAT1, OAT3, MRP2 and MRP4 and evaluate transport of the renally eliminated components of Stribild (FTC and T~~BFFV~~) by renal transporters OCT2, OAT1, OAT3 and MRP2.

Please let me know if you have any questions.

Kind regards,

Christophe

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**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

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**From:** Min, Stacey [mailto:Stacey.Min@fda.hhs.gov]  
**Sent:** Monday, August 20, 2012 8:03 AM  
**To:** Christophe Beraud  
**Subject:** FW: NDA 203100 Postmarketing Requirements

Hello Christophe:

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STACEY MIN  
08/21/2012

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

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FACSIMILE TRANSMITTAL SHEET

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DATE: August 15, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100 Labeling Edits on PPI</b>	

Total number of pages including cover: 11

**Comments:**

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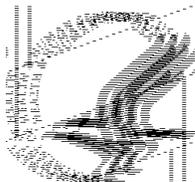
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**MEMORANDUM OF FACSIMILE:**

**Date:** August 15, 2012

**NDA:** 203100

**Drug:** Stribild [Fixed Dose Combination (FDC) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg]

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Subject:** NDA 203100 Labeling Edits on PPI

Please refer to your NDA 203100, Stribild for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. We are providing additional labeling edits on the PPI in track changes for your review. Please review the label and provide a response no later than **August 17, 2012**.

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

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/s/  
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STACEY MIN  
08/15/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 10, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100 Postmarketing Studies	

**Total number of pages including cover:** 5

**Comments:**

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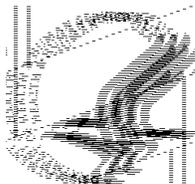
**Document to be mailed:** YES  NO

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**MEMORANDUM OF FACSIMILE:**

**Date:** August 10, 2012

**NDA:** 203100

**Drug:** Stribild™ [elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg]

**To:** Christophe Beraud, Ph.D., Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Subject:** NDA 203100 PMRs/PMCs

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Please refer to your NDA 203100, Stribild for the treatment of HIV-1 infection in adults, submitted on October 26, 2011. We are also providing a list of proposed Postmarketing Requirements (PMRs). Please review the revised studies and timelines and provide a response no later than **August 15, 2012**.

**Pediatric:**

- 1. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to <18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).**

Protocol Submission: September 2012

Trial Completion: March 2016

Final Report Submission: November 2016

- 2. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 6 to <12 years of age. Dose selection must be based on pharmacokinetic data for component drugs and must be discussed with FDA prior to initiation of the trial. Include in the trial safety monitoring assessment of potential renal toxicity (serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).**

Protocol Submission: April 2016  
Trial Completion: September 2018  
Final Report Submission: December 2018

**Clinical:**

- 3. Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, fractional excretion of phosphate, urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.**

Protocol Submission: October 2012  
Trial Completion: July 2016  
Final Report Submission: November 2016

**Non-Clinical:**

- 4. Evaluate the inhibition and transport of the components of Stribild by hepatic transporters, including OATP1B1, OATP1B3, OCT1, and BSEP transporters.**

Protocol Submission: September 2012  
Study Completion: November 2012  
Final Report Submission: December 2012

- 5. Evaluate the inhibition and transport of the components of Stribild by renal transporters, including OCT2, MATE1, OAT1, OAT3 and MRP4 transporters.**

Protocol Submission: September 2012  
Study Completion: November 2012  
Final Report Submission: December 2012

- 6. Evaluate the inhibition and transport of the components of Stribild by Pgp and BCRP.**

Protocol Submission: September 2012  
Study Completion: November 2012  
Final Report Submission: December 2012

**Clinical Pharmacology:**

- 7. Conduct a pharmacokinetic (PK) sub-trial of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives. Intensive pharmacokinetic data on each oral contraceptive, when given alone and when co-administered with Stribild, should be collected in an adequate number of subjects.**

Protocol Submission: October, 2012  
Trial Completion: July 2016  
Final Report Submission: November 2016

**8. Conduct an *in vivo* drug-drug interaction trial between Stribild and telaprevir.**

Protocol Submission: November 2012  
Trial Completion: September 2013  
Final Report Submission: October 2013

**9. Conduct an *in vivo* drug-drug interaction trial of Stribild and buprenorphine/naloxone.**

Protocol Submission: January 2011  
Trial Completion: September 2012  
Final Report Submission: January 2013

**10. Conduct an *in vivo* drug-drug interaction trial of Stribild and methadone.**

Protocol Submission: January 2011  
Trial Completion: September 2012  
Final Report Submission: January 2013

**Clinical Virology:**

**11. Assess possible cobicistat protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.**

Protocol Submission: December 2012  
Study Completion: October 2016  
Study Report Submission: February 2017

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

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/s/  
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STACEY MIN  
08/10/2012



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

---

---

FACSIMILE TRANSMITTAL SHEET

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DATE: August 10, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>

Subject: **NDA 203100 Labeling Edits**

Total number of pages including cover: **3 + label**

**Comments:**

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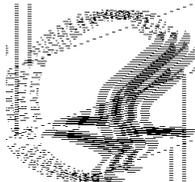
Document to be mailed:  YES  NO

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**MEMORANDUM OF FACSIMILE:**

**Date:** August 10, 2012

**NDA:** 203100

**Drug:** Stribild [Fixed Dose Combination (FDC) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg]

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Subject:** NDA 203100 Labeling Edits

Please refer to your NDA 203100, Stribild for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. We are providing additional labeling edits on the PI in track changes for your review. We will provide additional edits on the PPI sometime next week. Please review the label and provide a response no later than **August 15, 2012**.

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

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

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/s/  
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STACEY MIN  
08/10/2012

**Min, Stacey**


---

**From:** Christophe Beraud [Christophe.Beraud@gilead.com]  
**Sent:** Tuesday, August 07, 2012 4:15 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100 Teleconference  
**Follow Up Flag:** Follow up  
**Flag Status:** Orange

Dear Stacey:

In follow-up to our discussions at last week teleconference regarding the timelines of the pediatric study of Stribild in patients 6-12 years of age, Gilead proposes the following revised timetable:

Protocol Submission: 01 April 2016  
 Study Completion: 30 September 2018  
 Study Report Submission: 31 December 2018

The propose timetable is based on the following:

(b) (4)

These PK data will enable the development of appropriate formulation(s) of Stribild for patients 6–12 years of age in (b) (4). A BE study of the pediatric formulation(s) in healthy adult volunteers (b) (4) will be conducted in (b) (4) with data available in (b) (4). Discussions with FDA regarding the proposed dose selection (as requested by FDA in PMC #2) will occur (b) (4) with a final protocol for Stribild in patients 6–12 years of age (b) (4) available in (b) (4).

Please let me know if you have any questions.

Kind regards,

Christophe

---

**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

---

**From:** Christophe Beraud  
**Sent:** Thursday, August 02, 2012 5:03 PM  
**To:** Min, Stacey  
**Cc:** Regulatory Archives; Christophe Beraud  
**Subject:** RE: NDA 203100 Teleconference

Thank you Stacey.

As discussed during the teleconference, please see below for the list of 11 ongoing and 3 planned nonclinical studies in support of nonclinical PMC #4.

Please let me know if you have any questions.

Kind regards,

Christophe

**Ongoing In Vitro Studies:**

1. Inhibition of renal cationic transporters OCT2 and MATE1 by Stribild components
2. Inhibition of Pgp and BCRP by Stribild components
3. Inhibition of hepatic transporters OATP1B1 and OATP1B3 by Stribild components
4. Inhibition of renal anionic transporters OAT1, OAT3 and MRP4 by Stribild components
5. Inhibition of hepatic transporters OCT1 and BSEP by Stribild components
6. Effect of COBI and RTV on the accumulation of TFV in fresh isolated renal cortical tissue
7. Inhibition of OAT1 and OAT3-mediated TFV transport by COBI and RTV
8. Inhibition of MRP4-mediated TFV transport by COBI and RTV
9. Transport of EVG and COBI by hepatic transporters OATP1B1 and OATP1B3
10. Transport of Stribild components by Pgp
11. Transport of Stribild components by BCRP

**Planned In Vitro Studies:**

(b) (4)

---

**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

---

**From:** Min, Stacey [<mailto:Stacey.Min@fda.hhs.gov>]  
**Sent:** Thursday, August 02, 2012 12:14 PM  
**To:** Christophe Beraud  
**Subject:** RE: NDA 203100 Teleconference

Hi Christophe,

Here is the list of the FDA attendees:

Kendall Marcus, Deputy Director for Safety  
 Linda Lewis, Medical Team Leader  
 Adam Sherwat, Medical Officer  
 Peyton Myers, Pharmacology/Toxicology Reviewer  
 Hanan Ghantous, Pharmacology/Toxicology Team Leader  
 Stacey Min, Regulatory Project Manager

Also, there will be a short delay in getting the label to you. I hope to get it to you by next Wednesday. We are still waiting comments from our internal consultants and want to send one final version of the label with all the edits for your review.

Many thanks,  
 Stacey

---

**From:** Christophe Beraud [<mailto:Christophe.Beraud@gilead.com>]  
**Sent:** Thursday, August 02, 2012 2:57 PM  
**To:** Min, Stacey  
**Cc:** Regulatory Archives; Christophe Beraud  
**Subject:** NDA 203100 Teleconference

Hi Stacey:

Would you please provide me with the list of FDA attendees on the call today? It was a little difficult to hear all the names during the introduction.

Many thanks,

Christophe

---

**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

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STACEY MIN  
08/08/2012

**Min, Stacey**

---

**From:** Christophe Beraud [Christophe.Beraud@gilead.com]  
**Sent:** Thursday, August 02, 2012 8:03 PM  
**To:** Min, Stacey  
**Cc:** Regulatory Archives; Christophe Beraud  
**Subject:** RE: NDA 203100 Teleconference  
**Follow Up Flag:** Follow up  
**Flag Status:** Orange

Thank you Stacey.

As discussed during the teleconference, please see below for the list of 11 ongoing and 3 planned nonclinical studies in support of nonclinical PMC #4.

Please let me know if you have any questions.

Kind regards,

Christophe

**Ongoing In Vitro Studies:**

1. Inhibition of renal cationic transporters OCT2 and MATE1 by Stribild components
2. Inhibition of Pgp and BCRP by Stribild components
3. Inhibition of hepatic transporters OATP1B1 and OATP1B3 by Stribild components
4. Inhibition of renal anionic transporters OAT1, OAT3 and MRP4 by Stribild components
5. Inhibition of hepatic transporters OCT1 and BSEP by Stribild components
6. Effect of COBI and RTV on the accumulation of TFV in fresh isolated renal cortical tissue
7. Inhibition of OAT1 and OAT3-mediated TFV transport by COBI and RTV
8. Inhibition of MRP4-mediated TFV transport by COBI and RTV
9. Transport of EVG and COBI by hepatic transporters OATP1B1 and OATP1B3
10. Transport of Stribild components by Pgp
11. Transport of Stribild components by BCRP

**Planned In Vitro Studies:**

(b) (4)

---

**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

---

**From:** Min, Stacey [mailto:Stacey.Min@fda.hhs.gov]  
**Sent:** Thursday, August 02, 2012 12:14 PM  
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**Subject:** RE: NDA 203100 Teleconference

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Linda Lewis, Medical Team Leader  
Adam Sherwat, Medical Officer  
Peyton Myers, Pharmacology/Toxicology Reviewer  
Hanan Ghantous, Pharmacology/Toxicology Team Leader  
Stacey Min, Regulatory Project Manager

Also, there will be a short delay in getting the label to you. I hope to get it to you by next Wednesday. We are still waiting comments from our internal consultants and want to send one final version of the label with all the edits for your review.

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Stacey

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**Sent:** Thursday, August 02, 2012 2:57 PM  
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**Christophe Beraud, PhD** | Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

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/s/  
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STACEY MIN  
08/03/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 18, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100 PMCs/PMRs	

**Total number of pages including cover:** 5

**Comments:**

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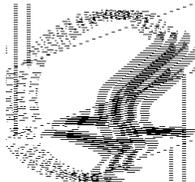
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**MEMORANDUM OF FACSIMILE:**

**Date:** July 18, 2012

**NDA:** 203100

**Drug:** Stribild [Fixed Dose Combination (FDC) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg]

**To:** Christophe Beraud, Ph.D., Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Subject:** NDA 203100 PMRs/PMCs

---

Please refer to your NDA 203100, Stribild for the treatment of HIV-1 infection in adults, submitted on October 26, 2011. We are also providing a list of proposed Postmarketing Commitments (PMCs) and Postmarketing Requirements (PMRs). Please review, propose timelines and provide your response no later than **July 25, 2012**.

**Pediatric:**

1. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to <18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

Protocol Submission:

Study Completion:

Study Report Submission:

2. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 6 to <12 years of age. Dose selection must be based on pharmacokinetic data for individual component drugs and discussed with FDA prior to initiation of trial. Include in the trial safety monitoring assessment of potential renal toxicity (serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

Protocol Submission:  
Study Completion:  
Study Report Submission:

**Clinical:**

- 3. Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, fractional excretion of phosphate, urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

- 4. [REDACTED] (b) (4)**

Protocol Submission:  
Study Completion:  
Study Report Submission:

**Clinical Pharmacology:**

- 5. Conduct a pharmacokinetic (PK) substudy of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives. Intensive pharmacokinetic data on each oral contraceptive, when given alone and when co-administered with Stribild, should be collected in an adequate number of subjects.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

- 6. Please conduct an *in vivo* drug-drug interaction trial between Stribild and telaprevir.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

- 7. [REDACTED] (b) (4)**

Protocol Submission:

Study Completion:  
Study Report Submission:

**8. Please conduct an *in vivo* drug-drug interaction trial of Stribild and buprenorphine/naloxone.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

**9. Please conduct an *in vivo* drug-drug interaction trial of Stribild and methadone.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

**Clinical Virology:**

**10. Assess possible cobicistat protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.**

Protocol Submission:  
Study Completion:  
Study Report Submission:

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

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/s/  
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STACEY MIN  
07/18/2012

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 16, 2012  
**TIME:** 2:20 PM – 1:50 PM  
**LOCATION:** Teleconference  
**APPLICATION:** NDA 203100  
**DRUG NAME:** Stribild [Fixed-Dose Combination Tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)]  
**TYPE OF MEETING:** Teleconference  
**MEETING CHAIR:** LCDR Tara Goen, Acting Branch Chief/OC/OMPQ/DGMPA/NDMAB  
**MEETING RECORDER:** Stacey Min, Pharm.D., Regulatory Project Manager

### FDA ATTENDEES:

Linda Lewis, Medical Team Lead, DAVP  
Adam Sherwat, Medical Officer, DAVP  
Stephen Miller, CMC Lead, ONDQA  
Milton Sloan, CMC Reviewer, ONDQA  
Fuqiang Liu, CMC Reviewer, ONDQA  
Jeannie David, CMC Project Manager, ONDQA IV  
Karen Winestock, Chief, Project Management Staff, DAVP  
LCDR Tara Goen, Acting Branch Chief/OC/OMPQ/DGMPA/NDMAB  
CDR Denise Digiulio, Compliance Officer, CDER/OC/OMPQ/DGMPA/GDMAB  
Stacey Min, Regulatory Project Manager, DAVP

### EXTERNAL CONSTITUENT ATTENDEES:

Norbert Bischofberger, EVP, R&D/Chief Scientific Officer  
Andrew Cheng, Senior Vice President, Development Operations and HIV Therapeutic Area Head  
Taiyin Yang, Senior Vice President, Pharmaceutical Development and Manufacturing  
Tom Weber, Vice President, Analytical Development  
Tobias Peschel, VP, Drug Safety & Public Health  
Javier Szwarcberg, Sr. Director, Clinical Research  
Paul Tomkins, Sr. Director, Regulatory Affairs  
Sujatha Narayan, Sr. Director, RA CMC, Regulatory Affairs  
Christophe Beraud, Associate Director, Regulatory Affairs

## BACKGROUND:

On October 26, 2011, Gilead Sciences submitted NME NDA 203100, Stribild for the treatment of HIV-infection in treatment-naïve adults. DAVP is currently reviewing the application with a PDUFA goal date of August 27, 2012. During the July 9, 2012, Wrap Up Meeting, Office of Compliance informed the Division that (b) (4) one of the contract manufacturing sites for NDA 203100 will be receiving a withhold recommendation. On July 11, 2012, FDA sent Gilead a facsimile stating that there is an issue pending at one of the manufacturing facilities that could potentially preclude the approval of the NDA. A teleconference was scheduled between Gilead Sciences and the FDA on July 16, 2012, to discuss this issue.

## DISCUSSION POINTS:

The FDA asked Gilead whether they have contacted the sites to see which ones are problematic. Gilead stated that they assumed that the site in question was (b) (4) but they asked whether the FDA could identify the site. The FDA responded that it is Gilead's responsibility to contact all of their contract manufacturing sites to see which ones have pending issues.

Gilead stated that (b) (4) had an inspection that closed in (b) (4) and asked whether this case has been closed with the FDA. The FDA responded that the case with (b) (4) has not been closed and instructed Gilead to take this into consideration when talking to the different contract sites. FDA reaffirmed that we cannot provide specifics about the issues at the site. Gilead stated that they will withdraw (b) (4) from the application as they can launch Stribild without this site.

Gilead stated that they provided a response to an information request from the FDA regarding the (b) (4) site in (b) (4). Gilead also stated that they do not have any issues with the (b) (4) site and have confidence that this site is following good manufacturing procedures. Gilead asked whether the FDA recommends withdrawal of the (b) (4) site. The FDA stated that we cannot speak to specifics about this site and that Gilead needs to work closely with the site to resolve any pending issues. The FDA also stated that review of the (b) (4) site is ongoing but we are not advising removal of this site at this time.

Gilead requested additional information on the (b) (4). The FDA recommended Gilead contact the (b) (4) district office to address any issues on the Form FDA-483 that was recently issued. The FDA recommended that Gilead work closely with the (b) (4) district office to resolve the issues as soon as possible since we are approaching the end of the review cycle for NDA 203100.

Gilead stated that they submitted (b) (4).  
Gilead stated that they decided (b) (4).  
The FDA stated that this is not the proper group to address the pending issues (b) (4) and recommended that Gilead work closely with the field office. Gilead stated that they will work with the field office.

ONDQA recommended that updated stability information on the non-U.S. Access version of Stribild tablets be included in the Annual Report, in parallel to the stability updates for the U.S. version. ONDQA requested that the lots be differentiated in the Annual Report to facilitate review. Gilead agreed to submit the requested information in future Annual Reports.

**ACTION ITEMS:**

- Gilead agreed to withdraw [REDACTED] <sup>(b)(4)</sup> from the application and submit a letter stating this to the NDA within two business days.

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/s/  
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STACEY MIN  
07/19/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: July 11, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100 General Correspondence</b>	

Total number of pages including cover: 3

**Comments:**

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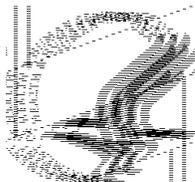
Document to be mailed: YES  NO

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**MEMORANDUM OF FACSIMILE:**

**Date:** July 11, 2012

**NDA:** 203100

**Drug:** Stribild (Fixed Dose Combination (FDC) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg)

**To:** Christophe Beraud, Ph.D., Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Subject:** NDA 203100

---

Please refer to your NDA 203100, Stribild for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. We are reviewing your application but there is an issue pending at one of the manufacturing facilities that could potentially preclude approval of the NDA. If you have any questions regarding this correspondence, we have allowed time for a teleconference to discuss this matter.

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.

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

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/s/  
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STACEY MIN  
07/11/2012

## Min, Stacey

---

**From:** Min, Stacey  
**Sent:** Monday, July 02, 2012 4:43 PM  
**To:** 'Christophe Beraud'  
**Subject:** NDA 203100 Information Request

Dear Christophe:

In addition to the follow-up information we requested today on the four subjects who were pregnant while on Studies GS-US-236-0102 and -0103, please also provide additional information related to the circumstances surrounding the 18 subjects in the Phase 3 trials of Stribild who reported an overdose of study drug.

Please provide this information to the NDA as soon as possible.

Many thanks,  
Stacey

Stacey Min, Pharm.D.  
Senior Regulatory Project Manager  
FDA\CDER\OND\Division of Antiviral Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Building 22, Room 6315  
Phone: 301-796-4253  
Fax: 301-796-9883  
stacey.min@fda.hhs.gov

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/s/  
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STACEY MIN  
07/02/2012

**From:** [David, Jeannie C](#)  
**To:** ["Linda McBride"](#)  
**Cc:** [Regulatory Archives](#); [Cuff, Althea](#); [Min, Stacey](#)  
**Subject:** NDA 203100 - CMC information request  
**Date:** Monday, June 25, 2012 1:25:56 PM

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Dear Linda,

We have the following CMC information requests for NDA 203100, and appreciate your written response by COB EST Wednesday, June 27, 2012. Please confirm receipt of this email.

*1. Indicate which, if any, of the bulk intermediates identified in the process flow diagram in 3.2.P.3.3. will be held for over 30 days. If so, provide the proposed bulk hold times and confirmation that adequate stability data exists to support these hold times.*

*2. Clarify how the Date of Manufacture (DOM) for the EVG/COBI/FTC/TDF tablets is set. We would expect that the DOM is defined as the date of entry of the first API to the drug product manufacturing process, regardless of which (b)(4) step. If following an alternative approach, provide adequate justification and rationale for the overall process.*

[FDA participants in the CMC teleconference on Monday, June 11, 2012, 10:00 am EST:](#)

Deepika Lakhani Arora, Ph.D., Biopharmaceutics, ONDQA  
Celia Cruz, Ph.D., Review Chemist, ONDQA  
Stephen Miller, Ph.D., CMC Lead, ONDQA  
Rapti Madurawe, Ph.D., Branch Chief, ONDQA

[FDA participants in the CMC teleconference on Monday, June 11, 2012, 2:30 pm EST:](#)

Deepika Lakhani Arora, Ph.D., Biopharmaceutics, ONDQA  
Sandra Suarez-Sharp, Ph.D., Biopharmaceutics, ONDQA  
Stephen Miller, Ph.D., CMC Lead, ONDQA  
Rapti Madurawe, Ph.D., Branch Chief, ONDQA  
Terrance Ocheltree, Ph.D., Division Director, ONDQA

Regards,

Jeannie

**Jeannie David, M.S.**  
**Regulatory Health Project Manager**  
**Food and Drug Administration**  
**Phone: (301) 796-4247**

---

**From:** Linda McBride [mailto:Linda.McBride@gilead.com]  
**Sent:** Wednesday, June 13, 2012 1:45 PM  
**To:** David, Jeannie C  
**Cc:** Cuff, Althea; Regulatory Archives  
**Subject:** NDA 203100 - Request for conference call attendees

Dear Jeannie,

Would you mind providing the list of attendees for both the teleconferences that were held on Monday, June 11<sup>th</sup>?

Thank you in advance,

Linda

*Linda McBride, R.Ph., RAC*

*Regulatory Affairs – CMC*

*Gilead Sciences, Inc.*

*333 Lakeside Drive*

*Foster City, CA 94404*

*Phone: 650.524.3854*

*Email: [linda.mcbride@gilead.com](mailto:linda.mcbride@gilead.com)*

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/s/  
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JEANNIE C DAVID  
06/25/2012



NDA 203100

**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 New Drug Application (NDA) dated October 26, 2011, received October 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate Tablets, 150 mg/150 mg/200 mg/300 mg.

We also refer to your March 28, 2012, correspondence, received March 29, 2012, requesting review of your proposed proprietary name, Stribild. We have completed our review of the proposed proprietary name, Stribild and have concluded that it is acceptable.

The proposed proprietary name, Stribild, 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.

If **any** of the proposed product characteristics as stated in your March 28, 2012 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 Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Stacey Min at (301) 796-4253.

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

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/s/  
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BRANTLEY H DORCH  
06/20/2012

CAROL A HOLQUIST  
06/20/2012



NDA 203100

**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/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR).

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 June 13, 2012, in order to continue our evaluation of your NDA.

**Drug Product Specifications**

1. Your proposal for setting the FTC and TDF dissolution acceptance criterion based on the dissolution performance of the slowest dissolving batch (BK0902B) tested in BE study GS-US-236-0110 is still not acceptable for the following reasons:

 (b) (4)

2. Therefore, the following dissolution acceptance criteria are recommended for your proposed product:

**EVG**

Q=  (b) (4) at 30 min

**FTC**

Q=  (b) (4) at 30 min

**TDF**

Q= (b) (4) at 30 min

**COBI**

Q= (b) (4) at 10 min

Our recommendation is based on the mean dissolution profiles observed for the pivotal phase 3 and stability batches. Revise the dissolution acceptance criteria accordingly and submit an updated sheet of specifications.

3. We acknowledge the data provided in support of the (b) (4) specification for EVG/COBI/FTC/TDF tablets in NDA 203100 and in your response to the IR dated 22 May 2012. However, we request that you update the (b) (4) specification for tablets to NMT (b) (4) for the following reasons:



**Drug Substance Specifications**

4. The proposal to not include a bulk density specification for Cobicistat on Colloidal Silica is not acceptable. Please submit a proposal for a tentative specification for bulk density at release; we recommend (b) (4). This specification can be updated post-approval, based on additional batch data or other supportive information, as proposed.

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

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/s/  
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RAPTI D MADURawe  
06/08/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: May 29, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100 Clinical Information Request</b>	

Total number of pages including cover: 4

**Comments:**

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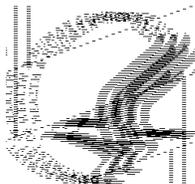
Document to be mailed: YES  NO

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**MEMORANDUM OF FACSIMILE:**

**Date:** May 29, 2012

**NDA:** 203100

**Drug:** Fixed Dose Combination (FDC) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

Please refer to your NDA 203100 for the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203100. We have the following comments and requests for additional information. Please provide a response no later than Monday, June 4, 2012.

**Clinical Comments:**

1. Please provide a summary table with demographic information for both the investigational and control arms in Study GS-US-216-0114, including numbers of subjects (and %) for sex, age, race, ethnicity, etc.
2. Please provide the specific dates for the submission of the final protocols for the clinical trials described in your EVG/COBI/FTC/TDF FDC pediatric investigational plan (b) (4). This information is required by the FDA's Pediatric Review Committee (PeRC) before a formal assessment of the Pediatric Plan can commence.

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.

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

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/s/  
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STACEY MIN  
05/29/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: May 24, 2012

<b>To: Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	<b>From: Stacey Min, Pharm.D.</b> Division of Antiviral Products
<b>Company: Gilead Sciences, Inc.</b>	<b>Title: Regulatory Project Manager</b>
<b>Fax number: 650-522-5489</b>	<b>Fax number: 301-796-9883</b>
<b>Phone number: 650-522-5093</b>	<b>Phone number: 301-796-4253</b>
<b>Subject: NDA 203100, Biometrics Information Request</b>	

Total number of pages including cover: 4

**Comments:**

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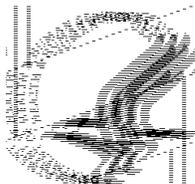
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**MEMORANDUM OF FACSIMILE:**

**Date:** May 24, 2012

**NDA:** 203100

**Drug:** Fixed-Dose Combination Tablet of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Wen Zeng, Ph.D., Biometrics Reviewer

**Concurrence:** Fraser Smith, Ph.D., Acting Biometrics Team Lead

**Subject:** NDA 203100 Biometrics Information Request

Please refer to your NDA 203100 for fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your May 18, 2012, submission in response to our April 30, 2012, information request. We have the following follow-up comment.

**Biometrics Comment:**

Thank you for your response about the 57 discrepancies involving sites. In your response, you noted that your IVRS vendor included the new site for subject 7022 in the random.xpt dataset.

Please submit the IVRS' SOP related to the site switch for review.

We are providing this above information via telephone facsimile for your convenience.

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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

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STACEY MIN  
05/24/2012



NDA 203,100

**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/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR).

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 May 30, 2012, in order to continue our evaluation of your NDA.

**Drug Product Specifications:**

1. Please update the drug product specifications in 3.2.P.5.1. as shown below.

COBI-related degradation product at shelf life:

NMT  
NMT  
NMT  
NMT  
NMT  
NMT  
NMT  
NMT  
NMT  
NMT

(b) (4)

(b) (4)  
NMT (b) (4)

**Post Approval Stability Commitments:**

2. Include microbiological purity testing for the EVG/COBI/FTC/TDF tablets in the stability protocol for the first three commercial batches and the annual commitment batches at initial time point and at shelf life.

3. Include reporting of  $t = 0$  in the stability protocols for the first three commercial batches and annual commitment batches. Update Tables 1 and 2 of Section 3.2.P.8.2, accordingly.

**Biopharmaceutics:**

4. Clarify if batch BK0901B was used in Phase 3 pivotal trials. If this is the case, provide the manufacturing conditions used during the development of this lot. Please note that manufacturing details are not requested but only the manufacturing ranges (for example, hardness, (b) (4) etc.) are requested.
5. Refer to Page 40 of the Quality Information Amendment dated 20-April-2012 that contained responses to our IR dated 23-March-2012. Explain the use of the (b) (4) lot as the reference lot for calculating  $f_2$  values. In addition, it is noted that the dissolution testing was conducted using (b) (4). Therefore, resubmit the calculations for Table 9, for each API, using a pivotal Phase 3 lot that is representative of the target manufacturing conditions as the reference lot and using 100 rpm for the paddle speed.
6. Your proposal for setting the FTC and TDF dissolution acceptance criterion (b) (4) is not acceptable for the following reasons:

(b) (4)

Therefore, dissolution acceptance criteria will be set based on the mean dissolution values of batches tested in pivotal phase 3 clinical and stability batches. For this purpose, submit the following information:

- Complete EVG, FTC and TDF dissolution profile data (raw data and mean values) from the pivotal phase 3 clinical and primary stability batches.

**Drug Product Analytical Methods:**

7. For TM-152, provide additional justification for the quantitation of unidentified impurities detected (b) (4) by the method of calculating the ratio of the peaks at those wavelengths, and then assigning to the API with the closest matching peak ratio.

- In your response, please include analysis of a batch with unidentified impurities detected at both wavelengths using different quantitation methods: such as assignment to COBI alone (lowest dose active ingredient) and assignment to TDF alone (ATRIPLA approach).
8. Please clarify the approach used for quantitation and reporting of unidentified impurities during stability testing, given that method TM-152 was not used throughout the study.

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

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RAPTI D MADURAWA  
05/22/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 15, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, CMC and Pharmacology/Toxicology Information Request	

**Total number of pages including cover:** 8

**Comments:**

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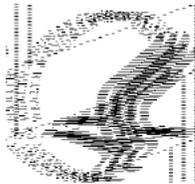
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**Date:** May 15, 2012

**NDA:** 203100

**Drug:** Fixed-Dose Combination Tablet of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Fuqiang Liu, Ph.D., CMC Reviewer  
Mark Powley, Ph.D., Pharmacology/Toxicology Reviewer

**Concurrence:** Stephen Miller, Ph.D., CMC Lead  
Rapti Madurawe, Ph.D., CMC Branch Chief  
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team  
Lead

**Subject:** NDA 203100: CMC and Pharmacology/Toxicology Information  
Request

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Please refer to your NDA 203100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg, submitted on October 26, 2011, for the treatment of HIV-1 infection in adults.

We have completed review of your April 26, 2012 response to the March 28, 2012 (Reference ID: 3107858), Information Request that outlined CMC and nonclinical deficiencies. The responses to several of the questions regarding potential genotoxic impurities were inadequate. Since information about these genotoxic impurities was not included in the initial risk assessment for genotoxic impurities, we request an urgent response. A list of outstanding deficiencies is provided below. Please address these deficiencies *comprehensively and in full*, no later than **May 21, 2012**. We have additional information requests and recommendations related to the EVG/COBI/FTC/TDF Tablet, which will be sent in a separate letter.

1. In your response to Question #1 on (b) (4), you provided data from a laboratory Proven Acceptable Range (PAR) study showing that (b) (4) however, this study was apparently performed at room temp. Since the temperature could be critical in this conversion from (b) (4) to its corresponding (b) (4) temperature range is require in your GMP (b) (4) manufacturing description (rather

than your current proposal of NMT (b)(4). An (b)(4) (b)(4) may also be appropriate. Additionally, from Table 5, we calculated (b)(4) to be (b)(4) fold; explain how you calculated (b)(4) by approximately (b)(4) fold.

2. Your response to Question #2 on (b)(4) is inadequate. (b)(4) is used (b)(4) and (b)(4) is the only part of the manufacturing process (b)(4).
  - a. In addition, because there is only limited information at present on the ability of the process (b)(4) to the safety threshold, include a test for (b)(4) in the COBI drug substance specification with an acceptance criterion of NMT (b)(4).
  - b. Provide a validated analytical method for this test. If this test is done by monitoring (b)(4), provide information to demonstrate that (b)(4) is measured by that validated method. Spiking studies or an additional quench that has been shown to quantitatively convert (b)(4) is recommended.
  - c. Provide details including the concentration, volumes and timing for the (b)(4) workup procedure (b)(4).
  - d. For Table 6 (in your response), provide COBI concentrations and convert from  $\mu\text{g/mL}$  to ppm level (b)(4) in COBI, so that these values are meaningful.
3. Your response to Question #2 on (b)(4) is inadequate. The data demonstrated that levels of (b)(4) vary (b)(4) in different batches of (b)(4). Given the safety threshold of (b)(4), and the absence of any data to show that this mutagenic impurity (b)(4) and COBI drug substance, control on (b)(4) is important. Include a test with an acceptance criterion of NMT (b)(4) in the COBI drug substance. If you have adequate data to show that the (b)(4) at all manufacturing sites reproducibly lower the level of this impurity, a higher acceptance criterion in (b)(4) may be acceptable.
4. We do not agree with the conclusion that (b)(4) lacks mutagenic potential. Due to the presence of (b)(4), this impurity was predicted to be Ames positive in both Derek Nexus (DX) 2.0 and MultiCase for PC (MC4PC) 2.4.07. No prediction was made by Leadscope Model Applier (LMA) 1.3.3-3 as the impurity was outside of the model's domain of applicability.

While DX alert (b)(4) summarized in Appendix 1) does exclude (b)(4), the exclusion rule is not applicable to (b)(4). This is clearly demonstrated by the DX positive prediction for (b)(4). Additional evidence suggesting mutagenic potential of this class is provided by three Ames positive (b)(4) (Figure 1). Furthermore, there is a high degree of confidence in the (b)(4) alert as shown by the high positive predictivity in several large datasets. The available data support both the irrelevance of the (b)(4) exclusion rule for (b)(4) and the DX positive prediction.

MC4PC also predicted (b) (4) to be mutagenic based on the presence of the (b) (4). The high positive predictivity, high RCA alert index, and high total projected (Q)SAR activity also indicates a high degree of confidence in the MC4PC alert (summarized in Appendix 2).

Overall, the (b) (4) alert is considered a relevant cause for concern. The mutagenic potential of this reliable alert resulted positive predictions in two separate *in silico* systems and is also described in the published literature. As such, (b) (4) should be treated as potentially genotoxic and evaluated in an Ames assay or controlled to appropriate levels as described in the FDA Guidance for Industry “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches”. In the absence of compelling evidence that this impurity is non-mutagenic (e.g., Ames results), we recommend a test for (b) (4) with an acceptance criterion of (b) (4).



**Appendix 1**

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Please feel free to contact Stacey Min, Regulatory Project Manager at 301-796-4253 if you have any questions regarding the contents of this transmission.

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Linda Lewis, M.D.  
Medical Team Leader  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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LINDA L LEWIS  
05/15/2012

**Min, Stacey**

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**From:** Min, Stacey  
**Sent:** Thursday, May 03, 2012 5:15 PM  
**To:** 'Christophe Beraud'  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Dear Christophe,

Thank you for providing your revised draft AC slides. We notice that you have changed your recommendation for the value of creatinine increase that would trigger more intensive patient monitoring (0.4 mg/dL (b) (4) as well as the method describing that cut-off. We were in agreement with the previous value and are surprised to learn of the change in approach at this late date. Our AC presentation describes 0.4 mg/dL as a proposed cut-off for increasing monitoring. We do not believe a tcon is necessary at this late date unless you have a specific issue that needs to be addressed.

Kind regards,  
Stacey

---

**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Thursday, May 03, 2012 1:54 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Dear Stacey:

Apologies for the delay in providing you an updated draft of our slide presentation. We are still working on these slides taking into account the Agency's preliminary questions to the committee and the comments w received on Wednesday.

As previous indicated, we would be interested in discussing additional comments on the slides during a teleconference.

Please let me know if you have any questions.

Kind regards,

Christophe

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**Christophe Beraud, PhD** | Associate Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

---

**From:** Christophe Beraud  
**Sent:** Thursday, May 03, 2012 6:02 AM  
**To:** 'Min, Stacey'  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Good morning Stacey:

We are running a little behind. I will check with the team when they get into the office.

Thanks,

Christophe

---

**From:** Min, Stacey [mailto:Stacey.Min@fda.hhs.gov]  
**Sent:** Thursday, May 03, 2012 5:42 AM  
**To:** Christophe Beraud  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Dear Christophe,

I wanted to check on the status of the slides. Please let me know when we can expect the slides.

Thank you,  
Stacey

---

**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Wednesday, May 02, 2012 2:53 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Dear Stacey:

In consideration of the little time left before the Advisory Committee meeting, Gilead would like to have a teleconference with the NDA 203100 review team before the end of the week, if possible, to discuss the Agency's comments on our draft slides, rather than respond in writing. In particular, we would like to discuss Comment #3 asking for Gilead to provide for review the section of our presentation exploring the value of change in urine protein, urine glucose, and serum creatinine for the purpose of monitoring.

Gilead plans to send a revised slide presentation to you by the end of our day today.

Please let me know if this is at all possible.

I appreciate your help.

Kind regards,

Christophe

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**Christophe Beraud, PhD** | Associate Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

---

**From:** Christophe Beraud  
**Sent:** Wednesday, May 02, 2012 6:53 AM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** RE: NDA 203100- Response to Comments on AC Briefing Document

Dear Stacey:

Thank you for very much for providing the Agency's response to our comments on the Advisory Committee briefing document, and comments on our slide presentation.

Kind regards,

Christophe

---

**Christophe Beraud, PhD** | Associate Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email [christophe.beraud@gilead.com](mailto:christophe.beraud@gilead.com)

---

**From:** Min, Stacey [<mailto:Stacey.Min@fda.hhs.gov>]  
**Sent:** Wednesday, May 02, 2012 6:25 AM  
**To:** Christophe Beraud  
**Subject:** NDA 203100- Response to Comments on AC Briefing Document  
**Importance:** High

Dear Christophe:

Attached is our response to your March 27, 2012, submission regarding our Advisory Committee (AC) Briefing Document. In addition to our response, we have provided comments on your draft slides for the AC. Please confirm receipt of the attachment and feel free to contact me with any questions.

Warm regards,  
Stacey

Stacey Min, Pharm.D.  
Senior Regulatory Project Manager  
FDA\CDER\OND\Division of Antiviral Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Building 22, Room 6315  
Phone: 301-796-4253  
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[stacey.min@fda.hhs.gov](mailto:stacey.min@fda.hhs.gov)

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/s/  
-----

STACEY MIN  
05/03/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: May 2, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>

Subject: **NDA 203100; Response to Gilead's Comments on the Agency's Briefing Document**

Total number of pages including cover: 8

**Comments:**

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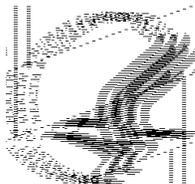
Document to be mailed: YES  NO

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**Date:** May 2, 2012

**NDA:** 203100

**Drug:** Fixed Dose Combination (FDC) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer  
Vikram Arya, Ph.D., Clinical Pharmacology Reviewer  
Takashi Komatsu, Ph.D., Clinical Virology Reviewer  
Sung Rhee, Ph.D., Clinical Virology Reviewer  
Stephen Miller, Ph.D., CMC-Lead  
Wen Zeng, Ph.D., Biometrics Reviewer

**Concurrence:** Linda Lewis, M.D., Medical Team Leader  
Kellie Reynolds, Pharm.D., Deputy Director, OCP IV  
Julian O’Rear, Ph.D., Clinical Virology Team Leader  
Fraser Smith, Ph.D., Acting Biometrics Team Leader

**Subject:** NDA 203100; Response to Gilead’s Comments on the Agency’s  
Advisory Committee Meeting Briefing Document

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Please refer to your NDA 203100 for the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; E/C/F/T) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203100. We also refer to the April 27, 2012, submission consisting of your comments on our briefing document for the May 11<sup>th</sup> Advisory Committee Meeting. We have reviewed your submission and have the following response and comments on your draft slides.

**Clinical Comments:**

**Comment 1**

**Page 6**

**Section: Secondary Efficacy Endpoints**

Secondary efficacy endpoints included assessing the change from baseline in CD4+cell count at Week 48. No significant difference in the change in CD4+ cells (in cells/ $\square$ l) from baseline through Week 48 between EVG/COBI/FTC/TDF and the comparator groups was

appreciated. In 236-0102, the mean change  $\pm$  SD in CD4+ cells from baseline at Week 48 was  $239 \pm 167$  for the EVG/COBI/FTC/TDF arm (325 subjects) and  $206 \pm 153$  for the ATR arm (315 subjects). In 236-0103, the mean change  $\pm$  SD in CD4+ cells from baseline at Week 48 was  $207 \pm 164$  for the EVG/COBI/FTC/TDF arm (334 subjects) and  $211 \pm 160$  for the ATV/r + TVD arm (321 subjects).

The paragraph above states that no significant difference in the change in CD4+ cells (in cells/ $\mu$ l) from baseline through Week 48 (pre-specified secondary endpoint) between EVG/COBI/FTC/TDF and the comparator groups was appreciated. However, in Study GS-US-236-0102, the mean change  $\pm$  SD in CD4+ cells from baseline at Week 48 was  $239 \pm 167$  for the EVG/COBI/FTC/TDF arm (325 subjects), and  $206 \pm 153$  for the ATR arm (315 subjects), and this difference was significant (p-value=0.009).

#### **FDA Response:**

The phrase "no significant difference" in the sentence in question relates to our impression that the change in CD4+ cells is not of apparent clinical significance. Although not optimal, we do not believe this wording warrants providing an Erratum. Please also note that although the P-value for CD4 change at Week 48 from baseline for study 0102 was 0.009, there was no alpha control for this secondary endpoint.

#### **Comment 2**

##### **Page 7**

##### **Section: Clinical Microbiology**

**In a pooled resistance analysis of Studies 236-0102, 236-0103, and 236-0104 (a small Phase 2 study of EVG/COBI/FTC/TVD versus ATR) in treatment-naïve subjects, genotypic and phenotypic resistance to the individual components of EVG/COBI/FTC/TDF was monitored in isolates from virologic failures who were treated with EVG/COBI/FTC/TDF and had HIV-1 RNA  $\geq$ 400 copies/mL at the time of virologic failure (or later while still on treatment). HIV-1 variants harboring EVG treatment emergent amino acid substitutions in the HIV-1 IN protein were detected in failure isolates from 20 of the 24 evaluated subjects. These failure isolates had reductions in susceptibility to EVG ranging from 1 to >198-fold that of wild-type HIV-1. IN substitutions previously identified in clinical trials or in cell culture as conferring reduced susceptibility to EVG were detected in 11 subjects' isolates (45.8% of evaluated EVG/COBI/FTC/TDF-treatment failures). These substitutions included T66I, E92Q, Q148R, and N155H (EVG resistance-associated substitutions) and H51Y, I68I/V, G140C, S153A, E157Q, and V165I IN substitutions. Isolates harboring these substitutions had reduced susceptibility to EVG (6- to >198-fold compared to wild-type HIV-1). The remaining 9 subjects' failure isolates harbored one or more treatment-emergent IN substitutions that have not been identified as associated with EVG resistance and had  $\leq$ 2.1 fold reduced susceptibility to EVG.**

Gilead requests to receive the list of the subjects receiving EVG/COBI/FTC/TDF identified as virologic failures by the Division and included in the resistance analysis population that was used for the analyses of the integrase gene, and, if different, the list of subjects used for the analyses of reverse transcriptase and protease described in the briefing document.

#### **FDA Response:**

Attached below is the list of 24 virologic failures receiving EVG/COBI/FTC/TDF who were included in the resistance analysis population.

Study 102	Study 103
0031-6257	0123-7332
0310-6332	0598-7203
0637-6041	1925-7108
0652-6556	2058-7359
0698-6012	2058-7461
0698-6182	2493-7299
0994-6667	2838-7562
1598-6101	4140-7130
1950-6503	5124-7476
1978-6091	Study 104
2140-6534	2475-4507
2154-6648	-
2838-6264	-
4140-6628	-

**Comment 3**

**Page 10-11**

**Section: Drug-Drug Interactions**

**Some commonly used medications may need to be dose-adjusted or given on a modified schedule when administered with EVG/COBI/FTC/TDF while others should not be coadministered. For example, omeprazole and other proton pump inhibitors can either be administered 2 hours before or staggered by 12 hours when given with EVG/COBI/FTC/TDF.**

Data from Study GS-US-183-0119 demonstrated that in contrast to the lower EVG exposures (40–50%, due to complexation in the gastrointestinal tract) observed upon simultaneous administration of boosted-EVG and antacids, staggered administration of these agents by at least two hours offsets this observed interaction and resulted in comparable EVG exposures as reference treatment (boosted EVG administered alone).

However, Studies GS-US-183-0119 and GS-US-216-0120 have demonstrated that multiple dose coadministration of boosted –EVG (RTV-boosted in Study -0119 and COBI-boosted in Study -0120) with a representative proton pump inhibitor, omeprazole, does not affect EVG or COBI exposures. In these studies, multiple doses of omeprazole were administered to achieve maximal acid reduction prior to administration with boosted-EVG. During codosing, study treatments were staggered by 1.5 to 2 hrs primarily due to their differing administration with food requirements (fed vs. fasting dosing for boosted-EVG and omeprazole, respectively) and not to mitigate the potential for interactions (since maximal acid suppression was expected).

Accordingly, there are no drug interactions upon coadministration of boosted-EVG and proton pump inhibitors and no need for any instruction regarding staggering of administration between QUAD and proton pump inhibitors or H2 receptor antagonists.

#### **FDA Response:**

The use of "modified schedule" was in the context of differences in timing of administration of proton pump inhibitors and E/C/F/T. In this case, the "modified schedule" is because PPIs should be taken under fasting conditions and E/C/F/T should be taken under fed conditions. The results of the trials specified in the comment do suggest that a drug-drug interaction is not anticipated between E/C/F/T and proton pump inhibitors.

#### **Comment 4**

##### **Page 14**

**Section: Common Adverse Events of the AEs outlined in Table 6, headache occurred more frequently in the EVG/COBI/FTC/TDF group than both the ATR and ATV/r + TVD groups. However, 95.6% of headache AEs in the EVG/COBI/FTC/TDF group were grade 1 in severity (4% grade 2, 0.4% grade 3) and only 1 subject discontinued EVG/COBI/FTC/TDF related to headache. The AEs ‘abnormal dreams’ and ‘insomnia’ occurred more frequently in the EVG/COBI/FTC/TDF group than in the ATV/r + TVD group but less frequently than in the ATR group. However, all these adverse events in the EVG/COBI/FTC/TDF group were mild or moderate (grade 1 or 2) severity except for 1 subject with grade 3 insomnia. No subjects in the EVG/COBI/FTC/TDF group discontinued study drug due to sleep disturbances. Gastrointestinal AEs, including diarrhea and nausea, were common in all groups.**

The above paragraph states that the AE of “abnormal dreams” occurred more frequently in the EVG/COBI/FTC/TDF group than in the ATV/r + TVD group based on pooled data from Studies GS-US-236-0102, -0103 and -0104. However, in Study 0103, rates of abnormal dreams were similar with EVG/COBI/FTC/TDF relative to ATV/r + TVD at 3.4% vs 3.9%.

#### **FDA Response:**

In Section 2.5, "Clinical Safety Results," subsection "Safety Review Strategy," it states the following: *This section will primarily focus on the safety data through Week 48 from the two Phase 3 trials, 236-0102 and 236-0103. As their study design was identical (with the exception of the comparator arms), the safety analysis has been conducted by pooling the safety data from the EVG/COBI/FTC/TDF groups.* Given these pre-specified review parameters, the statement in question is accurate.

#### **Comment 5**

##### **Page 16**

##### **Section: Cardiac Assessments**

**In study GS-US-216-0107, the Applicant evaluated the potential of COBI to affect electrocardiogram (ECG) parameters, particularly QT interval at therapeutic and suprathreshold concentrations. This study did not demonstrate any effects in QT interval but did show evidence of PR interval prolongation with a mean effect (placebo corrected) of 20.2 ms at the 400-mg dose and of 9.5 ms at the 250-mg dose at 3.5 hours post-dose. Five**

**subjects in the 400-mg arm and 2 in the 250-mg arm had an asymptomatic absolute PR >200 ms post-baseline.**

Study GS-US-216-0107 evaluated the effects of COBI on ECG parameters, following administration of single dose of 250 mg and 400 mg, which both provided suprathreshold mean (%CV)  $C_{max}$  of 2300 (23) ng/mL and 4030 (18) ng/mL, respectively, which are ~2- to 4-fold above the therapeutic concentrations as shown below.

Upon multiple dose administration of EVG/COBI/FTC/TDF in HIV-1 infected subjects, COBI mean (%CV)  $C_{max}$  is 1140 (36) ng/mL. At these COBI concentrations in Study GS-US-216-0107, the change from baseline in PR interval was 0.3 msec, and the PR interval difference relative to placebo was 4.2 msec, as shown in the Table 1 below. Thus at true therapeutic exposures, the effect of COBI on PR interval was lower than the maximum 9.5 to 20.2 msec values.

#### **FDA Response:**

In the study report for 216-0107, you provided the following justification for the choice of the 250 mg dose: "A 250-mg single dose of GS-9350 was predicted to produce representative therapeutic exposures of GS-9350 (predicted AUC<sub>inf</sub> of approximately 13,000 ng•h/mL and C<sub>max</sub> of approximately 1,700 ng/mL). Thus, a single 250-mg dose of GS-9350 was selected as appropriate for therapeutic exposure in this study." FDA reviewed the QT study in the context of doses chosen to represent the range of therapeutic to suprathreshold exposures as recommended for such studies.

#### **Comment 6**

##### **Page 24**

##### **Section: Treatment Emergent Renal Adverse Events in Phase 3 Trials**

##### **Table 12: Subjects Who Did Not Meet the Review Definition of Proximal Tubular Dysfunction but Developed Renal AEs Leading to Study Drug Discontinuation in Studies 236-0102 and 236-0103.**

This table lists Subject 0663-6014 as having discontinued study drug due to a renal AE. In Gilead's analysis included in our briefing document, this subject was not included in the list of subjects who discontinued study drug due to a renal AE since the reason for discontinuation was 'investigator's discretion' and not 'adverse event'.

#### **FDA Response:**

The subject in question had an AE of renal failure with worsening renal function that peaked at the time of study drug discontinuation due to "investigator discretion." We were not able to locate any additional information in the Application that would indicate that something other than the worsening renal failure led to discontinuation of study drug. If the primary cause for the "investigator discretion" related discontinuation of study drug was something other than worsening renal function, please provide documentation to that effect. We routinely review case reports of subjects reported as discontinuing drug due to "investigator discretion" or "other reasons," as these cases sometimes represent adverse events or poor tolerability that do not meet pre-specified safety withdrawal criteria.

#### **We have the following comments on your draft Advisory Committee Slides:**

1. In your Section entitled, "Review of Renal Safety," you provide pooled assessments of "QUAD or ATV/co (N=1137)" for graded creatinine and graded proteinuria. Please be aware that we have not reviewed the data related to graded creatinine and/or graded proteinuria from the non-E/C/F/T COBI studies as part of NDA 203100.
2. We suggest you include, as part of your slide presentation, your rationale for the proposed creatinine clearance threshold of  $\geq 70$  mL/min for initiation of treatment with E/C/F/T. Also, we suggest you comment on how clinicians will be advised to assess (particularly in patients with a baseline CrCl less than 90 mL/min) a drop in calculated creatinine clearance below 50 mL/min, the current limit for discontinuation of E/C/F/T.
3. Please provide for our review the section of your presentation exploring the value of change in urine protein, urine glucose, and serum creatinine for the purpose of monitoring.
4. We feel that some members of the Advisory Committee would be interested in hearing about the E/C/F/T tablet. For example: the bi-layer design; physical size comparison to Atripla, Complera, and/or other tablets, etc. If this seems appropriate from your perspective, you may wish to add a slide to your presentation.

**Additional Clinical Queries:**

1. Please provide the inclusion & exclusion criteria related to renal function as used in GS-US-216-0114.

We are providing this above information via telephone facsimile for your convenience.

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

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

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/s/  
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STACEY MIN  
05/02/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 30, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Biometrics Information Request	

**Total number of pages including cover:** 3

**Comments:**

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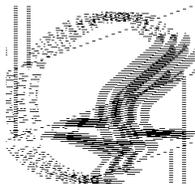
**Document to be mailed:** YES  NO

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**Date:** April 30, 2012

**NDA:** 203100

**Drug:** Fixed-Dose Combination Tablet of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Wen Zeng, Ph.D., Biometrics Reviewer

**Concurrence:** Fraser Smith, Ph.D., Acting Biometrics Team Lead

**Subject:** NDA 203100 Biometrics Information Request

Please refer to your NDA 203100 for fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your April 3, 2012, submission in response to our March 28, 2012, information request. We have the following comments and request for additional information.

**Biometrics Comment:**

When comparing the random.xpt file submitted April 3, 2012 to the ADSL dataset for study GS-US-236-0103, we identified 57 subjects with discrepancies involving sites. For example, subject 7022 was at site 765 in the random.xpt dataset but this subject did not appear in the ADSL dataset. A subject with subjid = 2728-7022 was found in the ADSL dataset which indicates that subject 7022 was at site 2728, not at site 765. Please provide an explanation for these 57 discrepancies.

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

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/s/  
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STACEY MIN  
04/30/2012

## Min, Stacey

---

**From:** Min, Stacey  
**Sent:** Friday, April 06, 2012 11:59 AM  
**To:** 'Christophe Beraud'  
**Subject:** NDA 203100 correspondence

Dear Christophe:

We understand that you will be presenting an overview of the renal toxicity reported with the use of TDF for the May 10 Advisory Committee considering PrEP. For the May 11 Advisory Committee considering COBI/EVG/TDF/FTC, please present a summary of the renal toxicity reported (e.g. graded increases in creatinine and graded proteinuria, renal SAEs, discontinuations due to renal AEs, specific reports of proximal tubulopathy) in prior treatment naïve licensure trials which included TDF (but not COBI) as part of the study regimen versus treatment naïve licensure trials which included both TDF and COBI as part of the study regimen.

We would appreciate receiving a copy of your draft slide presentation for the COBI/EVG/TDF/FTC meeting so that we can reduce duplication in the presentations to the committee.

Many thanks,  
Stacey

Stacey Min, Pharm.D.  
Senior Regulatory Project Manager  
FDA\CDER\OND\Division of Antiviral Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Building 22, Room 6315  
Phone: 301-796-4253  
Fax: 301-796-9883  
stacey.min@fda.hhs.gov

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/s/  
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STACEY MIN  
04/09/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 4, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100 Clinical Information Request	

**Total number of pages including cover:** 4

**Comments:**

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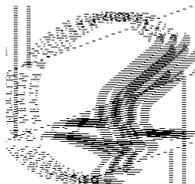
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**Date:** April 4, 2012

**NDA:** 203100

**Drug:** Fixed Dose Combination (FDC) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

Please refer to your NDA 203100 for the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203100. We also refer to the March 30, 2012, submission consisting of your response to our March 20, 2012, clinical information request. Lastly, we refer to the April 2, 2012, email correspondence requesting clarification on our comment #2. We have the following comments and requests for additional information.

**Clinical Comments:**

1. In regards to the your query related to our opinion on using an increase of 0.4 mg/dL as a means to differentiate COBI's effect on creatinine secretion from genuine renal dysfunction, at present, this issue is still under review and discussion.
2. Your response to our clinical information request of 01 March 2012 was appreciated. We agree with your selection of COBI/EVG/TDF/FTC subjects listed in Table 1 as probable tubulopathy cases leading to study drug discontinuation. In addition to the cases you identified in study 216-0114 (with which we also agree), we identified two additional cases in the ATV/co + TVD group (Subjects 4142-8361 and 4127-8204) as probable tubulopathy leading to study drug discontinuation and one subject in the ATV/r + TVD arm (Subject 4169-8476) as possible tubulopathy leading to study drug discontinuation. A brief discussion of our current rationale for the categorization of these additional subjects follows:

Subject 4142-8361: We noted that this subject developed new onset proteinuria (up to 2+) and a substantive increase in his FE of phosphate that significantly predated his

hospitalization for acute renal failure (which was complicated by Enterobacter bacteremia). Also per safety update narrative, "The hospital doctors' working hypothesis for the nephropathy was tenofovir-associated tubular nephropathy". If you are aware of and could provide the date of the 1st positive blood culture for Enterobacter in this subject it would be appreciated.

Subject 4127-8204: At the time of study drug discontinuation, the subject had 2+ proteinuria (baseline trace) and 1+ glycosuria (albeit with a slightly elevated serum glucose of 103). The subject also had a decline in CrCl and increase in serum creatinine (up to 0.51 mg/dL increase at maximum). FE of phosphate was not performed at baseline.

Subject 4169-8476: An increase in serum creatinine from 0.79 mg/dL at baseline to 1.26 mg/dL on SD 267 (date of discontinuation of study drug = 268) was recorded and she also developed new onset proteinuria (maximum 1+). Neither glycosuria nor increase in fractional excretion of phosphate was noted, however, glycosuria, proteinuria and FE of phosphate were not assessed at 3 of the 4 "Week 32" visits. At the subject's last recorded visit on SD 299, her serum creatinine had substantially improved (0.85 mg/dL) and her proteinuria had resolved.

We would appreciate hearing your thoughts on these subjects.

3. Please provide any follow-up data (laboratory and clinical) after Week 48 available for Subject 236-0102-0991-6633.
4. We agree with the following statement in your response to our clinical information request of 01 March 2012, "Increases in markers of tubular injury (glycosuria, proteinuria, and hypophosphatemia) are not expected with COBI, and changes in these laboratory parameters regardless of creatinine levels may herald possible TDF renal toxicity." Have you given consideration to incorporating assessment for glycosuria and proteinuria into your clinical management strategy for COBI/EVG/TDF/FTC?

We are providing this above information via telephone facsimile for your convenience.

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

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

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STACEY MIN  
04/04/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 28, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, CMC Information Request	

**Total number of pages including cover:** 11

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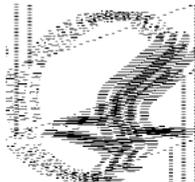
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**Date:** March 28, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Milton Sloan, Ph.D., CMC Reviewer  
Celia Cruz, Ph.D., CMC Reviewer  
Fuqiang Liu, Ph.D., CMC Reviewer  
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer  
Peyton Myers, Ph.D., Pharmacology/Toxicology Reviewer  
Mark Powley, Ph.D., Pharmacology/Toxicology Reviewer

**Concurrence:** Stephen Miller, Ph.D., CMC Lead  
Rapti Madurawe, Ph.D., CMC Branch Chief  
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team  
Lead

**Subject:** NDA 203100 CMC and Nonclinical Information Request

Please refer to your NDA 203100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. Please provide the following information to the NDA no later than April 27, 2012.

1. (b) (4) and (b) (4) were evaluated for mutagenic structural alerts using Derek Nexus, Leadscope Model Applier, and MultiCase 4 PC. (b) (4) was predicted to be an Ames mutagen based on the (b) (4). (b) (4) was also predicted to be mutagenic due to the (b) (4). Both impurities should be treated as potentially genotoxic and evaluated in an Ames assay or controlled to appropriate levels as described in the FDA Guidance for Industry "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches". In the latter situation, present analytical results to show the level of (b) (4) in the drug substance or in (b) (4) materials, including lots from both cobicistat manufacturing facilities.

2. We have concern over the use of (b) (4) in your COBI (b) (4) and (b) (4) in your (b) (4) that may generate (b) (4). There is publicly available information suggesting that (b) (4) (see section 11 of attached MSDS) and (b) (4) (see attached TOXNET information) are mutagenic in the Ames assay. Therefore, exposure to these impurities should be controlled to appropriate levels as described in the FDA Guidance for Industry “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches”. Present analytical results to show the level of (b) (4) in the drug substance or in (b) (4) materials, including lots from both cobicistat manufacturing facilities.
3. When calculating qualified levels of impurities, a body surface area conversion must be applied to adjust for differences between non-clinical species and humans (e.g., divide the non-clinical NOAEL by (b) (4) for rat). Please correct all impurity and degradant qualification summary tables using the appropriate conversion factor.
4. (b) (4) is a rodent carcinogen and should be controlled to the threshold of toxicological concern (TTC) (i.e., the level that yields an excess cancer risk of 1 in  $1 \times 10^5$ ). Based on the  $TD_{50}$  of (b) (4) reported from a rat carcinogenicity study (b) (4) the calculated TTC for (b) (4) is (b) (4).
5. The toxicological justification for (b) (4) refers to a reported “no untowards effect level” of (b) (4). Please provide a study report or reference for this data.
6. The qualification summary for degradation products of Tenofovir DF relies, in part, on toxicology studies no. R2000081 and 97-TOX-4331-002. Please provide these study reports or indicate where these were included in the submission.

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

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03/28/2012



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Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Antiviral Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 28, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Pharmacology/Toxicology Information Request	

**Total number of pages including cover:** 4

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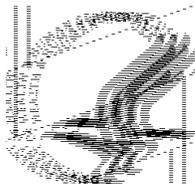
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**Date:** March 28, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer

**Concurrence:** Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team  
Lead

**Subject:** NDA 203100 Pharmacology/Toxicology Information Request

Please refer to your NDA 203100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. Please submit toxicokinetic data for the studies listed below. In case toxicokinetic data is not available, please explain how the safety factors (16 and 34X) were calculated.

1. Study Number: 04909  
Female Fertility Study of JTK-303 in Rats  
Report Number: JTK303-TX-019
2. Study Number: TX-183-2003  
Oral (Gavage) Fertility and General Reproduction Toxicity Study of GS-9137 in Male Rats

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Regulatory Project Manager  
Division of Antiviral Products

Center for Drug Evaluation and Research  
Food and Drug Administration

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**DATE:** March 28, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Biometrics Information Request	

**Total number of pages including cover:** 4

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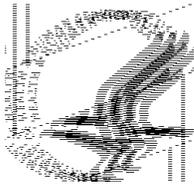
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**Date:** March 28, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Wen Zeng, Ph.D., Biometrics Reviewer

**Concurrence:** Fraser Smith, Ph.D., Acting Biometrics Team Lead

**Subject:** NDA 203100 Biometrics Information Request

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Please refer to your NDA 203100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203100. In addition, we refer to your March 7, 2012, response to our February 15, 2012, follow-up biometrics information request, which was in response to your January 10, 2012, submission to our December 23, 2011, original information request regarding the randomization list for Study GS-US-236-0103.

Thank you for submitting the randomization files for Study GS-US-236-0103. During our review of the PDF print out of the IVRS log file.csv in attachment #4 (dated March 7, 2012), we noticed that the treatment assignment was not properly ordered by time of subject randomization on a particular date, i.e., if there was more than one subject randomized on the same date (identified by the variable 'RANDDT'), the treatment assignment order may not match the order by randomization time (identified by the variable 'RANDT') within the same stratum. For example, subject 7021 (randomized at RANDDT=3-Jun-10 and RANDT=9:10:00) received their treatment assignment in block 4 before subject 7022 (randomized at RANDDT=3-Jun-10 and RANDT=8:17:00) received the treatment assignment in block 5 and both in the same viral load stratum ("less than or equal to 100000 copies/mL"). Multiple similar occurrences have been noted. Please provide an explanation for this phenomenon.

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

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STACEY MIN  
03/28/2012



NDA 203100

**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/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR).

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by April 13, 2012, in order to continue our evaluation of your NDA.

**Drug Product Components: Drug Substance**

1. Provide typical particle size distribution and bulk density data for cobicistat on silicon dioxide lots representative of the (b) (4) loading range used in the intended commercial process.

In addition, as a follow up to the Quality Information Request dated January 10, 2012, provide comparative particle size distribution and bulk density data for the cobicistat on silicon dioxide (b) (4)

2. (b) (4) the acceptance criterion for cobicistat on silicon dioxide (b) (4) in section 3.2.S.4.1 to a limit of not more than (NMT) (b) (4) or provide adequate justification for any proposed limit above NMT (b) (4). The (b) (4) temperature of cobicistat is stated as (b) (4) on the drug substance. Batch data and (b) (4) characterization information provided does not support the proposed acceptance criterion.

### General Biopharmaceutics

3. Explain the (b) (4) dissolution values observed at the (b) (4) time point for both TDF and FTC (mean dissolution values varying from (b) (4) Section 3.2.P.5.6, Figures 4 and 5).
  - Provide the FTC and TDF dissolution profiles (mean and individual data) as a function of drug substance particle size for all the Phase 3 clinical and registration stability batches.
4. Provide data to support the discriminating capability of the proposed dissolution method for FTC and TDF. In general, it is expected that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g. drug substance particle size, (b) (4) tablet hardness, etc.)

In addition, if available, submit data demonstrating the capability of the selected dissolution method to identify batches that are not bioequivalent.
5. Provide FTC, TDF, EVG, and COBI dissolution profiles (mean and individual values) for the drug product batches used in BA study GS-US-236-0110.

### General Manufacturing Process Description

6. Clarify the intended commercial batch size for EVG/COBI/TFC/TDF tablet. A batch size of (b) (4) is stated in Table 6 in Section 3.2.P.2.3 while (b) (4) range is stated in Table 1 in Section 3.2.P.3.2. In addition, provide the following:
  - A summary table Section 3.2.P.3.2 indicating the intended batch size for the (b) (4) (EVG, EVG/COBI and FTC/TDF), (b) (4) and film coating. If different scale equipment is used to accommodate varying batch sizes, please include in the description.
  - A description of when parts are combined or batches are split for further processing.
  - A summary table for each primary stability and scale-up batch shown in Table 2 of Section 3.2.P.3.4, to clearly indicate the lot number and scale of each part of (b) (4) (EVG, EVG/COBI, and FTC/TDF) and tablets used. Describe when parts were combined or batches were split for further processing
7. Include, in Table 1 of Section 3.2.P.3.3, the proposed target and/or operating parameters (b) (4) (b) (4) to provide a comprehensive description of the FTC/TDF (b) (4) process.

## Design Space Justification

8. The original design of experiment for ATRIPLA (b) (4) included variation of (b) (4). It is acknowledged that the conclusions on the main effects of these variables on (b) (4) properties would apply to NDA 203100. However, the impact of the resulting variation of (b) (4) properties on (b) (4) EVG/COBI/TDF/FTC has not been adequately addressed. In order to establish direct application of the FTC/TDF (b) (4) ranges to NDA 203100, provide the following information:

- For the FTC/TDF (b) (4) batches BK0904, BK1002, and BK1003 given in Table 7 in 3.2.P.2.3, clarify whether these were manufactured at target (b) (4) conditions (e.g. (b) (4) or under intentional variation of (b) (4) conditions.
- Justification and discussion on the impact of FTC/TDF (b) (4) properties manufactured across the proposed (b) (4) range on EVG/COBI/TDF/FTC tablet (b) (4) and final drug product performance, for example dissolution (b) (4).
- If there is no additional studies justifying the (b) (4) ranges beyond what is currently approved in the validated ATRIPLA process, revert to the following ranges of operating parameters (b) (4):

(b) (4)

9. 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 information:

- f2 statistical testing for FTC, TDF, and EVG dissolution profile comparisons of EVG/COBI/FTC/TDF tablets manufactured across the EVG (b) (4) design space (Figure 5-8 in 3.3.P.2.3).
- f2 statistical testing for FTC, TDF, and EVG dissolution profile comparisons of EVG/COBI/FTC/TDF tablets manufactured across the final hardness range (Figure 11-14 in 3.2.P.2.3).

If available, provide dissolution profiles and f2 statistical testing for FTC, TDF, and EVG dissolution profile comparisons of EVG/COBI/FTC/TDF tablets manufactured across (b) (4)

(b) (4)

### Design Space Verification upon Scale Up

10. The stated operating ranges for the scale up batches in Section 3.2.P.2.3 is inconsistent and requires some clarification to finalize review.

- For the EVG (b) (4) operating ranges, Table 11 in 3.2.P.2.3 states that (b) (4)

(b) (4)  
Reconcile the information regarding the process ranges used for stability and scale up batches, and provide a summary of the data which supports verification of the design space upon scale up.

- For FTC/TDF (b) (4) ranges, Table 12 in 3.2.P.2.3 states that a (b) (4)

- For the (b) (4) operating ranges, Table 13 in 3.2.P.2.3 states that the (b) (4)

(b) (4)  
Reconcile the information regarding the process ranges used for the stability and (b) (4) batches, and provide a summary of the data which supports verification of the design space (b) (4)

### Container Closure System

11. Provide relevant Drug Master Files and Letter(s) of Authorization for the container closure system components and desiccant used in the packaging of EVG/COBI/FTC/TDF tablets.

If you have any questions regarding this CMC letter, call Althea Cuff 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

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/s/  
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STEPHEN MILLER  
03/23/2012  
For Rapti Madurawe



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 20, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Katherine Schumann, M.S. for Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253

**Subject:** NDA 203100 Clinical Information Request

**Total number of pages including cover:** 4

**Comments:**

**Document will not be faxed or mailed. This facsimile will be provided by electronic mail. Please reply by email to acknowledge receipt.**

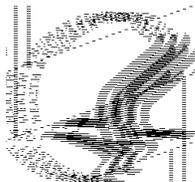
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**Document to be mailed:** YES  NO

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**Date:** March 20, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager for  
Stacey Min, Pharm.D., Regulatory Project Manager

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

Please refer to your NDA 203100 for the Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203100. We also refer to the February 3, 2012, submission consisting of the Safety Update Report for NDA 203100. We have the following request for additional information.

**Clinical Comments:**

1. Please provide a list (by subject ID and clinical trial) of subjects receiving tenofovir DF in any clinical trials of treatment-naïve subjects whom the Applicant (i.e. Gilead) judges to have developed proximal tubulopathy related to study drug(s). This review should specifically include but should not be limited to: GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, GS-US-216-0114, GS-US-216-0105, and the original Viread studies 903 and 934. Please also provide information for the following treatment experienced trials: GS-US-183-0145 & GS-US-183-0130. Please provide narratives for any subjects whose narratives are not included in the current NDA submission.
2. During the Q&A period after the presentation of data from GS-US-236-0102 at CROI 2012, the speaker indicated that an increase in serum creatinine of greater than or equal to 0.4 mg/dL may be used to discriminate a COBI-related increase in serum creatinine (due to inhibition of creatinine secretion) from genuine renal dysfunction. Is the use of this laboratory cutoff (i.e. a creatinine increase  $\geq 0.4$  mg/dL) intended to be part of your suggested clinical management strategy for health care providers? Do you have an analogous

laboratory cutoff for decline in calculated creatinine clearance (by Cockcroft-Gault) that would discriminate a COBI-related increase in serum creatinine due to inhibition of creatinine secretion from genuine renal dysfunction? If so, please provide your suggested laboratory cutoff.

Please provide responses as soon as possible, but no later than March 27, 2012.

We are providing this above information via telephone facsimile for your convenience.

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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KATHERINE SCHUMANN  
03/20/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 19, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Katherine Schumann, M.S. for Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253

**Subject:** NDA 203100, Clinical Virology Information Request

**Total number of pages including cover:** 3

**Comments:**

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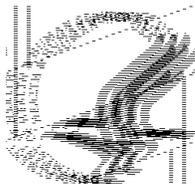
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**Date:** March 19, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager  
for Stacey Min, Pharm.D., Regulatory Project Manager

**Through:** Sung Rhee, Ph.D, Clinical Virology Reviewer  
Jules O'Rear, Ph.D., Clinical Virology Team Lead

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203-100. We have the following request for additional information.

In Study GS-US-236-0102, it was observed that all virologic failures whose isolates harbored primary EVG resistance-associated substitutions in IN also developed Truvada resistance-associated substitutions in RT (M184I/V ± K65R). In contrast, Truvada resistance-associated substitutions (M184I/V + K65R) were observed in only a small percentage of the virologic failures who developed EFV resistance-associated substitutions in RT. Please provide an explanation for the noted differences in the development of drug-resistance. Please also provide information on linkage of the observed substitutions on the same viral genome.

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
If you have any questions regarding the contents of this transmission, please contact Stacey Min at (301) 796-4253.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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KATHERINE SCHUMANN  
03/19/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: March 1, 2012

<b>To: Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	<b>From: Stacey Min, Pharm.D.</b> Division of Antiviral Products
<b>Company: Gilead Sciences, Inc.</b>	<b>Title: Regulatory Project Manager</b>
<b>Fax number: 650-522-5489</b>	<b>Fax number: 301-796-9883</b>
<b>Phone number: 650-522-5093</b>	<b>Phone number: 301-796-4253</b>
<b>Subject: NDA 203100, Clinical Information Request</b>	

Total number of pages including cover: 4

**Comments:**

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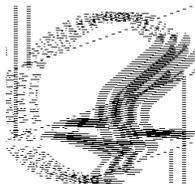
**Document to be mailed:** YES  NO

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**Date:** March 1, 2012

**NDA:** 203100

**Drug:** Single Tablet Regimen (STR) of  
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate  
(EVG/COBI/FTC/TDF) 150/150/200/300 mg

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

---

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults and your October 26, 2011, submission consisting of your original application of NDA 203-100. We also refer to the February 3, 2012, submission consisting of the Safety Update Report for NDA 203100. We have the following request for additional information.

**Clinical Comments:**

1. In which country or countries was study GS-US-216-0114 performed?
2. Please provide the median duration of exposure to study drug in Cohort 1 and Cohort 2 of GS-US-236-0118 covering the period reported in the Safety Update Summary.
3. Please provide narratives for the following subjects in the EVG/COBI/FTC/TDF group: 236-0102-2475-6092 (lumbar vertebral fracture), 236-0103-3034-7430 (lumbar vertebral fracture), 236-0103-0352-7697 (femur fracture). Please also comment as to whether these fractures were related to trauma.
4. As we begin planning for the Advisory Committee meeting, please provide us with the name(s) and area of expertise of any consultants you plan to have available at the meeting and whether these consultants will be making presentations.
5. Do you plan to present data related to EVG/COBI/FTC/TDF at CROI 2012?

Please provide responses as soon as possible, but no later than March 12, 2012.

We are providing this above information via telephone facsimile for your convenience.

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

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

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/s/

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STACEY MIN  
03/01/2012



NDA 203100

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

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

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

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated October 26, 2011, received October 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate Tablets, 150 mg/150 mg/200 mg/300 mg.

We acknowledge receipt of your February 15, 2012, correspondence, on February 16, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4) and alternate name, (b) (4). This proposed proprietary name request is considered withdrawn as of February 16, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Brantley Dorch, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Stacey Min at (301) 796-4253.

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

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/s/  
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BRANTLEY H DORCH  
02/24/2012

CAROL A HOLQUIST  
02/27/2012

**Min, Stacey**

---

**From:** Min, Stacey  
**Sent:** Wednesday, February 22, 2012 9:15 AM  
**To:** 'Christophe Beraud'  
**Subject:** RE: NDA 203100 Biometrics Comments

Dear Christophe:

I consulted our Biometrics group and they provided the following clarification:

Please provide the file the IVRS system generated to include the order of subjects who were randomized along with the information regarding subjID, randomization date/time, treatment arm, and "caseno" used in the full randomization list file. This is what we mean by the 'IVRS log file in the original randomization order'.

Please let me know if you have additional questions.

Regards,  
Stacey

---

**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Friday, February 17, 2012 2:55 PM  
**To:** Min, Stacey  
**Cc:** Regulatory Archives; Christophe Beraud  
**Subject:** RE: NDA 203100 Biometrics Comments

Dear Stacey:

Our team has reviewed the request for information from the Biometrics group that you sent on Wednesday February 15 2012, and we are currently working on preparing a response.

In order to ensure that we provide you with the correct information, would you please be able to get further details regarding the request for the 'IVRS log file in the original randomization order'?

Our IVRS vendor (b) (4) is not clear about this request. They indicated to us that they could provide a copy of the internal ticket which was used to create and burn the final randomization list to their secure server. This ticket has date and time stamps, clearly indicating that the final list was created on 08-Jan-2010, internally verified on 11-Jan-2010, and burned to our secure server on 12-Jan-2010.

Thank you for your help in clarifying this request.

Kind regards,

Christophe

---

**Christophe Beraud, PhD** | Associate Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

---

**From:** Min, Stacey [mailto:Stacey.Min@fda.hhs.gov]  
**Sent:** Wednesday, February 15, 2012 8:23 AM

**To:** Christophe Beraud  
**Subject:** NDA 203100 Biometrics Comments

Dear Christophe:

Attached is an electronic correspondence from DAVP regarding your NDA 203100. Please confirm receipt of the attachment.

Best regards,  
Stacey

Stacey Min, Pharm.D.  
Senior Regulatory Project Manager  
FDA\CDER\OND\Division of Antiviral Products  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Building 22, Room 6315  
Phone: 301-796-4253  
Fax: 301-796-9883  
stacey.min@fda.hhs.gov

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/s/  
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STACEY MIN  
02/22/2012



NDA 203100

**METHODS VALIDATION  
MATERIALS RECEIVED**

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

Dear Dr. Christophe Beraud:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/200 mg/300 mg Tablets and to our 1/20/2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 2/14/2012 and 2/16/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
02/16/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: February 15, 2012

<b>To: Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	<b>From: Stacey Min, Pharm.D.</b> Division of Antiviral Products
<b>Company: Gilead Sciences, Inc.</b>	<b>Title: Regulatory Project Manager</b>
<b>Fax number: 650-522-5489</b>	<b>Fax number: 301-796-9883</b>
<b>Phone number: 650-522-5093</b>	<b>Phone number: 301-796-4253</b>
<b>Subject: NDA 203100 Follow-Up Biometrics Comments</b>	

Total number of pages including cover: 4

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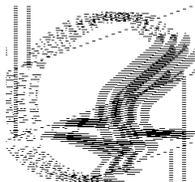
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**Date:** February 15, 2012

**NDA:** 203100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Wen Zeng, Ph.D., Biometrics Reviewer

**Concurrence:** Fraser Smith, Ph.D., Biometrics Acting Team Lead

**Subject:** NDA 203100

---

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your January 10, 2012, submission consisting of your response to our December 23, 2011, filing letter comments. We have reviewed your submission and have the one additional follow-up question for clarification.

**Comment 2 (December 23, 2011)**

If RandDate is the generation date of the final randomization list, it appears that the full randomization list for study GS-US-236-0103 was generated after the last subject was randomized, which contradicts the (b) (4) SOP-OP-002. Please provide an explanation.

**Gilead's Response (January 10, 2012)**

In the final Randomization list provided by (b) (4) (Gilead IVRS vendor), file name "gs-us-236-0103-final-randlist-ver-1.pdf", the field "randdate" is intended to define the date on which the list was generated. In this case, the date displayed in this field is incorrect due to typographic error in the programming code used to generate the PDF file. It should display 08 Jan 2010, but instead it incorrectly displays 08 Dec 2010. (b) (4) can provide the original copy of the final randomization list in .csv format if desired, which will provide evidence that the list was created on 08 Jan 2010. Once created on 08 Jan 2010, the randomization list was written to a secure read-only drive preventing alteration. (b) (4) has confirmed that the list was not altered after 08 Jan 2010. This error is a date/versioning error within the randomization list and had no functional impact on the system or randomization logic. All subjects were randomized after the creation of the list.

**Follow-up Comment from FDA**

Yes, please provide the original copy of the final randomization list in .csv format. In addition, please clarify how the typographical error in the programming code used to generate the PDF file occurred. Please submit the programming code used to generate the PDF file as well as the IVRS log file in the original randomization order.

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

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

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/s/  
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STACEY MIN  
02/15/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 2, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Clinical Information Request	

**Total number of pages including cover:** 4

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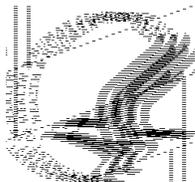
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**Date:** February 2, 2012

**NDA:** 203100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

---

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. We have the following request for additional information.

**Clinical Comments:**

Please provide additional details (e.g. a step-wise procedure) as to how you derived Table 11-12 and 11-13 in the Week 48 Interim Clinical Study Report for GS-US-236-0103. We are having difficulty confirming your results, which also appear in the draft label. Please specify the analysis variables that were used to select the subject population. For example, foot note 'b' specifies that only subjects with non-missing spine or hip BMD for the baseline visit and at least one post-baseline visit were included in the DEXA substudy analysis set. Is this subpopulation automatically selected for when applying the "DEXA substudy flag"?

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

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

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/s/  
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STACEY MIN  
02/02/2012

**From:** [Linda McBride](#)  
**To:** [David, Jeannie C](#)  
**Cc:** [Regulatory Archives](#); [Min, Stacey](#)  
**Subject:** RE: NDA 203100  
**Date:** Monday, January 23, 2012 8:59:33 PM

---

Dear Jeannie,

All the sites involved with the DS or DP manufacturing, testing, packaging and labeling for the Access quad tablets are identified in the NDA, therefore not amendment is required.

If you have any further comments or questions, please don't hesitate to ask.

Best regards,

Linda

*Linda McBride, R.Ph., RAC*

*Regulatory Affairs*

*Gilead Sciences, Inc.*

*Email: [linda.mcbride@gilead.com](mailto:linda.mcbride@gilead.com)*

*Phone: 650.524.3854*

---

**From:** David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]  
**Sent:** Friday, January 20, 2012 2:45 PM  
**To:** Linda McBride  
**Cc:** Regulatory Archives; Min, Stacey  
**Subject:** NDA 203100

Dear Linda,

As discussed in our call today, please respond to the following information request:

Please verify that all sites that are involved with DS or DP manufacturing, testing, packaging and labeling for the Access quad tablet are identified in the NDA. If any additional sites are involved for the Access tablet, please amend the NDA with the appropriate establishment information (e.g., function(s), local site contact information, etc.).

If there are any further questions, please let me know.

Regards,

Jeannie

**Jeannie David, MS**  
**Regulatory Health Project Manager**  
**CDER/OPS/ONDQA**  
**Food and Drug Administration**  
**10903 New Hampshire Avenue**  
**Building 22, Room 1475**

Silver Spring, MD 20993  
Phone: (301) 796-4247  
Fax: (301) 796-9877  
jeannie.david@fda.hhs.gov

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JEANNIE C DAVID  
02/07/2012

**From:** [David, Jeannie C](#)  
**To:** ["Linda McBride"](#)  
**Cc:** [Regulatory Archives](#); [Min. Stacey](#)  
**Subject:** NDA 203100  
**Date:** Friday, January 20, 2012 5:44:00 PM

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Dear Linda,

As discussed in our call today, please respond to the following information request:

Please verify that all sites that are involved with DS or DP manufacturing, testing, packaging and labeling for the Access quad tablet are identified in the NDA. If any additional sites are involved for the Access tablet, please amend the NDA with the appropriate establishment information (e.g., function(s), local site contact information, etc.).

If there are any further questions, please let me know.

Regards,

Jeannie

**Jeannie David, MS**  
**Regulatory Health Project Manager**  
**CDER/OPS/ONDQA**  
**Food and Drug Administration**  
**10903 New Hampshire Avenue**  
**Building 22, Room 1475**  
**Silver Spring, MD 20993**  
**Phone: (301) 796-4247**  
**Fax: (301) 796-9877**  
**[jeannie.david@fda.hhs.gov](mailto:jeannie.david@fda.hhs.gov)**

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/s/  
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JEANNIE C DAVID  
01/23/2012



NDA 203100

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

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

Dear Dr. Christophe Beraud:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/ 200 mg/300 mg Tablet.

We will be performing methods validation studies on Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/ 200 mg/300 mg Tablet, as described in NDA 203100

In order to perform the necessary testing, we request the following sample materials and equipments:

**Samples and Reference Standards**

- |        |   |
|--------|---|
| 30     | Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/ 200 mg/300 mg Tablet |
| 100 mg | Elvitegravir (EVG) Reference Standard   |
| 100 mg | Cobicistat (COBI) Reference Standard  |
| 150 mg | Emtricitabine (FTC) Reference Standard  |
| 225 mg | Tenofovir DF (TDF) Reference Standard   |
| 100 mg | EVG/COBI/FTC/TDF system suitability standard  |

(b) (4)



**Equipment**



Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email ([James.Allgire@fda.hhs.gov](mailto:James.Allgire@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
01/20/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 18, 2012

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Clinical Information Request	

**Total number of pages including cover:** 4

**Comments:**

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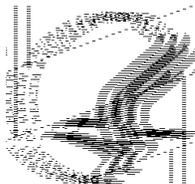
**Document to be mailed:** YES  NO

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**Date:** January 18, 2012

**NDA:** 203100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

---

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. We have the following request for additional information.

**Clinical Comments:**

1. Please provide the location of the dataset for Study GS-US-236-0102 and Study GS-US-236-0103 that contains the subjects' vital signs (e.g., blood pressure, pulse, and temperature). Please note that the only content of the dataset labeled 'vital signs' in the submission was height and weight.
2. If testing for the genetic polymorphism ABCC2 was performed for any of the subjects who developed renally-related AEs, please provide those results.

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.

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

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/s/  
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STACEY MIN  
01/18/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: January 11, 2012

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100, Virology Information Request</b>	

Total number of pages including cover: 3

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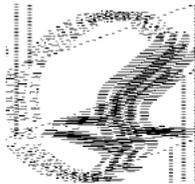
Document to be mailed: YES  NO

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**Date:** January 11, 2012

**NDA:** 203-100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Sung Rhee, Ph.D., Clinical Virology Reviewer  
Takashi Komatsu, Ph.D., Clinical Virology Reviewer

**Concurrence:** Julian O'Rear, Ph.D., Clinical Virology Team Lead

**Subject:** NDA 203-100 Virology Information Request

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. Please provide the following information to the NDA as soon as possible.

**Clinical Virology Comment:**

1. There is a discrepancy between the viral load dataset and your study report. Please provide the viral load data for Subjects 0302-6041 and 1645-6358 (both in Study 102) included in your resistance analysis population (n=53; Integrated Virology Listing 2) in Report PC-236-2006 (pages 250-264) but not present in the dataset.
2. Please provide EVG susceptibility data in your ADVIRO resistance dataset for Subjects 0031-6257 and 0994-6667 (both in Study 102) that were included in Table 3 in Report PC-236-2006 (page 15) but not present in the dataset.
3. Please confirm IN genotypic changes detected in the on-treatment isolates from Subject 1978-6091 (Study 102) in your ADVIRO resistance dataset:

ISOLATE	ADY	Genotypic changes in HIV-1 IN
BASELINE	1	-
WEEK 24	171	G284G/R
WEEK 40	281	R262G/R, R263G/R, R269G/R, G284G

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Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

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

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STACEY MIN  
01/11/2012



NDA 203100

**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/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR).

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

Please provide your responses to the following requests no later than January 20, 2012:

1. Provide data to support the selection of 2% polysorbate 80 for the proposed dissolution medium for each API.

Responses to the remainder of the requests may be provided by January 27, 2012:

2. FDA regulations require an applicant to submit with each application either an Environmental Assessment (EA) or a claim of categorical exclusion. According to information provided under NDA 203100, the expected introduction concentrations (EICs) for elvitegravir, cobicistat and emtricitabine will be below 1 ppb and, therefore, eligible for categorical exclusion under 21CFR25.31(b).

Please submit claims for categorical exclusion for elvitegravir, cobicistat and emtricitabine as described at

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088977.htm>.

As a reminder the EIC is calculated based on anticipated patient use of the highest annual quantity of the active moieties expected to be produced for use during the next five years; the quantity used in all dosage forms and strengths included in this application and your related applications.

An EA is required for the active ingredient, tenofovir disoproxil fumarate (TDF). As the EA for TDF is submitted to NDA 21-356, please update the EA for TDF in NDA 21-356 as appropriate,

under sections 2, 4.1.4, 4.2.2, 4.2.3, 4.3, Confidential Appendix 10.1, and any other sections requiring specific revision as a result of your new application(s). Please also amend Section 1.12.14 in NDA 203100 to reference this updated EA information, once it has been submitted.

3. Submit a sample of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate 150 mg/150 mg/200 mg/300 mg tablets packaged in the proposed 30's count bottle configuration.
4. Provide the complete specifications (or certificate of analysis) for the proposed [REDACTED] (b) (4) excipient. Also, provide a justification [REDACTED] (b) (4) based on excipient physical and chemical attributes that could impact tablet properties, and on any development data supporting this change.
5. Provide a reference and Letter of Authorization to the Drug Master File [REDACTED] (b) (4)
6. We note that the tables of cross-reference in Module 1.4.4 for the drug substances, emtricitabine and tenofovir disoproxil fumarate, list a representative document across applications for each CTD section. As these documents have been further updated, and to expedite review, submit a review aid to include a history of supplemental changes, highlighting the last updates for each change, and include a brief statement of the type of change, the application and supplement numbers, volume and page numbers, and the date of approval or that the change is pending. If more convenient, you may submit the updated documents directly, noting the relevant application and supplement numbers.

To facilitate prompt review of the response, please also provide an electronic courtesy copy of the response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Stacey Min, Regulatory Project Manager the Office of New Drugs (Stacey.Min@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

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

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RAPTI D MADURawe  
01/10/2012



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: December 28, 2011

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100, Clinical Information Request</b>	

Total number of pages including cover: 4

**Comments:**

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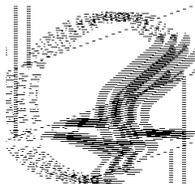
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**Date:** December 28, 2011

**NDA:** 203100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

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Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. We have the following request for additional information.

**Clinical Comments:**

1. Please provide full subject narratives in the same format as Section 15.2 (Narratives of Deaths, Serious Adverse Events, and Certain Other Significant Adverse Events) of the Week 48 Interim Clinical Study Report for studies 236-0102 and 236-0103 for the following subjects:

2058-6709  
2675-6010  
0033-6681  
2493-7299  
0663-7326  
3957-7510

In addition, include any available follow-up information beyond Week 48.

2. Please provide your reference range (i.e. normal range of values) for the laboratory parameter "fractional excretion of phosphate." Please also provide your basis for choosing the

reference range (e.g. was the reference range provided by the laboratory, was it based on the scientific literature, etc).

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.

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

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/s/  
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STACEY MIN  
12/28/2011

**Min, Stacey**

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**From:** Min, Stacey  
**Sent:** Tuesday, December 27, 2011 10:31 AM  
**To:** 'Christophe Beraud'  
**Subject:** RE: NDA 203100 - Coding Dictionary Request

Dear Christophe:

Yes, what we're looking for is information on who is assigned to match verbatim terms to MedDRA preferred terms during data collection, what instructions they're given to do that, how consistency is assured if more than one person does this task, and then we may need the listing of all verbatim terms as matched to preferred term as offered in the email below.

Please let me know if you have additional follow-up questions.

Regards,  
Stacey

---

**From:** Christophe Beraud [mailto:Christophe.Beraud@gilead.com]  
**Sent:** Friday, December 23, 2011 3:55 PM  
**To:** Min, Stacey  
**Cc:** Christophe Beraud; Regulatory Archives  
**Subject:** NDA 203100 - Coding Dictionary Request

Dear Stacey:

I wanted to follow-up on the request for the coding dictionary in the filing letter dated 23 December 2011:

1. Please provide a "coding dictionary" that consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). If you already submitted a "coding dictionary, please indicate its location in the submission.

I was informed by our Biometrics group that both the adverse event verbatim and preferred terms are present in the SDTM AE domain. The verbatim term is AETERM and the preferred term is AEDECOD in the SDTM AE domain.

Would you please clarify whether the information contained in the datasets submitted is not sufficient and that you want a separate SAS dataset that contains all unique AETERM-AEDECOD combinations?

Thank you in advance for the clarification.

Kind regards,

Christophe

---

**Christophe Beraud, PhD** | Associate Director, Regulatory Affairs | Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 USA | Phone 650 522 5093 | Fax 650 522 5489 | Email christophe.beraud@gilead.com

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/s/  
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STACEY MIN  
12/27/2011



NDA 203-100

**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 October 26, 2011, received October 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR).

We also refer to your amendments dated October 27, 2011, November 16, 2011, November 21, 2011, November 28, 2011, and December 14, 2011.

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 August 27, 2012.

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 July 9, 2012.

During our filing review of your application, we identified the following potential review issues:

Our initial filing review identified renal adverse events as a potential safety signal for this product. Please provide any additional information available related to the renal status of the subjects in clinical trials GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

who experienced a renal adverse event of interest, discontinued study drug due to renal causes, or had notable renal laboratory abnormalities.

We note that females only comprised 10% of the study population in the pivotal phase 3 trials (GS-US-236-0102 & GS-US-236-0103). The limited safety and efficacy evaluation in females may need to be reflected in product labeling. Additionally, safety concerns may need to be addressed in a postmarketing trial.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

**Clinical and Statistical Information:**

1. Please provide a “coding dictionary” that consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). If you already submitted a “coding dictionary, please indicate its location in the submission.
2. If RandDate is the generation date of the final randomization list, it appears that the full randomization list for study GS-US-236-0103 was generated after the last subject was randomized, which contradicts the (b) (4) SOP-OP-002. Please provide an explanation.

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.

**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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

We acknowledge receipt of your request for a (b)(4) deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b)(4) deferral request is denied.

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

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/s/  
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DEBRA B BIRNKRANT  
12/23/2011



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: December 22, 2011

To: <b>Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	From: <b>Stacey Min, Pharm.D.</b> Division of Antiviral Products
Company: <b>Gilead Sciences, Inc.</b>	Title: <b>Regulatory Project Manager</b>
Fax number: <b>650-522-5489</b>	Fax number: <b>301-796-9883</b>
Phone number: <b>650-522-5093</b>	Phone number: <b>301-796-4253</b>
Subject: <b>NDA 203100, Clinical Information Request</b>	

Total number of pages including cover: 3

**Comments:**

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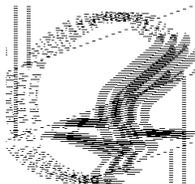
Document to be mailed: YES  NO

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**Date:** December 22, 2011

**NDA:** 203100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Adam Sherwat, M.D., Medical Officer

**Concurrence:** Linda Lewis, M.D., Medical Team Lead

**Subject:** NDA 203100 Clinical Information Request

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Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. We have the following questions and requests for information.

**Clinical Comments:**

1. Please provide additional details as to how you derived Table 18.2 in the ISS ("Treatment-emergent laboratory abnormalities, studies GS-US-236-0102 and GS-US-236-0103, Safety Analysis Set"). We are having difficulty confirming your results. Specifically, what variables were used to calculate the proportions of patients with each grade laboratory abnormality (e.g. was "analysis criteria 2" used, was the "safety analysis flag" used, were only labs drawn from specific visits used, etc.)?
2. Please explain why there are two blood chemistry datasets (i.e. "Chemistry 1" and "Chemistry 2") under "Parameter Category 1" which contain the same variables. Were both of these datasets (i.e. Chemistry 1 and Chemistry 2) used in creating your laboratory safety tables and performing your safety analyses?

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

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/s/  
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STACEY MIN  
12/22/2011



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 8, 2011

<b>To:</b> Christophe Beraud, Ph.D. Senior Manager, Regulatory Affairs	<b>From:</b> Stacey Min, Pharm.D. Division of Antiviral Products
<b>Company:</b> Gilead Sciences, Inc.	<b>Title:</b> Regulatory Project Manager
<b>Fax number:</b> 650-522-5489	<b>Fax number:</b> 301-796-9883
<b>Phone number:</b> 650-522-5093	<b>Phone number:</b> 301-796-4253
<b>Subject:</b> NDA 203100, Virology Information Request	

**Total number of pages including cover:** 3

**Comments:**

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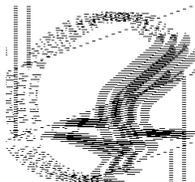
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**Date:** December 8, 2011

**NDA:** 203-100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Sung Rhee, Ph.D., Clinical Virology Reviewer  
Takashi Komatsu, Ph.D., Clinical Virology Reviewer

**Concurrence:** Julian O'Rear, Ph.D., Clinical Virology Team Lead

**Subject:** NDA 203-100 Virology Information Request

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. Please provide the following information to the NDA as soon as possible.

**Clinical Virology Comment:**

We noticed that columns for some IN, PR, and RT amino acid positions are not present in your ADVIRO resistance datasets. Please provide (or locate) revised datasets or an explanation as to why columns for some residues were deleted in the datasets.

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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

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/s/  
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STACEY MIN  
12/08/2011



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

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**FACSIMILE TRANSMITTAL SHEET**

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DATE: November 16, 2011

<b>To: Christophe Beraud, Ph.D.</b> Senior Manager, Regulatory Affairs	<b>From: Stacey Min, Pharm.D.</b> Division of Antiviral Products
<b>Company: Gilead Sciences, Inc.</b>	<b>Title: Regulatory Project Manager</b>
<b>Fax number: 650-522-5489</b>	<b>Fax number: 301-796-9883</b>
<b>Phone number: 650-522-5093</b>	<b>Phone number: 301-796-4253</b>
<b>Subject: NDA 203100, CMC Information Request</b>	

Total number of pages including cover: 4

**Comments:**

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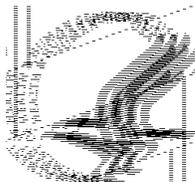
**Document to be mailed:** YES  NO

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**Date:** November 16, 2011

**NDA:** 203-100

**Drug:** elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**To:** Christophe Beraud, Ph.D, Senior Manager, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

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

**Through:** Milton Sloan, Ph.D., CMC Reviewer  
Celia Cruz, Ph.D., CMC Reviewer  
Fuqiang Liu, Ph.D., CMC Reviewer

**Concurrence:** Stephen Miller, Ph.D., CMC Lead  
Rapti Madurawe, Ph.D., CMC Branch Chief

**Subject:** NDA 203-100 CMC Information Request

Please refer to your NDA 203-100 for Single Tablet Regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg for the treatment of HIV-1 infection in adults. We also refer to your October 26, 2011, submission consisting of your original application of NDA 203-100. Please provide the following information to the NDA as soon as possible.

**CMC Comment:**

Please submit cross reference to current CMC information in a DMF or NDA for emtricitabine and tenofovir and indicate the specific locations (submission number, volume, file name, etc..) where the referenced information can be found.

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.

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Stacey Min, Pharm.D.  
Regulatory Project Manager  
Division of Antiviral Products

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/s/  
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STACEY MIN  
11/16/2011



NDA 203100

**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/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

Date of Application: October 26, 2011

Date of Receipt: October 27, 2011

Our Reference Number: NDA 203100

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 December 26, 2011, 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.

**FDAAA TITLE VIII RESPONSIBILITIES**

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).

## **SUBMISSION REQUIREMENTS**

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>.

If you have 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

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/s/  
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STACEY MIN  
11/03/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 103,093

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/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) fixed-dose combination tablets.

We also refer to your February 24, 2011, correspondence, received February 24, 2011, requesting a Type B, pre-NDA meeting to discuss the key aspects related to the content and format of the application, including the NDA Safety Update, proposed pediatric development plan and the potential extrapolation of drug interaction information between RTV-boosted PIs and COBI-boosted PIs as discussed during the March 12, 2010, End-of-Phase 2 meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 13, 2011, from 10:00 – 11:30 AM, at 10903 New Hampshire Avenue, White Oak Building 2, Room 2045 between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

### Question 1

**Does the Agency agree with the proposal to submit the NDA for EVG/COBI/FTC/TDF tablets in December 2011, followed by the NDAs for EVG and COBI tablets in the March-April 2012 timeframe?**

FDA's response dated 08 April 2011:

We agree with your proposed sequence of submission for the three NDAs; the NDA for the fixed-dose combination (FDC) tablet in December 2011, followed by the NDAs for EVG tablets and COBI tablets in March - April 2012. (b) (5)

FDA response, 08 July 2011:

As noted previously, we agree with the proposed sequence of submissions. However, we request that you streamline the proposed NDA for EVG/COBI/FTC/TDF tablets to include only the trials considered essential for the efficacy and safety review of the product under consideration. Namely, we agree with submission of the trial data from Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104. Summaries of safety data from the individual COBI and EVG development program clinical trials should be submitted with this NDA as part of the integrated summary of safety, consisting of a summary of deaths, serious adverse events, discontinuations due to adverse events, and adverse events of interest (renal, hepatotoxicity, etc.). Full trial data from the remaining studies outlined in Table 3 of your meeting package should be submitted with their respective NDAs. An exception to this is that we request safety data from Study GS-US-236-0118 be submitted as soon as possible or as part of the Safety Update for the EVG/COBI/FTC/TDF tablets NDA.

We also note you plan to request priority review for this application. Please submit adequate justification for your request taking into consideration the proposed indication and the available therapies on the market.

### Question 2

**Does the Agency agree with the proposal for submission of Type II DMFs for both for EVG and COBI drug substances?**

Yes, we agree with your proposal to submit DMFs for both EVG and COBI drug substances prior to the submission of the Tier 1 filing of the NDA. As indicated in your question, LOAs should be provided in the NDA and a copy provided in the DMF. Please note that we will not be able to schedule inspection of the facilities (including the drug substance facility) until the drug product part of the NDA has been submitted. Please factor the lead time (typically up to 1 month) to process new DMF's when planning the submission for the drug substance.

In the DMF's for EVG and COBI, please plan to include a proposal (b) (4) for the drug substance. The proposal should include the following: (b) (4)

[REDACTED] (b) (4)

In addition, please clarify [REDACTED] (b) (4) route for the planned commercial process.

**Question 3**

**Would the Agency want the opportunity to receive the EVG/COBI/FTC/TDF dossier via a rolling NDA as proposed?**

We agree with your proposal to submit the components of the application as a rolling NDA. Please clarify if you intend to submit Tier 2 in November or December, 2011.

**Question 4**

**Does the Agency have comments on the NDA Table of Contents, or on the approach regarding the location of nonclinical reports of studies pertinent to pharmacokinetics using human biomaterials and nonclinical virology?**

There are no comments.

**Question 5**

**Does the Agency agree with the proposed approach for summarizing data from nonclinical studies pertinent to pharmacokinetics using human biomaterials and from nonclinical virology studies in Module 2?**

The virology summary should be placed in Section 2.7.2.4 Special Studies with links to relevant data.

**Question 6**

**The primary pharmacodynamic effect of COBI is inhibition of human CYP3A enzymes. As such, the primary pharmacodynamics of this drug will be briefly noted in the Pharmacology Written Summary (Module 2.6.2), with more specific details (mechanism of inhibition, enzyme inactivation parameters, and species specificity of CYP inhibition) provided in the Pharmacokinetics Written Summary, Pharmacokinetic Drug Interactions (Module 2.6.4), to facilitate the presentation and interpretation of this information in the context of the overall drug-drug interaction profile. Nonclinical reports of studies pertinent to the pharmacodynamic effect on CYP3A inhibition [REDACTED] (b) (4)**

**[REDACTED] will be included in Modules 4.2.2.6 and 5.3.2.2, respectively (see Table of Contents provided in Attachment 2).**

**Does the Agency agree with this proposal?**

Your proposal is acceptable.

**Question 7**

**Does the Agency agree with the proposal to cross reference nonclinical and clinical studies with FTC, TDF and FTC/TDF?**

We agree with your proposal to cross reference nonclinical and clinical studies with FTC, TDF, and FTC/TDF.

**Question 8**

**Does the Agency agree that the generic name to be used in labeling should be elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate?**

FDA's response dated 08 April 2011:

We agree and recommend "TRADENAME (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate) tablets, Wmg/Xmg/Ymg/Zmg", with salt-form equivalence statements as appropriate.

**Question 9**

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

We agree with your proposal for the provision of references.

**Question 10**

**Does the Agency agree with the proposal that electronic datasets and ECG waveforms arising from the thorough QTc studies do not have to be resubmitted in support of their relevant NDAs, including EVG/COBI/FTC/TDF tablets?**

We agree that electronic datasets and ECG waveforms from the thorough QTc studies do not have to be resubmitted in support of their relevant NDAs, including EVG/COBI/FTC/TDF tablets.

**Question 11**

**Gilead is committed to make EVG/COBI/FTC/TDF tablets available in the developing world through the Gilead Access Program. Gilead is developing an alternate trade dress for these tablets as described in Table 2 below together with the trade dress intended for the US market.**

**Table 2. EVG/COBI/FTC/TDF Tablets US/Access Program Trade Dress**

<b>Tablet Shape and Dimensions</b>	<b>US Trade Dress</b>	<b>Access Program Trade Dress</b>
Capsule-shaped tablet, 20 × 10 mm	Debossing: GSI / 1; Color: Green, (b) (4)	Debossing: GSI / 1A; Color: White, (b) (4)

Gilead plans to include in the NDA submission the required quality information for this alternate trade dress, including the required stability data to support the use of the tablet in climatic zones where the drug will be distributed as part of the Gilead Access Program. In Module 1, Gilead will include the draft Prescribing Information for both the US and Access Program presentations of the tablets. The prescribing information for the US presentation will be provided in SPL format as required. However, the prescribing information for the Access Program presentation will be provided as PDF and Word files. Both the prescribing information and packaging for the Access program presentation will include the statement "for Gilead Access Program."

**Does the Agency agree with this proposal?**

The proposed plan for submitting quality and labeling information on the alternate trade dress for the US and Gilead Access Program is acceptable. However, the adequacy of information submitted for quality can be determined only upon review of the submitted information. The NDA should contain long-term stability data at 30°C/75%RH for both the US Trade Dress and the Access Program tablets. This would facilitate comparisons, and may have value if both versions are ultimately used in climatic zones III and IV. Also, please note that we expect at least 6 months of stability data under accelerated conditions and 12 months under long-term conditions for 3 batches in the NDA for the drug substances and the drug product.

**Question 12**

**Does the Agency agree with the proposal for the data cut-off of ongoing clinical studies for inclusion in the NDA for EVG/COBI/FTC/TDF tablets?**

The proposal for the data cut-off of ongoing clinical studies is acceptable.

**Question 13**

**Does the Agency agree with the proposal for the timing and content of the EVG/COBI/FTC/TDF tablets NDA Safety Update?**

Please see the general response included under Question 1 regarding the content of the NDA Safety Update. Trial safety data from Study GS-US-216-0114 for COBI can be summarized as part of the Safety Update.

**Question 14**

**Are the proposed sensitivity analyses to be conducted for Phase 3 Studies GS-US-236-0102 and GS-US-236-0103 with EVG/COBI/FTC/TDF tablets acceptable to the Agency?**

The first sensitivity analysis you propose to exclude subjects who discontinued study drug prior to or in the Week 48 window due to reasons other than lack of efficacy, adverse events or death and have no virologic data in the Week 48 window, and who have the last available HIV-1 RNA on randomized treatment < 50 copies/mL appears acceptable. These subjects, however, could also be counted as responders in an additional sensitivity analysis.

The other sensitivity analyses also appear to be acceptable.

#### **Question 15**

**Are the proposed time-to-event analyses of safety endpoints acceptable to the Agency?**

We do not concur with your proposal to do time-to-event analyses only when the p-value from the log rank test for the time to premature discontinuation of study drug is <0.05. Even if p-values from these tests are not statistically significant at the 0.05 level it may be necessary to perform time-to-event analyses of safety endpoints if there appear to be substantially different lengths of follow-up in each treatment group.

#### **Question 16**

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

The proposal for the analyses to be included in the ISE is acceptable.

#### **Question 17**

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

The proposal for the analyses to be included in the ISS is acceptable.

#### **Question 18**

**Per FDA's Guidance for Industry entitled "*Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*" (April 2009), Gilead proposes to include the ISE and ISS text within the Summary of Clinical Efficacy (Module 2.7.3) and Summary of Clinical Safety (Module 2.7.4), respectively. eCTD cross-reference leaves to Modules 2.7.3 and 2.7.4 will be provided in Module 5.3.5.3 together with supporting statistical outputs and electronic datasets. Gilead anticipates that the size of Modules 2.7.3 and 2.7.4 will be approximately 200 pages each, including the integrated data analyzes described in the ISE and ISS SAPs (see Question 16 and Question 17).**

**Does the Agency agree with this proposal?**

We agree with this proposal.

### Question 19

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

We agree with your proposal to submit narratives and CRFs for the active arms of the Phase 2 and 3 studies; however, we request you also submit the narratives for the indicated events for the comparator arms as well.

### Question 20

**Based on the nonclinical and clinical information that has been previously submitted to IND 103,093 for EVG/COBI/FTC/TDF tablets, IND [REDACTED] (b)(4) for EVG tablets, and IND [REDACTED] (b)(4) for COBI tablets, Gilead does not intend to include a Risk Evaluation and Mitigation Strategy (REMS) in the NDA for EVG/COBI/FTC/TDF tablets. Gilead will further consider any potential need for a REMS following availability of data from Phase 3 Studies GS-US-236-0102 and GS-US-236-0103.**

**Does the Agency have any comments about this proposal?**

We do not anticipate a REMS will be needed for this NDA but a final decision will be made after review of the safety data.

### Question 21

**Does the Agency agree with these resistance analysis plans as fully described in PC-236-2002 and PC-236-2003 submitted to IND 103,093 on 09 February 2010 (Serial No. 0061)?**

The IN, PR, and RT regions of baseline isolates from all virologic failures should be genotyped regardless of the failure isolates' phenotype. Please confirm that the PR region of failure isolates will be genotyped from all COBI-exposed failures.

Please conduct integrated resistance analyses on pooled genotypic/phenotypic data from all EVG-exposed virologic failure subjects in 3 studies, GS-US-236-0102, -0103, and -0104, and submit the results as a virology study report including descriptions of assays for viral load, and genotypic and phenotypic resistance assessments in Section 5.3.5.4 Other Study Reports and Related Information (resistance datasets should be placed in this section).

### Question 22

**Does the Agency agree with the proposal for submission of reports from carcinogenicity studies post-approval?**

Please submit an estimated date for submission of the COBI carcinogenicity studies.

**Question 23**

**Based on the nonclinical and clinical information that has been previously submitted to IND 103,093 for EVG/COBI/FTC/TDF tablets, IND (b) (4) for EVG tablets, and IND (b) (4) for COBI tablets, does the Agency anticipate that the NDA for EVG/COBI/FTC/TDF tablets will be the subject of an FDA Advisory Committee Meeting?**

We anticipate that an Advisory Committee (AC) Meeting will be a part of the review process for one or more of your applications as there are 2 new molecular entities (NMEs) under consideration. The subject(s) of the AC meeting will depend on the type of reviews your applications receive and the timing of the review processes in relation to the scheduling of the meeting.

**Question 24**

**Does the Agency agree with expediting the study of EVG/COBI/FTC/TDF in HIV-1 infected adolescents before COBI has been studied in that population? Does the Agency agree with the proposed development plan for EVG/COBI/FTC/TDF in pediatric patients  $\geq 6$  to  $< 18$  years of age, and the proposed waiver for pediatric subjects  $< 6$  years of age?**

PK data and at least some safety data are available for three of the four components of EVG/COBI/FTC/TDF tablets. We agree, in principle, with your proposal to study EVG/COBI/FTC/TDF tablets in adolescents based on the currently available information. We recommend that any proposed protocol in this population include the collection of intensive PK data for EVG and COBI as an objective. We do not agree with the plan to limit the study of EVG/COBI/FTC/TDF tablets to treatment-experienced adolescents as we see a potential benefit of this product in the treatment naïve adolescent population. Further discussion regarding the specifics of a U.S. protocol can be held as you prepare to submit a PPSR for review. Although we acknowledge the EMA's request for a "switch" study in treatment-experienced subjects, we do not favor this trial design. At this time, we do not agree with your proposal to request a waiver for pediatric subjects  $< 6$  year of age because we have limited PK data for some components of the fixed dose combination tablet and do not know if a waiver is warranted.

**Clinical Pharmacology Response 4.8 (Action Item from EOP2 Meeting):**

The Division is reviewing the table which compares the drug-drug interactions between ritonavir or cobicistat-boosted darunavir and atazanavir when co-administered with other non-antiretroviral drugs. Please provide a similarly structured table which compares the drug-drug interactions between ritonavir or cobicistat-boosted darunavir and atazanavir when co-administered with other antiretroviral drugs. The Division will provide consolidated feedback on both the tables.

**ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:**

1. At the time of NDA submission, please submit final study reports for only those drug-drug interaction (and other clinical pharmacology/pharmacokinetics) trials which will be used to support the proposed package insert for the EVG/COBI/FTC/TDF tablet.

2. Please provide a table outlining how the drug-drug interaction information between the EVG/COBI/FTC/TDF tablet and other non-antiretroviral drugs will be described in the package insert of the EVG/COBI/FTC/TDF tablet. For each drug-drug interaction, clearly describe if the proposed recommendation is based on an actual drug-drug interaction trial (if so, include the trial number in the table) or on extrapolations.
3. Please perform exposure-response analyses for the Phase 2 Study GS-US-236-0104 and pivotal Phase 3 Studies GS-US-236-0102 and GS-US-236-0103 in addition to the proposed population pharmacokinetic report. These analyses should include efficacy (i.e., virologic success, virologic failure) and important safety events dependent on exposure variables (i.e.,  $C_{\text{trough}}$  for efficacy;  $C_{\text{max}}$  and  $AUC_{\tau}$  for safety).
4. Please submit the datasets and codes/scripts for reviewers to recreate modeling and simulations:
  - All datasets used for model development and validation should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
  - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
  - The exposure-response dataset should include unique subject identifiers, study identification numbers, a binary listings of all efficacy and safety events included in the exposure-response analysis, key demographics and stratification groups, baseline viral load and CD4 cell count, adherence data, baseline and maximum on-treatment serum creatinine values, baseline and minimum on-treatment calculated glomerular filtration rate, and exposure data for all compounds in the fixed-dose combination.

#### **ADDITIONAL PHARMACOLOGY/TOXICOLOGY COMMENT:**

5. When submitting your NDA, under each header (e.g., single dose, repeat dose, etc), please list the EVG studies first, the COBI studies next, followed by any combination studies last. This will simplify the review process for the P/T team.

#### **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 Division 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 Stacey Min, Pharm.D., Regulatory Project Manager, at (301) 796-4253.

Sincerely,

*{See appended electronic signature page}*

Linda Lewis, M.D.  
Medical Team Lead  
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.**  
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/s/  
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LINDA L LEWIS  
07/08/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND (b) (4)

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

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** March 12, 2010

**TIME:** 1:00 – 2:30 PM

**LOCATION:** White Oak, CSU, E-2046

**APPLICATION:** IND (b) (4)

**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)

Meeting Minutes  
Type B, EOP2 Meeting  
March 12, 2010

Office of Antimicrobial Products  
Division of Antiviral Products

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

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

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

## 1. BACKGROUND

Gilead Sciences Inc. is developing a new chemical entity, GS-9350 under IND (b) (4) 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 (b) (4) to support the efficacy of DRV when boosted with GS-9350. The Agency asked if Gilead had any arrangement with (b) (4). Gilead indicated there was no formal arrangement, but that they have been in communication with (b) (4) 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.* (b) (5)

**Discussion:**

(b) (5)  
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, (b) (4) 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, the use of GS-9350 (b) (4) will be evaluated. (b) (4)

(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 (b) (4) (b) (4) 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 (b) (4) 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 (b) (4) study and planned drug interaction studies (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 (b) (4) studies as a means to evaluate GS-9350 (b) (4) (b) (4) 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 (b) (4) (b) (4) 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. (b) (4)

(b) (4) 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 (b) (4) studies to evaluate GS-9350 (b) (4) (b) (4) as the Agency's experience with (b) (4) studies has shown them to be prone to failure. Gilead plans to evaluate (b) (4) only. The Agency advised Gilead to consider other study designs because tolerability and adherence issues (b) (4) 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 (b) (4) 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 Cmax of GS-9137 observed in all the pharmacokinetic and clinical studies conducted so far with the Cmax observed at the supratherapeutic dose in the QT study.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND- (b) (4)

GI-1

GILEAD SCIENCES  
INC

GS-9350

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/s/  
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DEBRA B BIRNKRANT  
04/09/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

INDs (b) (4) 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 (b) (4)), GS-9350 (IND (b) (4)) 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 (b) (4) 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 (b) (4). 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 <sup>1</sup> )
Elvitegravir tablets	535	1420
EVG/FTC/TDF/GS-9350 tablets	550	714
<b>Total</b>	<b>1085</b>	<b>2134</b>

<sup>1</sup> 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 <sup>1</sup> )
GS-9350 tablets	300	468
EVG/FTC/TDF/GS-9350 tablets	550	714
<b>Total</b>	<b>850</b>	<b>1182</b>

<sup>1</sup> 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 (b) (4)), 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 103093

Gilead Sciences LLC

Elvitegravir/Emtricitabine/Tenofavir  
Disoproxil Fumarate/GS-9350

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/s/

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JEFFREY S MURRAY

01/13/2009