

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210251Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 210251	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A – Original NDA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: BICTARVY® Established/Proper Name: bictegravir, emtricitabine, and tenofovir alafenamide Dosage Form: Tablets (fixed-dose combination)		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): N/A
RPM: Suzanne Strayhorn		Division: DAVP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Not applicable – not a 505(b)(2) application <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____ <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is February 12, 2018 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

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

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

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

Review priority: Standard Priority (Tropical Disease Voucher Used)
 Chemical classification (new NDAs only): Type 1, NME & Type 4, New Combination
 (confirm chemical classification at time of approval)

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	07 Feb 2018
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included Received 25 Jan 2018
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Received 12 Jun 2017
❖ Medication Guide/ Patient Package Insert /Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included Received 25 Jan 2018
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Received 12 Jun 2017
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included, Received 25 Jan 2018: Container US
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Letter: 24 Aug 2017 Review: 22 Aug 2017
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 07 Aug 2017 (PLR Format) DMEPA: 11 Sep 2017 DMPP/PLT: 28 Dec 2017 OPDP: 28 Dec 2017 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: Included with integrated quality assessment document Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	12 Jul 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed (Do not include) 29 Jan 2018
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC If PeRC review not necessary, explain: N/A – PeRC Reviewed 	PeRC Review: January 10, 2018
❖ Breakthrough Therapy Designation	N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	N/A
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	N/A
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	24 Jan 2018: IR Labeling 19 Jan 2018: IR Carton 17 Jan 2018: IR Labeling 04 Jan 2018: IR Snapshot 04 Jan 2018: IR Labeling 21 Nov 2017: Late-Cycle Backg. 16 Nov 2017: IR Labeling 02 Nov 2017: IR Carton/Contain 25 Oct 2017: Labeling Comments 13 Oct 2017: IR OPQ 02 Oct 2017: IR Subject Narrative 28 Sep 2017: IR Subject Narrative 27 Sep 2017: IR SF Datasets 25 Sep 2017: IR OPQ 14 Sep 2017: IR OPQ 23 Aug 2017: IR OPQ 18 Aug 2017: IR Subject Narrative 08 Aug 2017: IR OPQ 08 Aug 2017: Filing Letter 30 Jun 2017: IR – Formulation 28 Jun 2017: IR – Foreign Data (DARRTs date) 22 Jun 2017: Ack Prop. Name 20 Jun 2017: IR - Enrollment v FD 14 Jun 2017: Ack. NDA Letter
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	Date of Meeting: 28 Nov 2017 Date of Minutes: 18 Dec 2017
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	Date of Planned Meeting: 25 Sep 2017 (not-needed per applicant). Final Communication Dated: 28

	Sep 2017
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) – under IND 125589, Type C- Submission planning 	Date of Meeting: none / WRO Date of Minutes: 26 Jan 2017
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	No Meeting.
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) – under IND 125589 	Date of Meeting: 21 Oct 2015 Date of Minutes: 28 Oct 2015
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	6 Feb 2018. Refer to multidisciplinary document which incorporates review
Division Director Summary Review (<i>indicate date for each review</i>)	6 Feb 2018. Refer to multidisciplinary document which incorporates review
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	Date of Review: 12 Jan 2018
PMR/PMC Development Templates (<i>indicate total number</i>) – 3 PREA PMRs	26 Jan 2018
Multidisciplinary Review (MDR)	
❖ Multidisciplinary Review Document	06 Feb 2018
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	12 Feb 2018: CDTL Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	09 Nov 2017: Primary Review Memo
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	None N/A – not an OTC drug
❖ 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>)	Refer to the multidisciplinary review document which includes the financial disclosure review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A – No REMS with this application N/A 09 Nov 2017: REMS Review

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

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	04 Dec 2017 – Clinical Inspection Summary 06 Feb2018- Letter to Inv. 06 Feb2018- Letter to Inv. 06 Feb2018- Letter to Inv. 14 Nov 2017 – Letter to Inv. 13 Nov 2017 Letter to Inv.
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	None
Clinical Microbiology Review(s) (indicate date for each review)	13 Nov 2017 (NGS Data) 08 Nov 2017 (Clin. Virol.)
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	None
Statistical Team Leader Review(s) (indicate date for each review)	None
Statistical Review(s) (indicate date for each review)	09 Nov 2017
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	None
Clinical Pharmacology review(s) (indicate date for each review)	09 Nov 2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	None
• Supervisory Review(s) (indicate date for each review)	None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	30 Oct 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No stat. carc. review
❖ ECAC/CAC report/memo of meeting	13 Sep 2017
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<p><u>Final Review:</u> 10Jan2018: Executive Summary 20Oct2017: Drug Substance 08Nov2017: Drug Product 01Nov2017: Environmental 01Nov2017: FONSI & Environmental Assessment 13Nov2017: Labeling Review 31Oct2017: Process Review 05Jan2018: Facilities Review 30Oct2017: Biopharm Review 14Nov2017: Attachment 1. Final Risk Assessment</p> <p><u>Review 1:</u> 14Nov2017: Executive Summary 20Oct2017: Drug Substance 08Nov2017: Drug Product 01 Nov2017: Environmental 01Nov2017: FONSI & Environmental Assessment 13Nov2017: Labeling Review 31Oct2017: Process Review 30Oct2017: Biopharm Review 14Nov2017: Attachment 1. Final Risk Assessment</p>
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	01Nov2017 – refer to Integrated Quality Assessment
<input checked="" type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	01Nov2017 – refer to Integrated Quality Assessment
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	No environmental impact statement required refer to Integrated Quality Assessment for review
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	05Jan2018 – refer to Integrated Quality Assessment Confirmed acceptable: 1Feb2017 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

Day of Approval Activities	
For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	N/A – Not a 505(b)(2) <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	N/A – Not a 505(b)(2) <input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A – Not in BTD Status <input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	Emailed PeRC 07 Feb 2018
❖ Send approval email within one business day to CDER-APPROVALS	Email sent 07 Feb 2018
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	Completed 07 Feb 2019

Strayhorn, Suzanne

From: Wackes, Frank
Sent: Thursday, February 01, 2018 2:52 PM
To: Strayhorn, Suzanne; Ponta, Andrei
Cc: Smith, Derek
Subject: RE: Please Confirm Inspections (required 1 week prior to action)- NDA 201251

Hello Suzanne,

There are no alerts and the facilities remain acceptable for NDA 210251.

Frank Wackes
Consumer Safety Officer

From: Strayhorn, Suzanne
Sent: Thursday, February 01, 2018 2:42 PM
To: Ponta, Andrei <Andrei.Ponta@fda.hhs.gov>; Wackes, Frank <Frank.Wackes@fda.hhs.gov>
Subject: Please Confirm Inspections (required 1 week prior to action)- NDA 201251
Importance: High

Hi Andrei and Frank,

We plan to take action on the BIKTARVY NDA 210251 next Tuesday, February 6, 2018. Per requirement, around 1 week before approval, I am to confirm facilities remain acceptable prior to issuing approval.

Could you confirm please?

Thanks so much for all your help!!

Warm Regards,
Suzanne

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, January 24, 2018 1:04 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: Draft Labeling for Review - NDA 210251
Attachments: NDA 210251_Draft PI_rec 18Jan2018_sent 24Jan2018.docx; NDA 210251_Draft PPI_rec 18Jan2018_sent 24Jan2018.docx

Dear Kim,

Please find attached a few more recommendations to the draft labeling for BIKTARVY under NDA 210251, version received January 18, 2018. Please note that the PPI remains as a separate word document, at this time.

- Please keep this patient labeling separated until such a time as we have finalized labeling negotiations. Once we are complete with labeling negotiations, we will ask that you merge the two documents back together again.
- When returning the labeling back to us, please do accept the proposed changes you agree to and include redlined word versions with your new comments and proposed text changes.

To facilitate review timelines, could you provide update labeling on / or before January 26th, 2018, please? Could you also respond to this email to confirm receipt?

Thanking you in advance,

Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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

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/s/

SUZANNE K STRAYHORN
01/24/2018

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Friday, January 19, 2018 12:52 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: NDA 210251 - Carton and Container - -BIKTARVY (b/f/taf) registered versus trademark

Importance: High

Dear Kim,

Reference is made to the carton and container labels submitted on January 10, 2018 to NDA 210251. The team noted that you have changed the unregistered trademark symbol (i.e., BIKTARVY™) to the registered trademark symbol (i.e., BIKTARVY®) on the commercial container label, but this same change was not made on the (b) (4) container label or carton labeling. This may be intentional (b) (4) will have different trademark), but we wanted to verify with you if this is indeed the case.

Thanking you in advance for an update.

Kind Regards,
Suzanne

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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/s/

SUZANNE K STRAYHORN
01/19/2018

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, January 17, 2018 3:01 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: Draft Labeling-NDA 210251
Attachments: NDA 210251_BIKTARVY_Draft PI_rec 10Jan2018_sent 17Jan2018.docx; NDA 210251_BIKTARVY_Draft PPI_rec 10Jan2018_sent 17Jan2018.docx

Dear Kim,

The Division has reviewed the draft BIKTARVY (b/f/taf) labeling you submitted on January 10, 2018 and we have a few more editorial suggestions. Please refer to the attached documents. If your team could review and submit any further edits on/or before EOB on January 22nd that would be most helpful to the continued review process.

As previously, the Patient Prescribing Information remains as a separate document. Please keep documents separated until such a time as we have completed negotiations (thereafter we will ask that you merge the two documents back again).

We are still internally reviewing the proposed PMR's and I do hope to get these to you by the end of the week, schedule permitting. I will have to ask for date input when I send. I will follow-up with a call to you tomorrow, when I am back in the main office.

Kind Regards,

Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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/s/

SUZANNE K STRAYHORN
01/17/2018

**PeRC Meeting Minutes
January 10, 2018**

PeRC Members Attending:

Lynne Yao
Meshaun Payne
Jacqueline Yancy
Rosemary Addy
Hari Cheryl Sachs
Gerri Bauer
Raquel Tapia
James Travis
Dionna Greene
Victor Baum
Gil Burkhart
Kevin Krudys
Kristiana Brugger
Julia Pinto
Barb Buchs
Jingjing Ye
Raquel Tapia
Mark Rothmann
Susan McCune
Wiley Chambers
Thomas Smith
George Greeley
Adrienne Hornatko Munoz

Agenda

NON-RESPONSIVE

9:20	NDA 210251	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) FDC Tablets (Partial Waiver/Deferral/Plan)	DAVP	Suzanne Strayhorn	Treatment of HIV-1
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NON-RESPONSIVE

NON-RESPONSIVE

Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) FDC Tablets (Partial Waiver/Deferral/Plan)

- Proposed Indication: Treatment of HIV-1 infection in adults who are HIV-1 antiretroviral (b) (4) associated with resistance to the individual components of B/F/TAF.
- This application triggers PREA as a new active ingredient, new indication and new dosage form and has a PDUFA goal date of February 12, 2018.
- The sponsor is requesting a partial waiver for neonates because the studies would be impossible or highly impracticable, as outlined in the agreed iPSP. However, now that earlier diagnosis is available, the studies are feasible. Therefore, the Division disagrees with this waiver request and they will be requiring PK and short term safety data in neonates with high risk of HIV infection. (b) (4)

Therefore, the division believes it is

both reasonable and necessary to add the neonatal study as part of the PREA requirements for this product. The PeRC agrees.

- *PeRC Recommendations:*
 - The PeRC agrees with the division that studies in neonates should not be waived and recommends deferral of pediatrics birth to less than 18 years (See discussion above).

NON-RESPONSIVE

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/s/

JACQUILINE A YANCY
01/22/2018

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Thursday, January 04, 2018 5:18 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: NDA 210251 - Information Request

Dear Kim,

I have an additional request for information for NDA 210251, as we are preparing an FDA Drug Snapshot for this product.

- Could you please provide forest plots based on treatment difference and corresponding confidence intervals for the primary endpoint by race, age (<65 vs >=65 and <50 vs >=50 years) and gender for the four Phase 3 trials. Please label the arrows in the plots by the drug trade names.
- If we could have this information on or before January 26, 2018 that would be very helpful.

Thanking you in advance. Kindly acknowledge receipt of this email.

Kind Regards,
Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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/s/

SUZANNE K STRAYHORN
01/04/2018

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Thursday, January 04, 2018 3:49 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: NDA 210251_Draft Labeling for Review
Attachments: NDA 210251 PPI_ver rec 27Nov2017_sent 04Jan2018.docx; NDA 210251_BIKTARVY Draft PI_ver rec_27Nov2017_sent 04Jan2018.docx

Dear Kim,

Please find attached the Division's review comments to the draft labeling for BIKTARVY under NDA 210251, version received November 27, 2018. Please note that we have separated out the PPI as a separate word document and included our review comments.

- Please keep this patient labeling separated until such a time as we have finalized labeling negotiations. Once we are complete with labeling negotiations, we will ask that you merge the two documents back together again.
- When returning the labeling back to us, please do accept the proposed changes you agree to and include redlined word versions with your new comments and proposed text changes.

To facilitate review timelines, could you provide update labeling on / or before January 11th, 2018, please? Could you also respond to this email to confirm receipt?

Thanking you in advance,

Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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

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/s/

SUZANNE K STRAYHORN
01/04/2018

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, October 25, 2017 2:40 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Cc: Strayhorn, Suzanne (Suzanne.Strayhorn@fda.hhs.gov)
Subject: NDA-210251 Carton/Container Comments

Dear Kim,

In addition to the review comments we sent today regarding the USPI and PI submitted with the Original NDA 210251. We also have the following comments regarding the carton and container labels we received with the original NDA submission for b/f/taf:

We recommend the following updates to the carton and container labels:

1. Ensure both the lot number and expiration date are included on the container labels. Expiration date should be in the following format: MMMYYYY (e.g., JAN2018) or MMMDDYYYY (e.g., JAN012013).
2. On the commercial container label, (b) (4) container label, and (b) (4) carton labeling, replace the proprietary name placeholder, "TRADENAME", with the conditionally acceptable proprietary name, BIKTARVY.

Could you kindly acknowledge receipt of this email request?

Kind Regards,
Suzanne

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



From: Strayhorn, Suzanne
Sent: Wednesday, October 25, 2017 2:09 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com) <Kim.Lindstrom@gilead.com>
Subject: NDA-210251 Labeling Comments (COR-NDAIR-23)

Dear Kim,

I hope this email finds you very well. Please find attached the Division's review of the USPI provided to us with the NDA 210251 submission for BICTARVY (b/f/taf).

We hope that you might be able to return your review comments on/or before November 1, 2017. Please return word version's (clean and redlined) of the labeling and please accept the changes you agree to and add only new changes or comments/response to comments.

I have also attached a word version of labeling with our edits for your convenience.

Best Regards,
Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Antimicrobial Products

Division of Antiviral Products

U.S. Food and Drug Administration

Tel: 240 402-4247

suzanne.strayhorn@fda.hhs.gov



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/s/

SUZANNE K STRAYHORN
11/02/2017



NDA 210251

LABELING COMMENTS

Gilead Sciences, Inc.
Attention: Kimberly Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 10, 2017, received on June 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BIKTARVY™, (50 mg bicitgravir/200 mg emtricitabine/ 25 mg tenofovir alafenamide, B/F/TAF) Fixed-Dose Combination (FDC) tablet.

We also refer to our August 8, 2017, letter in which we notified you of our target date of November 19, 2017, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2018 Through 2022.”

On June 12, 2017, we received your June 10, 2017, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by November 1, 2017. The resubmitted labeling will be used for further labeling discussions.

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

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.
If you have any questions, call me at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

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

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/s/

SUZANNE K STRAYHORN
10/25/2017



NDA 210251

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 9, 2017, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, Tablet

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. We request a written response by **Thursday, October 19, 2017**, in order to continue our evaluation of your NDA:

- The levels of (b) (4) and total TAF related degradation products at 12 months of storage on stability at (b) (4) RH are (b) (4) respectively. The statistical projections provided in the NDA indicate the levels of (b) (4) and total TAF related degradation products after 24 month storage at (b) (4) RH will be below the proposed limits. Therefore, tighten your drug product specification acceptance criteria for (b) (4) and total TAF related degradation products from (b) (4) respectively.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,
{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: October 2, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: Subject Narrative Request – Subject Number: 1878-00698-4125

Please refer to your submission received on June 12, 2017, containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults. Further reference is made to the Phase 3 clinical trial GS-US-380-1878 included with this submission.

We are reviewing the content of your application and would like to request the following information at this time:

- Please provide a narrative detailing influenza, liver injury, and other AEs for Subject 1878-00698-4125. In addition, please include follow up on liver related laboratories after Week 48 where the subject had a Grade 4 ALT elevation if data are available.

Please provide this information by COB October 11, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager
Division of Antiviral Products

Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
10/02/2017



NDA 210251

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BIKTARVY (bictegravir/emtricitabine/tenofovir alafenamide tablets), 50 mg/200 mg/25 mg.

We also refer to the planned Mid-Cycle Communication teleconference between representatives of your firm and the FDA, scheduled for September 25, 2017. The purpose of this teleconference was to provide you an update on the status of the review of your application. Following review of the Mid-Cycle Communication Agenda we sent to you on September 20, 2017, you requested cancellation of this teleconference, noting that the items identified to date did not require substantive discussion (communications and agenda appended). We cancelled the planned teleconference and this document serves as a record of our communication with you at this point in the application review cycle.

If you have any questions, call me at (240) 402-4247 or at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Mid-Cycle Agenda
Email Communications

Strayhorn, Suzanne

From: Kim C Lindstrom <Kim.Lindstrom@gilead.com>
Sent: Thursday, September 21, 2017 4:00 PM
To: Strayhorn, Suzanne
Cc: Regulatory Archives
Subject: RE: NDA 210251 _ Agenda for Mid-Cycle Communication

Dear Suzanne,

Thank you for forwarding the Mid-Cycle Communication Agenda. Gilead has reviewed the Agenda and acknowledges the issues identified by the Agency to date. In consideration of the coordination required to facilitate a teleconference, and in the absence of Agenda items requiring substantive discussion, Gilead requests to cancel the planned teleconference scheduled for 25 September 2017.

Please feel free to reach out if you have any questions or concerns regarding this request.

Best,
Kim

Kim Lindstrom, PhD | Senior Manager, HIV Regulatory Affairs | kim.lindstrom@gilead.com
Gilead Sciences, Inc. | 333 Lakeside Drive | Foster City, CA 94404 | Phone: 650.372.4425

From: Strayhorn, Suzanne [<mailto:Suzanne.Strayhorn@fda.hhs.gov>]
Sent: Wednesday, September 20, 2017 8:13 AM
To: Kim C Lindstrom
Subject: NDA 210251 _ Agenda for Mid-Cycle Communication

Dear Kim,

Please find attached our planned Agenda for our NDA 210251 Mid-Cycle Communication scheduled for September 25, 2017, 1:30-3:00 pm, EDT.

Could you kindly confirm receipt.

Best Regards,
Suzanne

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Wednesday, September 20, 2017 11:13 AM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: NDA 210251 _ Agenda for Mid-Cycle Communication
Attachments: NDA 210251 Post Midcycle Communication Agenda.pdf

Dear Kim,

Please find attached our planned Agenda for our NDA 210251 Mid-Cycle Communication scheduled for September 25, 2017, 1:30-3:00 pm, EDT.

Could you kindly confirm receipt.

Best Regards,
Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247

suzanne.strayhorn@fda.hhs.gov



AGENDA

NDA 210251

BICTARVY (bictegravir/emtricitabine/tenofovir alafenamide) Post Mid-Cycle Communication Agenda September 25, 2017, 1:30-3:00 pm, EDT

- 1. Introductions (FDA and Applicant)**
- 2. Introductory Comments – FDA**
- 3. Significant Review Issues (by Review Disciplines)**

a. Clinical / Biometrics: We have identified the following finding:

- Because the success rates and confidence intervals are different for the efficacy results of the B/F/TAF arm between trials 1489 and 1490, (b) (4)
[REDACTED] (b) (4)
we strongly recommend presenting the efficacy results of the two treatment-naïve trials 1489 and 1490 separately.

4. Information Requests

a. Chemistry, Manufacturing and Controls: Responses to the following information request, sent on September 14, 2017, are pending:

- The dissolution profile data provided for the pivotal clinical trial batches and the dissolution method development study results support a dissolution acceptance criterion of “Q = (b) (4) % in 30 minutes for all three APIs” of the proposed to-be-marketed B/F/TAF Tablets. Revise the Finished Drug Product QC Specifications and other pertinent NDA documents accordingly.
- Refer to CTD section 1.12.14, Environmental Analysis. The claim for a categorical exclusion from an environmental assessment (EA) for TAF based on 21 CFR 25.31(b), which is for substances that increase in use but have an expected introduction concentration (EIC) of < 1 ppb, may not be acceptable. The active moiety, tenofovir, is the same as that of the previously approved tenofovir disoproxil fumarate (TDF), which currently has an EIC of ≥ 1 ppb. If there will be an increase in tenofovir use due to approval of this application, with an overall tenofovir EIC of ≥ 1 ppb, as

described in Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications (USFDA, 1998), then an EA would be required. Alternatively, if there will be no change or a decrease in the use of tenofovir, then a categorical exclusion under 21 CFR 25.31(a) (no increased use) would be appropriate. If an EA is required, the environmental risk assessment (ERA) that the applicant has submitted to the European Medicines Agency (EMA), modified as needed to reflect new information, including the expected environmental concentrations in the US, would appear to be appropriate.

b. Biometrics: The following information request will be forthcoming:

- The ADSL datasets submitted for trial 1489, 1844 and 1878 show a few more screening failure subjects than what is stated in the respective final study reports. Specifically, there were 90 screening failure subjects in the ADSL for trial 1489, instead of 89; 72 screening failure subjects in ADSL for trial 1844, instead of 67; and 115 screening failure subjects in ADSL for trial 1878, instead of 112. Please clarify these discrepancies.

5. Major Safety Concerns/Risk Management Update

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

6. Advisory Committee Meeting Plans

- No Advisory Committee Meeting is scheduled for this application.

7. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

- The Late Cycle Meeting (LCM) is scheduled for November 28, 2017. The purpose of the LCM is to share information and discuss any review issues identified to date, as well as objectives for the remainder of the review cycle. The Division will send the meeting backgrounder package for the LCM by secure e-mail by November 22, 2017.

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/s/

SUZANNE K STRAYHORN
09/28/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: September 28, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: Subject Narratives – Phase 3 Clinical Trials

Please refer to your submission received on June 12, 2017, containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults. Further reference is made to the Phase 3 clinical trials, GS-US-380-1489, GS-US-380-1844 and GS-US-380-1878 included with this submission.

We are reviewing the content of your application and would like to request the following information at this time:

Please provide complete narratives with details regarding the reported AEs in the following subjects:

- Subject 1878-07880-4237 with patellarluxation (joint dislocation)
- Subject 1878-00315-4042 with Vitamin D deficiency with left foot stress fracture
- Subject 1489-02000-1387 with jaw fracture
- Subject 1844-00315-3209 with angioedema
- Subject 1844-07881-3397 please provide details of both suicide ideation events. The submitted narrative describes only the first event.
- Subject 1878-00828-4037 with long QT syndrome
- Subject 1878-00417-4231 with sinus bradycardia and palpitation ongoing

In addition, please provide the status and/or results of the autopsy for Subject 1844-00365-3221.

Please provide this information by COB October 11, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
09/28/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: September 27, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: ADSL Datasets – Screen Failures in Trials 1489, 1844 and 1878

Please refer to your submission received on June 12, 2017, containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults.

We are reviewing the content of your application and would like to request the following information at this time:

Biometrics:

1. The ADSL datasets submitted for trial 1489, 1844 and 1878 show a few more screening failure subjects than what is stated in the respective final study reports. Specifically, there were 90 screening failure subjects in the ADSL for trial 1489, instead of 89; 72 screening failure subjects in ADSL for trial 1844, instead of 67; and 115 screening failure subjects in ADSL for trial 1878, instead of 112.

Please clarify these discrepancies.

Please provide this information by October 4, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt.

If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
09/27/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/25/2017 09:00:43 AM

To: Kim.lindstrom@gilead.com

CC: luz.e.rivera@fda.hhs.gov

BCC: michael.hadwiger@fda.hhs.gov, andrei.ponta@fda.hhs.gov, yong.wang@fda.hhs.gov

Subject: Method Verification Materials Received for NDA 210251

Good morning,

Please see the attached letter confirming receipt of the requested Method Verification Materials on September 19th.

Thank you,

Laura C. Pogue, Ph.D.

Project Manager

Division of Pharmaceutical Analysis | Office of Testing and Research

FOOD AND DRUG ADMINISTRATION - CENTER FOR DRUG EVALUATION AND RESEARCH

645 S. Newstead Ave | St Louis, MO 63110

314-539-2155 (w) | Laura.Pogue@fda.hhs.gov (e)



**METHOD VERIFICATION
MATERIALS RECEIVED**

NDA 210251

September 25, 2017

Kim Lindstrom, Ph.D.
Senior Manager, Regulatory Affairs
Kim.lindstrom@gilead.com
Gilead Sciences, Inc.
333 Lakeside Dr
Foster City CA 94404

Dear Kim Lindstrom, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, 50 mg B/ 200 mg F/ 25mg, Tablets and to our August 23, 2017, letter requesting sample materials for method verification testing.

We acknowledge receipt on September 19, 2017, 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 (314-539-2155) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,
**Laura C.
Pogue -S**

Digitally signed by Laura C. Pogue -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Laura C. Pogue -
S,
0.9.2342.19200300.100.1.1=2000606027
Date: 2017.09.25 07:56:06 -05'00'

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/14/2017 01:09:39 PM
To: kim.lindstrom@gilead.com
CC: luz.e.rivera@fda.hhs.gov; Suzanne.Strayhorn@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST NDA 210251

NDA 210251
INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 9, 2017, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, Tablet.

Please find attached the Product Quality information request. We request a written response by Thursday, September 28, 2017.

If you have any questions, please contact me at (301) 796-4013.

We request that you acknowledge this communication upon receipt.

Regards,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 210251

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 9, 2017, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, Tablet

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. We request a written response by **Thursday, September 28, 2017**, in order to continue our evaluation of your NDA:

1. The dissolution profile data provided for the pivotal clinical trial batches and the dissolution method development study results support a dissolution acceptance criterion of “Q = ^{(b) (4)} % in 30 minutes for all three APIs” of the proposed to-be-marketed B/F/TAF Tablets. Revise the Finished Drug Product QC Specifications and other pertinent NDA documents accordingly.
2. Refer to CTD section 1.12.14, Environmental Analysis. The claim for a categorical exclusion from an environmental assessment (EA) for TAF based on 21 CFR 25.31(b), which is for substances that increase in use but have an expected introduction concentration (EIC) of < 1 ppb, may not be acceptable. The active moiety, tenofovir, is the same as that of the previously approved tenofovir disoproxil fumarate (TDF), which currently has an EIC of ≥ 1 ppb. If there will be an increase in tenofovir use due to approval of this application, with an overall tenofovir EIC of ≥ 1 ppb, as described in Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications (USFDA, 1998), then an EA would be required. Alternatively, if there will be no change or a decrease in the use of tenofovir, then a categorical exclusion under 21 CFR 25.31(a) (no increased use) would be appropriate. If an EA is required, the environmental risk assessment (ERA) that the applicant has submitted to the European

Medicines Agency (EMA), modified as needed to reflect new information, including the expected environmental concentrations in the US, would appear to be appropriate.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 9/14/2017 12:57:09PM
GUID: 502abbaa000025b89fdb52a977a3d336

Executive CAC

Date of Meeting: September 12, 2017

Committee: Paul Brown, PhD, OND IO, Acting Chair
Aisar Atrakchi, PhD, DPP, Alternate Member
Lois Freed, PhD, DNP, Alternate Member
Peyton Myers, PhD, DAVP, Acting Pharm Tox Supervisor
John Dubinion, PhD, DAVP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 210251 (IND 121318)

Drug Name: Bictegravir (Biktarvy; B/F/TAF: 50/200/25 mg)

Sponsor: Gilead Sciences Inc.

Background:

Biktarvy™, a once daily fixed-dose combination (FDC) tablet containing bictegravir (BIC; B), emtricitabine (FTC; F), and tenofovir alafenamide (TAF), is intended for the treatment of HIV-1 infection in adults. Bictegravir (previously referred to as GS-9883) is a potent integrase strand-transfer inhibitor (INSTI) that blocks HIV-1 replication, and is the only component of the FDC which has not been previously approved for use by the FDA. FTC and TAF have been approved for marketing in the U.S. as standalone agents (Emtriva® and Vemlidy®, respectively) or in multiple FDC products (Genvoya®, Descovy®, and Odefsey®). The current transgenic mouse carcinogenicity study for BIC was submitted with NDA #210251, and a 2-year rat study is currently in progress.

Mouse Carcinogenicity Study

TgrasH2 mice were dosed orally with BIC (in 0.5% (w/w) hydroxypropyl methylcellulose (Methocel K100 LV) and 0.1% (w/w) Tween® 20 in reverse osmosis water) at doses recommended by the ExecCAC (Meeting Minutes, dated November 18, 2015). Males received 0, 5, 15, 100 mg/kg and females received 0, 10, 30, 300 mg/kg once daily for 26 weeks. The positive control was a single IP injection of NMU on Day 1. No BIC-related increases in the incidence of neoplasms were noted.

Executive CAC Conclusions

- The Committee concurred that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms in the 6-month Tg.rasH2 mouse study in males or females.

Paul Brown, Ph.D.

Acting Chair, Executive CAC

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/s/

STEPHANIE J QUINN
09/13/2017

PAUL C BROWN
09/13/2017



NDA 210251

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Kim Lindstrom, Ph.D.
Senior Manager, Regulatory Affairs

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 10, 2017, received June 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bictegravir/Emtricitabine/Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg.

We also refer to your correspondence dated and received June 20, 2017, requesting review of your proposed proprietary name, Biktarvy.

We have completed our review of the proposed proprietary name, Biktarvy and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 20, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Suzanne Strayhorn, Regulatory Project Manager in the Office of New Drugs, at 240-402-4247.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
08/23/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
08/24/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/23/2017 11:24:15 AM

To: kim.lindstrom@gilead.com

CC: Luz.Rivera@fda.hhs.gov

BCC: yong.wang@fda.hhs.gov, andrei.ponta@fda.hhs.gov,

Gaetan.Ladouceur@fda.hhs.gov, michael.hadwiger@fda.hhs.gov

Subject: Method Verification Materials Request for NDA 210251

Good morning,

Please see the attached letter requesting Method Verification Materials for NDA 210251 and respond to Laura.Pogue@fda.hhs.gov to confirm receipt.

Thank you,

Laura C. Pogue, Ph.D.

Method Verification Program (MVP) Coordinator

Division of Pharmaceutical Analysis | Office of Testing and Research

FOOD AND DRUG ADMINISTRATION - CENTER FOR DRUG EVALUATION AND RESEARCH

645 S. Newstead Ave | St Louis, MO 63110

314-539-2155 (w) | Laura.Pogue@fda.hhs.gov (e)



REQUEST FOR METHOD VERIFICATION MATERIALS

NDA 210251

August 23, 2017

Kim Lindstrom, Ph.D.
Senior Manager, Regulatory Affairs
Kim.lindstrom@gilead.com
Gilead Sciences, Inc.
333 Lakeside Dr
Foster City CA 94404

Dear Kim Lindstrom, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, 50 mg B/ 200 mg F/ 25mg, Tablet.

We will be performing method verification studies on Bictegravir/Emtricitabine/Tenofovir Alafenamide, 50 mg B/ 200 mg F/ 25mg TAF tablets as described in NDA 210251.

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

Method, current version

- 1) TM 306: Identification, Assay, and Impurity content of the Drug Substance by UPLC
- 2) TM 311: Enantiomeric Purity of Drug Substance
- 3) TM 313: Identification, Assay, and Degradation Products of BIC in B/F/TAF Tablets by UPLC
- 4) TM 315: Degradation Products of FTC and TAF in B/F/TAF Tablets by UPLC

Chemicals, Samples and Reference Standards

- 1) **BIC sodium (GS-9883-01) reference standard (2 x 1g)**
- 2) **Bictegravir (BIC) sodium drug substance (2 x 1g)**
- 3) **BIC system suitability standard (500 mg)**
- 4) **BIC related impurities and degradation products, provided individually (300 mg**
(b) (4)
- 5) 



- 6) **Tenofovir alafenamide fumarate (GS-7340-03) reference standard (2 x 1g)**
- 7) **Tenofovir alafenamide fumarate (TAF) drug substance (2 x 1g)**
- 8) **TAF system suitability standard (500 mg)**
- 9) **TAF-related impurities and degradation products, provided individually (300 mg** (b) (4)

- 10) **Emtricitabine (GS-9019 or GS-9036) reference standard (2 x 1g)**
- 11) **Emtricitabine (FTC) drug substance (2 x 1g)**
- 12) **FTC related substance ID mixture (500 mg)**
- 13) **FTC-Related Impurities and Degradation Products, provided individually (300** (b) (4)

- 15) **Bictegravir/Emtricitabine/Tenofovir Alafenamide Drug Product (50 mg BIC/200 mg FTC/25mg TAF): 3 x 100 tablets** (b) (4)

Equipment

- 1) 1 Halo 2 ES-CN UPLC Column, 2.0 µm, 2.1x100 mm
- 2) 1 CHIRALCEL OD-3 HPLC Column, 3 µm, 4.6 × 250 mm
- 3) 1 Waters Acquity CSH C18 UPLC Column, 130Å, 1.7 µm, 2.1 mm × 150 mm
- 4) 100 Acrodisc nylon membrane syringe filters, 0.2 µm, 25 mm diameter
- 5) 1 XSelect CSH C18 XP UPLC Column, 130Å, 2.5 µm, 3 mm × 150 mm

Please include the SDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.

If materials are being imported to the United States, be sure your firm is the Importer of Record (IOR). Do not claim the FDA as the IOR.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110



Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

Laura C. Pogue Digitally signed by Laura C. Pogue -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Laura C. Pogue -
S, 0.9.2342.19200300.100.1.1=2000606027
Date: 2017.08.23 10:11:14 -05'00'

-S
Laura C Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: August 18, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: Subject Narratives – Clinical Trials GS-US-380-1489 and GS-US-380-1490

Please refer to your submission received on June 12, 2017, containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults. Further reference is made to the Phase 3, randomized, double-blind, active-controlled clinical trials, GS-US-380-1489 and GS-US-380-1490, included with this submission.

We are reviewing the content of your application and would like to request the following information at this time:

1. Please provide narratives for Subject 1489-01808-1160 and Subject 1489-01691-1596.
2. Please provide narratives, including any additional bilirubin levels that are available after those reported with the NDA application submission for Subjects 1489-02859-1583 and 1490-00986-2447.

Please provide this information by COB August 30, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager

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

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/s/

SUZANNE K STRAYHORN
08/18/2017



NDA 210251

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 9, 2017, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF, Tablet

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. We request a written response by **Tuesday, August 22, 2017**, in order to continue our evaluation of your NDA:

1. For the particle size distribution test in the drug substance specification, add acceptance criteria for D₁₀ and D₅₀ in addition to D₉₀. Also, provide the D₁₀ and D₅₀ values for the developmental Lot# 10041-87-01.
2. In order for FDA to grant a (b) (4) retest period for the drug substance, you will need to update the stability data of batch# 9883-01-AC-2P and batch# 9883-01-AC-3P from your propose commercial site (Gilead Alberta ULC) to cover a period of 12 months instead of 9 months. As per the ICH Q1E guideline, the retest period of the drug substance can be extended up to 2X from the time investigated in long-term storage condition for three batches.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 8/08/2017 10:12:16PM
GUID: 502abbaa000025b89fdb52a977a3d336



NDA 210251

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

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 10, 2017, received on June 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for bictegrovir/emtricitabine/tenofovir alafenamide tablets, 50 mg/200 mg/25 mg.

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 **Priority**. Therefore, the user fee goal date is February 12, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 19, 2017. In addition, the planned date for our internal mid-cycle review meeting is September 14, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

If you have any questions, call Suzanne Strayhorn, MS, Regulatory Project Manager, at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
08/08/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: June 30, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: B/F/TAF Formulation

Please refer to your submission received on June 12, 2017, containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults.

We are reviewing the content of your application and would like to request the following information at this time:

1. Table 1 of Section 2.7.1 (Summary of Biopharmaceutics Studies and Associated Analytical Methods; Page 9) indicates that Fixed Dose Combination Tablet “Original Formulation” and Fixed Dose Combination “Designated Commercial Formulation” were both used in Phase 3 efficacy and safety trials.
 - For each phase 3 trial, please provide a detailed breakdown of the number of subjects who were administered the “Designated Commercial Formulation” and subjects who were transitioned from the “Original Formulation” to the “Designated Commercial Formulation”.

Please provide this information by July 7, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
06/30/2017

Strayhorn, Suzanne

From: Strayhorn, Suzanne
Sent: Thursday, June 22, 2017 4:51 PM
To: Kim C Lindstrom (Kim.Lindstrom@gilead.com)
Subject: Information Request for NDA 210251 - Foreign Data

Dear Kim,

Reference is made to the submission of your original NDA 210251 for B/F/TAF. Could you please provide the rationale for assuming the applicability of foreign data to U.S. population/practice of medicine. If this information is already available in the NDA please provide the location by COB 6/28/2017.

Could you kindly acknowledge receipt of this email request.

Thanking you in advance,
Suzanne

Suzanne Strayhorn, MS

Sr. Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240 402-4247
suzanne.strayhorn@fda.hhs.gov



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/s/

SUZANNE K STRAYHORN
06/28/2017



NDA 210251

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Kim Lindstrom, Ph.D.
Senior Manager, Regulatory Affairs

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) dated June 10, 2017, received June 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bictegravir/Emtricitabine/Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg.

We acknowledge receipt of your correspondence dated and received June 20, 2017, requesting a review of your proposed proprietary name, Biktarvy.

The target date is September 18, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Suzanne Strayhorn, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
06/22/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

NDA: 210251

Drug: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF)

Date: June 20, 2017

To: Kim Lindstrom, PhD, Senior Manager, Regulatory Affairs

Applicant: Gilead Sciences, Inc.

From: Suzanne Strayhorn, Sr. Regulatory Project Manager

Subject: Investigator Information

Please refer to your submission dated containing a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B; GS-9883), emtricitabine (FTC; F), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults.

We are reviewing the content of your application and would like to request the following information at this time:

Please populate an excel spreadsheet with following information for the one hundred and fourteen (114) investigators with disclosable financial interest. Please break out the fields for each trial (i.e. from GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878, and GS-US-141-1475).

In the table please include the following as headers of the columns:

1. Principle Investigator
2. Sub-Investigator(s)
3. Amount and characteristic of disclosable financial interest
4. Site Number
5. Site address
6. Number (No.) of screen failures
7. No. of enrolled subjects
8. No. of AEs reported by site
9. No. of SAEs reported by site

10. No. subjects that discontinued study

Additionally, please create a separate spreadsheet cross referencing the 114 investigators with the trials (i.e. from GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878, and GS-US-141-1475) in which they participated.

Please provide this detailed list by close of business on June 26, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 240-402-4247 or 301-796-1500.

Suzanne Strayhorn, MS
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
06/20/2017



NDA 210251

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

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: bictegravir/emtricitabine/tenofovir alafenamide tablet, 50 mg/200 mg/25 mg

Date of Application: June 10, 2017

Date of Receipt: June 12, 2017

Our Reference Number: NDA 210251

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 11, 2017, in accordance with 21 CFR 314.101(a).

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

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

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

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (240) 402-4247 or at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, MS
Sr. Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
06/14/2017



IND 125589

**MEETING REQUEST-
WRITTEN RESPONSES**

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) fixed-dose combination (FDC) tablet.

We also refer to your submission dated November 21, 2016, containing a Type C meeting request. The purpose of the requested meeting was to reach agreement on the strategy for the submission of the NDA for B/F/TAF FDC, planned for June 2017, and to agree to key aspects related to the content and format of the application.

Further reference is made to our Meeting Granted letter dated December 5, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 22, 2016, background package.

If you have any questions, call me at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

Suzanne Strayhorn, MS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance
Application Number: 125589
Product Name: Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) fixed-dose combination (FDC) tablet
Indication: Treatment of HIV-1
Sponsor/Applicant Name: Gilead Sciences, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

On November 21, 2016, Gilead requested a Type C meeting with the Agency to review the proposed NDA submission strategy for Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) fixed-dose combination (FDC) tablet, indicated for the treatment of HIV-1. The primary purpose for this meeting request is to gain alignment on the technical aspects related to the content and format of the planned NDA. The timing for this NDA submission is currently planned for June 2017, and it is anticipated that a Pre-NDA meeting will take place in the near future.

Based on the statement of purpose, objectives, and proposed agenda accompanying the current meeting request, FDA granted the meeting as a Type C Meeting on December 5, 2016, and determined that written responses would be the most appropriate means for responding to the meeting request. On December 22, 2016, Gilead submitted the meeting background package, which included eleven questions subdivided into the following categories: NDA Structure and Content, Clinical/Statistical Questions and a Clinical Virology Question.

2.0 QUESTIONS AND RESPONSES

Questions submitted by Gilead within the December 22, 2016, background package are repeated below in **bold** font. FDA responses follow each question and are presented in normal font.

2.1. NDA Structure and Content Questions

Question 1

For the B/F/TAF FDC NDA, Gilead plans to resubmit study reports previously provided in the BIC IND (IND121318) or the B/F/TAF FDCIND (IND 125589). The draft proposed Table of Contents for the B/F/TAF FDC NDA is provided as Attachment 1.

- a. **Does the Agency have any comments regarding the NDA Table of Contents for the B/F/TAF FDC NDA?**

For the B/F/TAF FDC NDA, Gilead does not plan to resubmit nonclinical and clinical study reports submitted previously to approved NDAs. The nonclinical and clinical summaries to be included in the B/F/TAF FDC NDA will cross-reference relevant TAF and FTC study reports in the appropriate NDAs for these compounds, as needed. Lists of nonclinical and clinical studies cross-referenced in this application will be provided in Module 1.4.4–Cross Reference to Other Applications.

- b. Does the Agency agree that nonclinical and clinical study reports for FTC and TAF previously submitted to another NDA(s) do not need to be resubmitted to the B/F/TAF FDC NDA to facilitate review of the NDA**

FDA Response to Question 1

The Division agrees with not resubmitting nonclinical and clinical study reports submitted previously to approved NDAs. We would urge you to cross reference, with hyperlinks, specific pertinent information when feasible.

Question 2

Gilead intends to provide information on primary pharmacodynamics(PD), secondary PD, safety pharmacology, virology (nonclinical and clinical) and nonclinical disposition, metabolism, pharmacokinetics, and excretion (DMPK) using human matrices as described in Table 2.

Table 2. Location of Discipline-Specific Information in the B/F/TAFFDC NDA

Topic	Report Location	CTD Summary Location
Primary Pharmacodynamics	Module 4.2.1.1	<ul style="list-style-type: none"> Module 2.6.2 (Nonclinical Pharmacology Written Summary) Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Virology (nonclinical)	Module 4.2.1.1	<ul style="list-style-type: none"> Module 2.6.2 (Nonclinical Pharmacology Written Summary) Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Cytotoxicity, mitochondrial toxicity, and cellular polymerases assessment	Module 4.2.1.2	<ul style="list-style-type: none"> Module 2.6.2 (Nonclinical Pharmacology Written Summary) Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Secondary Pharmacodynamics	Module 4.2.1.2	<ul style="list-style-type: none"> Module 2.6.2 (Nonclinical Pharmacology Written Summary) Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Safety Pharmacology	Module 4.2.1.3	<ul style="list-style-type: none"> Module 2.6.2 (Nonclinical Pharmacology Written Summary) Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Nonclinical In Vitro DMPK Using Human Matrices	Module 5.3.2, with cross-reference leaf in appropriate sections of Module 4	<ul style="list-style-type: none"> Module 2.6.4 (Nonclinical Pharmacokinetics Written Summary) Module 2.6.5 (Nonclinical Pharmacokinetics Tabulated Summary)
Virology (clinical)	Module 5.3.5.4	<ul style="list-style-type: none"> Module 2.7.2 (Clinical Pharmacology Written Summary)

Does the Agency agree with the report location and CTD summary location as presented in Table 2?

FDA Response to Question 2

We agree with the report location and CTD summary location as presented in Table 2. Please include a separate virology summary with links in Module 2.7.2.4 Special Studies.

Question 3

If the proposal to cross-reference the reports of TAF and FTC nonclinical studies containing data pertinent to the B/F/TAF FDC NDA is acceptable, only reports of nonclinical studies of BIC and nonclinical studies of TAF and FTC that were completed after submission of NDA208351 (Odefsey®) or NDA 208464 (Vemlidy®) will be included as appropriate in the initial B/F/TAF FDC NDA. These studies are listed in the draft proposed Table of Contents (Attachment1) and include a comprehensive set of primary and secondary PD studies; a complete core battery of safety pharmacology studies; a complete DMPK evaluation; repeat-dose oral toxicity studies in rodents and nonrodents; genotoxicity studies; assessment of fertility; early embryonic development; prenatal and

postnatal development studies; evaluation of skin and eye irritation; phototoxicity; and qualification of impurities. Summaries for all relevant BIC, FTC, and TAF nonclinical studies will be provided in Module 2.6.

The Agency agreed via electronic correspondence received on 06 June 2014 that, in principle, the NDA may be submitted without final carcinogenicity study reports for BIC. A 26-week oral gavage carcinogenicity study in transgenic rasH2 mice will be submitted with the NDA, and a 104-week oral gavage carcinogenicity study in rat will be submitted at a later date.

Does the Agency concur that the nonclinical studies listed in the draft proposed Table of Contents for the B/F/TAF FDC NDA support the registration of B/F/TAF FDC?

FDA Response to Question 3

We concur. Please include a study report describing the combination effect of TAF and sofosbuvir on the TAF anti-HIV-1 activity.

Question 4

Gilead proposes to include in Module 1 of the B/F/TAF FDC NDA documentation for investigator financial disclosure, source documents for treatment allocation codes, and disclosure of financial agreements with vendors used to manage treatment allocation codes for the clinical studies as detailed in Attachment1. Investigator contact information will be included with the Bioresearch Monitoring (BIMO) datasets in Module 5. Gilead plans to submit BIMO Items I and II as well as a BIMO Reviewer Guide as outlined in the End-of-Phase 2 preliminary comments (RefID:3835302). Gilead respectfully declines participation in Office of Scientific Investigation's voluntary risk-based model for site selection (Item III). For the purposes of the items listed in Table 3, Gilead considers the following studies as covered: GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, and GS-US-380-1474.

Table 3. List of Documentation for Covered Clinical Studies¹

eCTD Section	Document Description
Module.1.3.4	Financial certification and disclosure ²
Module 1.11.3	Source documents for treatment allocation codes ³
Module 1.11.3	Disclosure of Financial Agreements with vendor(s) used to generate and manage treatment allocation codes ³
Module 1.11.3	AE Dictionary and Coding Process
Module 5.3.5.4	BIMO Items I and II

-
- 1 Includes registrational studies as follows: GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, and GS-US-380-1474.
 - 2 The following information will be included: Total number of investigators identified (including all principal investigators as well as sub-investigators), number of investigators who are sponsor employees (including both full-time and part-time employees), number of investigators with disclosable financial interests/arrangements (Form FDA 3455). For investigators with disclosable financial interests/arrangements, Gilead will identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): 1) Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study, 2) Significant payments of other sorts, 3) Proprietary interest in the product tested held by investigator, 4) Significant equity interest held by investigator in sponsor of covered study, and 5) The number of investigators with certification of due diligence (Form FDA 3454, box 3).
 - 3 Information regarding treatment allocation codes will only be provided for randomized studies.

Additionally, Gilead plans to include a ‘Guide to Reviewers’ in Module 1.2. The Guide to Reviewers will provide a general overview of the information contained in the NDA, as well as the overall structure and format of the application. The intention of this guide is to provide the reviewer with a tool for navigation through the application

Does the Agency agree with the proposal for provision of the documentation in Modules 1 and 5 described above and in Table 3?

FDA Response to Question 4

The Division agrees with the proposal for investigator financial documentation, for investigator financial disclosure, source documents for treatment allocation codes, and disclosure of financial agreements with vendors used to manage treatment allocation codes for the clinical studies as detailed. Additionally, the Division requests a list of investigators from each of the investigational studies receiving payments in excess of \$25,000 and having equity in excess of \$50,000 per CFR 54.2.

We acknowledge that Gilead declines participation in Office of Scientific Investigation’s voluntary risk-based model for site selection. We also acknowledge Gilead’s intent to submit BIMO items I and II and a BIMO Review Guide, as mentioned, for all of the pivotal Phase III studies.

Question 5

As with recent NDA submissions to the DAVP (e.g., NDAs 204671, 205834, and 208341), Gilead proposes to include in the B/F/TAF FDC NDA literature references cited in the Nonclinical Overview and Clinical Overview only (Modules 2.4 and 2.5, respectively). Referenced guidelines, prescribing information, and other similar documents will not be included in the application. All other documents referenced in the application will be available upon request.

Does the Agency agree with this proposal for provision of referenced documents?

FDA Response to Question 5

The Division agrees with the proposal for provision of referenced documents.

Question 6

A thorough QT/QTc study for BIC (Study GS-US-141-1480) has been conducted per ICH E14 guidance. The clinical study report was submitted to BIC IND 121318 (SN 0060; 10February2016). This submission included the electronic datasets, and the ECG waveforms were uploaded to the ECG warehouse. No additional QT/QTc studies have been conducted. Gilead plans to provide the clinical study report for this study in the B/F/TAF FDC NDA, but does not plan to resubmit the electronic datasets from this study in the B/F/TAF FDC NDA or the ECG waveforms to the ECG warehouse.

The thorough QT/QTc study for TAF (Study GS-US-120-0107) has been previously submitted, and will be incorporated via cross-reference to NDA 207651.

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

FDA Response to Question 6

The Division agrees that the inclusion of the clinical study report for the thorough QT/QTc study is adequate.

2.2. Clinical/Statistical Questions

Question 7

For the purpose of the ISE and the ISS, Gilead plans to conduct integrated analyses on pooled data from the 2 pivotal Phase 3 studies in treatment-naïve subjects: GS-US-380-1489 and GS-US-380-1490. Studies GS-US-380-1844 (double-blind study in virologically suppressed subjects) and GS-US-380-1878 (open-label study in virologically suppressed subjects) are not proposed for integrated analysis due to the differences in study population (virologically suppressed vs treatment naïve) and study design (double-blind vs open label). Draft SAPs for the ISE (Attachment 4) and ISS (Attachment 5) are included as attachments. Key elements of the ISS and ISE SAPs are summarized in Attachment 6.

Does the Agency concur with the proposed analysis strategy for the ISE and ISS?

FDA Response to Question 7

The Division concurs with the proposed analysis strategy for the ISE and ISS (pooled analysis of GS-US-380-1489 and GS-US-380-1490; and separate analysis of both GS-US-1844 and GS-US-1878).

Question 8

As with recent NDA submissions to the Division, Gilead proposes to include ISE summary within the Summary of Clinical Efficacy (Module 2.7.3) and ISS summary within the Summary of Clinical Safety (Module 2.7.4). The eCTD cross-reference leafs to Modules 2.7.3 and 2.7.4 will be provided in Module5.3.5.3 with supporting statistical outputs and

electronic datasets. The length of Modules 2.7.3 and 2.7.4, including the integrated data analyses described in the ISE and ISS SAPs will be consistent with those described in the FDA's April 2009 *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

Does the Agency agree with the proposal for inclusion of the ISE and ISS summaries in Modules 2.7.3 and 2.7.4, respectively, with supporting statistical outputs and electronic datasets in Module 5.3.5.3, as described above?

FDA Response to Question 8

The Division agrees with inclusion of ISE and ISS summaries and datasets in the proposed modules above.

Question 9

A summary of the Week 48 data from the Phase 2 study of BIC + F/TAF is provided in Investigator's Brochure for B/F/TAF (IND 125589, SN 0088). These data provide an initial evaluation of the safety profile of BIC coadministered with F/TAF in the clinic. Based on the available safety data for B/F/TAF, Gilead is planning to include in the Phase 3 clinical study reports narratives for all deaths, serious adverse events, pregnancies, and discontinuations due to adverse events. Similarly, only case report forms (CRFs) for deaths, serious adverse events, and discontinuations due to adverse events will be provided in the application.

No AEs of special interest have been identified for the B/F/TAF FDC program to date.

Does the Agency agree with this proposal regarding the provision of study narratives and CRFs as described above?

FDA Response to Question 9

The Division agrees to the proposal of study narratives and CRFs as described above. Additionally, we request that you provide verbatim reasons for withdrawal of consent for subjects who discontinue early.

Question 10

Gilead proposes to submit SDTM, ADaM, and HIV Template datasets, as well as BIMO Listings, to the Agency as outlined in Table 4.

Table 4. Datasets Proposed to be Included in B/F/TAF FDC NDA

Study Phase	Standard SDTM/ADaM Datasets	HIV Template Datasets	BIMO Listings
Phase 3	Yes	Yes	Yes
Phase 2	Yes	Yes	No
Phase 1 ^a	Yes	No	No

a As described in Question 6, Gilead does not plan to resubmit the electronic datasets from the TQT study of BIC (GS-US-141-1480) in the B/F/TAF FDC NDA.

Does the Agency agree with the proposed scope for datasets to be submitted to the B/F/TAF FDC NDA?

FDA Response to Question 10:

The Division agrees with the proposal for the datasets as detailed in Table 4, provided the HIV template datasets represent datasets specified in the HIV Efficacy Dataset Specification. Also please create a reviewer program guide within the subfolder which contains all the SAS programs used to generate the ADaM datasets and main efficacy results. The reviewer program guide should contain the following information: the program names, details on the input and output datasets, and algorithms which were used to create key derived variables, if any. This information will aid in the reviewer’s ability to navigate through the programs and derived datasets.

2.3. Virology Question

Question 11

Gilead will provide virology data as summarized in Table 5. Gilead will provide a summary of the virology data and clinical virology listings for the Phase 3 studies in treatment-naïve subjects (GS-US-380-1489 and GS-US-380-1490) in an integrated virology study report. Individual virology study reports will be prepared for the Phase 3 studies in virologically suppressed subjects (GS-US-380-1844 and GS-US-380-1878), and the Phase 2/3 study in pediatric subjects (GS-US-380-1474). Virology data for the Phase2 study (GS-US-141-1475) will be presented within the clinical study report.

Table 5. Virology Datasets Proposed to be Included in B/F/TAF FDC NDA

Clinical Study	Phase	ADVR	Virology Listings	Next Generation Sequencing (NGS)
GS-US-141-1475	2	Yes	Yes	No
GS-US-380-1489 ^a	3	Yes	Yes	Yes; baseline samples only
GS-US-380-1490 ^a	3	Yes	Yes	Yes; baseline samples only
GS-US-380-1844	3	Yes	Yes	No
GS-US-380-1878	3	Yes	Yes	No
GS-US-380-1474	2/3	Yes	Yes	No

a To be summarized in an integrated virology study report.

The draft Virology Analysis Plan (VAP) for the Phase 3 pivotal studies of B/F/TAF FDC was previously provided in the meeting information package to support the Type B, End of Phase 2 meeting for this program (IND 125589, SN 0013). In the context of that meeting, the Agency agreed that, in general, the proposed VAP for resistance analyses is acceptable. Next generation sequencing data for the integrase gene will be reported for baseline samples from Studies GS-US-380-1489 and GS-US-380-1490 as described in Gilead's response to the Agency's Preliminary Comments at the Type B, End of Phase 2 meeting for the B/F/TAF FDC (IND125589, SN 0025). These data will include raw and tabulated NGS files according to the guidance, "*Submitting Next Generation Sequencing Data to the Division of Antiviral Products.*" The final VAP for the pivotal studies of the B/F/TAF FDC will reflect Gilead's response (IND125589, SN 0051) to the Agency's advice regarding repeat testing of samples as it relates to inclusion in the resistance analysis population.

Does the Agency agree with the proposal for provision of virology data?

FDA Response to Question 11:

We agree with the proposal for provision of virology data.

3.0 PREA REQUIREMENTS

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

We reference your Agreed PSP dated June 29, 2016. Please provide your Agreed PSP and any requests for waivers or deferrals, with your original NDA submission.

4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study

Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on

Use of SI Units for Lab Tests website found at
<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

6.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

7.0 MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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

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

Corresponding names and titles of onsite contact:

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

8.0 Office of Scientific Investigations (OSI) Requests

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

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

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

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

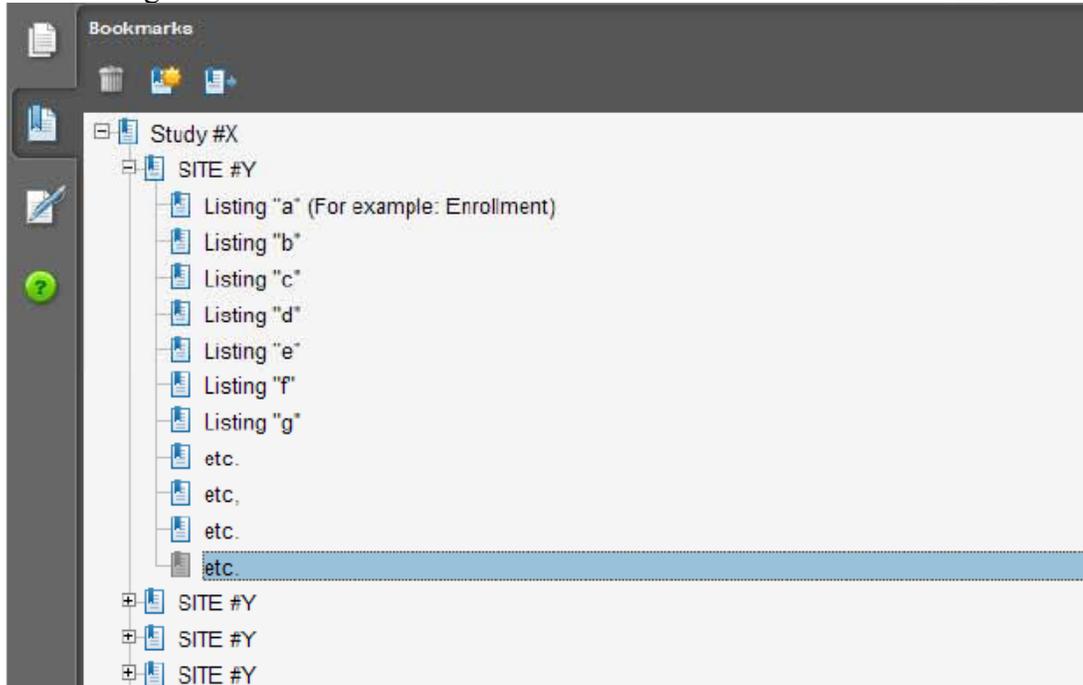
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 -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

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

II. Request for Subject Level Data Listings by Site

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

- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

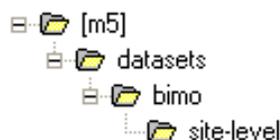
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

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

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

SUZANNE K STRAYHORN
01/26/2017



IND125589

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GS-9883/F/TAF.

We also refer to the teleconference between representatives of your firm and the FDA on October 21, 2015. The purpose of the meeting was to discuss and reach agreement on the proposed nonclinical and clinical development plans to support the proposed indication for use of GS-9883/F/TAF FDC.

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

If you have any questions, call me at (240) 402-2567.

Sincerely,

{See appended electronic signature page}

Garrette Martin-Yeboah, PharmD, CGP, PMP
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: October 21, 2015, 3:00pm to 4:30pm
Meeting Location: Teleconference

Application Number: IND 125589
Product Name: GS-9883/F/TAF FDC
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Russell Fleischer, PA-C, MPH
Meeting Recorder: Garrette Martin-Yeboah, PharmD, CGP, PMP

FDA ATTENDEES

OND/OAP/DAVP

Debra Birnkrant, MD, Director, Division of Antiviral Products
Jeffrey Murray, MD, MPH, Deputy Director
Russell Fleischer, PA-C, MPH, Medical Officer Team Leader
Peter Miele, MD, Medical Officer
Tanvir Bell, MD, Medical Officer
Sung Rhee, PhD, Clinical Virology Reviewer
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Leader
Mark Powley, PhD, Pharmacology/Toxicology Reviewer
Jasminder Kumar, PharmD, Risk Management Analyst, Division of Risk Management
Elizabeth Thompson, MS, Chief, Project Management Staff
Garrette Martin-Yeboah, PharmD, PMP, Regulatory Project Manager
Suzanne Strayhorn, MS, Regulatory Project Manager
Alicia Moruf, PharmD, MPH, Regulatory Project Manager

OTS/OCP/DCP4

Islam Younis, PhD, Clinical Pharmacology Team Leader
Mario Sampson, PharmD, Clinical Pharmacology Reviewer

OTS/OB/DBIV

Wen Zeng, PhD, Statistics Reviewer
Thamban Valappil, PhD, Statistics Team Leader

SPONSOR ATTENDEES

Andrew Cheng, MD, PhD, Executive Vice-President, Clinical Research and Development
Operations

Javier Szwarcberg, MD, Senior Director, Clinical Research

Brian Kearney, PharmD, Vice President, Clinical Pharmacology

Julia Zack, PharmD, Director, Clinical Pharmacology

Kimberly Lindstrom, PhD, Associate Manager, Regulatory Affairs

1.0 BACKGROUND

GS-9883/emtricitabine/tenofovir alafenamide (GS-9883/F/TAF) fixed-dose combination (FDC) tablet is being developed to provide an additional option for HIV-1-infected patients. This product is a TAF-based, non-boosted integrase strand transfer inhibitor (INSTI)-containing FDC that can be administered as one tablet once daily without regard to food. Gilead has fully enrolled, GS-US-141-1475, a Phase 2, randomized, double-blinded, active-controlled study to assess the safety, tolerability, and efficacy of a once-daily regimen containing GS-9883+F/TAF versus DTG+F/TAF in HIV-1-infected ART-naïve adults. The meeting background package includes 12-week interim data from this trial.

Gilead submitted a meeting request on June 4, 2015. The purpose of this meeting is to discuss, obtain feedback and reach agreement on the following issues:

- The completed and planned non-clinical studies are adequate to support registration of GS-9883/F/TAF;
- The completed and planned clinical pharmacology studies are adequate to support registration and inform the drug-drug interaction profile of GS-9883/F/TAF FDC for labeling;
- The design of the Phase 3 trials in treatment-naïve and virologically suppressed HIV-1-infected adults are adequate to support registration of the GS-9883/F/TAF FDC for the proposed indication;
- The Virology Analysis Plan;
- The proposed pediatric study in virologically suppressed subjects aged 6 years of age and older who are able to swallow intact tablets is adequate to support registration of GS-9883/F/TAF FDC;
- The proposed safety database for the GS-9883/F/TAF program is adequate for registration; and
- Plans and the proposed study design of a clinical trial to evaluate GS-9883/F/TAF in treatment-experienced adults with INSTI-resistant HIV-1 virus.

FDA sent Preliminary Comments to Gilead Sciences, Inc. on October 19, 2015.

2.0 DISCUSSION

Based on Gilead's responses to FDA preliminary comments provided on October 19, 2015, the following items were planned for discussion during the teleconference:

- Question 2A-comment 4
- Question 3A-comment 1 and 2
- Question 3C
- Question 3D

Gilead provided additional clarification to these items on October 21, 2015 (in italics below). FDA concurred with the additional information provided by Gilead and discussion was only needed for Question 2 A-comment 4.

Clinical Pharmacology

Question 2A: Does the Agency agree that the completed and planned Clinical Pharmacology studies of GS-9883 and GS-9883/F/TAF are adequate to support registration of the GS-9883/F/TAF FDC?

FDA Response to Question 2A:

4. The food effect study needs to be completed prior to initiating the Phase 3 trials in order to justify administration of GS-9883/F/TAF without regard to food. Alternatively, collect food intake information for all PK study visits and evaluate the effect of food as a covariate in the population PK analysis.

Sponsor Response to Question 2A Comment prior to meeting:

- *Gilead is evaluating the effect of food as part of study GS-US-141-1233, and expects data to be available prior to initiating patients in phase 3.*
- *Gilead will obtain food intake information for all PK study visits in phase 3 studies, and evaluate food effect as a covariate in the population PK analysis.*

Meeting Discussion Question 2A:

Since food effect is being evaluated as a part of study GS-US-141-1233, Gilead does not need to collect food intake information in the Phase 3 trials.

Clinical/Clinical Virology

Question 3A: Upon review of the clinical data available at the time of the EOP2 meeting, does the Agency agree that Gilead can proceed with initiation of Phase 3?

FDA Response to Question 3A: Pending resolution of the bioavailability and food effect issues with the GS-9883 50 mg/F/TAF FDC tablet, we concur with initiation of Phase 3. We also have the following general comments regarding the Phase 3 trials:

1. Monitor lipid levels and uric acid levels in all clinical trials. Provisions should be made in the protocols to treat elevated cholesterol levels according to current guidelines.
2. We suggest excluding and withdrawing patients with active tuberculosis requiring rifampin given decreased levels of GS-9883 with rifampin.

Sponsor Response to Question 3A Comment 1 and 2 prior to meeting (no additional discussion required):

Comment 1

- *Gilead will monitor lipids and uric acid levels in all trials, and highlight the importance of treating elevated cholesterol levels per local guidelines to all investigators at the investigator meetings. Gilead will also include reminders in newsletters regularly distributed to sites during the course of the studies.*

Comment 2

- *Rifampin is a disallowed medication in all studies containing 9883. Patients identified at screening to have active TB will be excluded from the trial. Also, patients with active TB diagnosed during the course of the study requiring treatment with Rifampin will be discontinued.*

Question 3C: Does the Agency agree that the planned trial in virologically suppressed women, GS-US-380-1961, will provide meaningful clinical data in HIV-1-infected women, and be suitable for inclusion in labeling?

FDA Response to Question 3C:

We concur with your efforts to collect clinical safety data in women in Phase 3. However, the Division also encourages you to increase representation of women in your other Phase 3 trials, particularly the trials in naïve patients.

With that said, we have concerns about the interpretability of results from this study. Given that all subjects will be switched to potentially new FDC regimens, please elaborate on the investigational question you seek to answer with this particular study design.

Sponsor Response to Question 3C prior to meeting (no additional discussion required):

- *Gilead will make every effort to ensure adequate representation of women in the Phase 3 program, particularly in the naïve trials. Efforts will include selection of high enrolling sites from the Stribild WAVES study, as well as implementing a robust women enrollment and retention campaign.*
- *Given the agency's feedback on the interpretability of results from the GS-US-380-1961 study as designed, Gilead will reassess the current design and will submit a protocol in late November for the agency's review.*

Question 3D: Does the Agency agree that patients coinfecting with HBV or HCV can be included in the Phase 3 trials, as described above?

FDA Response to Question 3D: It is reasonable to include HBV-co-infected patients in the trials that administer F/TAF. Please include strict monitoring and management plans for HBV-related flares and describe how patients who discontinue F/TAF would be managed.

For HCV-coinfecting patients, the Division agrees that once adequate drug-drug interaction data are available for various DAA regimens, it would be acceptable to include these patients in the clinical trials. Please include assessments of HCV viral load and safety labs related to HCV infection.

Sponsor Response to Question 3D prior to meeting (no additional discussion required):

- *Gilead will include strict laboratory monitoring and management of HIV patients co-infected with Hepatitis B or with Hepatitis C in the trials.*
- *To ensure the safety of HBV co-infected subjects, those with high HBV viral loads at screening will be excluded. In addition, the protocol defines management of HBV related flares while on treatment, and management of patients who discontinue F/TAF.*
- *Gilead has conducted a clinical pharmacology study of GS-9883 STR co-administered with Harvoni, and found no clinically significant drug-drug interaction. In Q2 2016, Gilead plans to initiate an additional clinical pharmacology study of GS-9883 with other DAA, which may expand the list of allowed DAA as appropriate.*

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdet-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For

clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

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

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

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

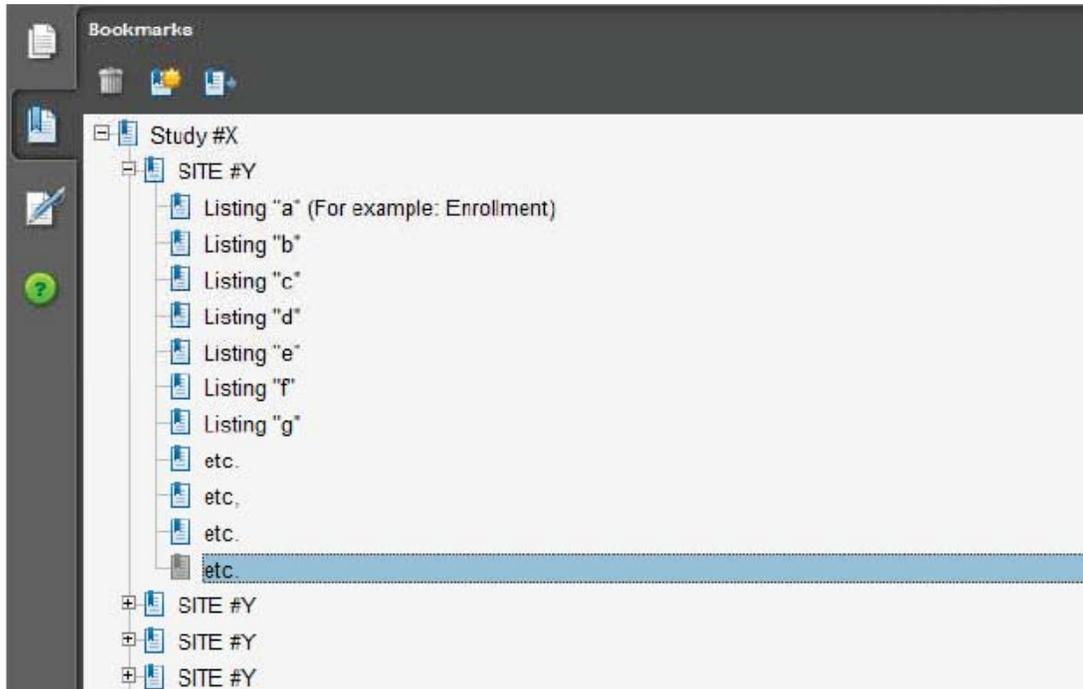
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

- f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

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

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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

/s/

JEFFREY S MURRAY
10/28/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 210251

LATE-CYCLE MEETING MINUTES

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BIKTARVY™ (bictegravir/emtricitabine/tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 28, 2017.

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

If you have any questions, call Suzanne Strayhorn, Regulatory Project Manager at (240) 402-4247

Sincerely,

{See appended electronic signature page}

Wendy Carter, DO
Medical Team Leader, Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 28, 2017, 3:00 pm – 4:30 pm, EST
Meeting Location: Teleconference

Application Number: NDA 210251
Product Name: BIKTARVY™ (bictegravir/emtricitabine/tenofovir alafenamide) tablets
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Wendy Carter, DO, Medical Team Leader
Meeting Recorder: Suzanne Strayhorn, MS, Sr. Regulatory Project Manager

FDA ATTENDEES

OND/Office of Antimicrobial Products (OAP)

John Farley, MD, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)

Debra Birnkrant, MD, Director
Jeffrey S. Murray, MD, MPH, Deputy Director
Wendy Carter, DO, Medical Team Leader
Tanvir Bell, MD, Medical Officer
Julian O’Rear, PhD, Virology Team Leader
Sung Rhee, PhD, Virology Reviewer
Hanan Ghantous, PhD, Pharm/Tox Team Leader
John Dubinion, PhD, Pharm/Tox Reviewer
Suzanne Strayhorn, MS, Sr. Regulatory Project Manager
Elizabeth Thompson, MS, Chief Project Management Staff

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)

Islam Younis, PhD, Clinical Pharmacology Team Leader
Vikram Arya PhD, Clinical Pharmacology Reviewer

OTS/OB/Division of Biometrics IV (DBIV)

Thamban Valappil, PhD, Acting Statistical Team Leader
Wen Zeng, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)

Naomi Redd, PhD, Epidemiologist

Office of Pharmaceutical Quality (OPQ)

Stephen Miller, Pharmaceutical Quality Team Leader

APPLICANT ATTENDEES

Andrew Cheng, Executive Vice President, HIV Clinical Research
Erin Quirk, Vice President, HIV Clinical Research
Hal Martin, Director, HIV Clinical Research
Joseph Custodio, Associate Director, Clinical Pharmacology
Vahid Zia, Director, Formulation and Process Development
Mae Lai, Senior Director, Regulatory Affairs
Kim Lindstrom, Senior Manager, Regulatory Affairs
Garland Lee, Senior Associate, Regulatory Affairs
Sonja Tong, Director, Regulatory Affairs Labeling
Eric Stauffer, Associate Director, Regulatory Affairs Labeling
Doris Graupe, Senior Manager, Regulatory Affairs Chemistry Manufacturing and Controls

1.0 BACKGROUND

NDA 201251 was submitted on June 10, 2017, and received on June 12, 2017, for BIKTARVY™ (bictegravir/emtricitabine/tenofovir alafenamide) tablets.

Proposed indication(s): Treatment of HIV-1 infection in adults who are HIV-1 antiretroviral (ARV) therapy (b) (4) associated with resistance to the individual components of BIKTARVY™.

PDUFA goal date: February 12, 2018

FDA issued a Background Package in preparation for this meeting on November 21, 2017.

2.0 DISCUSSION

1. Introductory Comments

FDA thanked Gilead for taking the time to attend the meeting via teleconference. FDA clarified the purpose and objective of the Late-Cycle Meeting for NDA 210251 for BICTARVY™ was to provide for an opportunity to share information and to discuss any substantive review issues that have been identified to date with Gilead as well as to discuss FDA review objectives for the remainder of the review cycle. FDA stated that the intent of this late-cycle meeting was to promote a collaborative and successful discussion.

FDA noted the Late-Cycle Meeting background package and agenda for this meeting were sent to Gilead on November 21, 2017. FDA also acknowledged that Gilead had submitted new information in response to some of the items identified in the background package on November 27, 2017, but FDA has not reviewed this information in its entirety and therefore may not be able to fully discuss at today's meeting.

2. Discussion of Substantive Review Issues

Discussion:

- Product Quality: FDA noted that the evaluation of the manufacturing facilities remains in progress. FDA reminded Gilead to contact their contract manufacturers and DMF holders to confirm continued facilities adequacy/acceptability.

3. Information Requests

Discussion:

- FDA again acknowledged Gilead's submission dated November 27, 2017, which contained responses to the information requested included in the late-cycle background package and noted that this information has not yet been fully reviewed.

4. Postmarketing Requirements/Postmarketing Commitments

Discussion:

- The FDA review division indicated that the PREA PMR [REDACTED] (b) (4) [REDACTED] remained under internal review and discussion. The Division plans to provide updated communication to Gilead after internal meetings are completed.

5. Labeling Issues

Discussion:

- The FDA review division stated that they are having internal discussions regarding the clinical recommendation for the use of BIKTARVY™ with antacids and supplements. FDA previously included related comments as part of the labeling changes sent to Gilead on November 16, 2017.

6. Review Plans

Discussion:

- FDA reviewed the plans moving forward which include:
 - Complete review of the application by the Signatory Authority, Division Director, and Cross-Discipline Team Leader
 - Await completion of CMC facility evaluation and address any issues that may arise
 - Finalize labeling
 - Finalize PMR/PMCs

7. Wrap-Up and Action Items

This application has not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

WENDY W CARTER
12/18/2017



NDA 210251

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BIKTARVY (bictegravir/emtricitabine/tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 28, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at suzanne.strayhorn@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Suzanne Strayhorn, MS, Sr. Regulatory Project Manager, at (240) 402-4247.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 28, 2017, 3:00 pm – 4:30 pm, EST
Meeting Location: Teleconference

Application Number: 210251
Product Name: BIKTARVY (bictegravir/emtricitabine/tenofovir alafenamide)
tablets, 50 mg/200 mg/25 mg
Indication: Treatment of HIV-1
Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative)

OND/Office of Antimicrobial Products (OAP)

Edward M. Cox, MD, MPH, Director
John Farley, MD, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)

Debra Birnkrant, MD, Director
Jeffrey S. Murray, MD, MPH, Deputy Director
Wendy Carter, DO, Medical Team Leader
Tanvir Bell, MD, Medical Officer
Julian O’Rear, PhD, Virology Team Leader
Sung Rhee, PhD, Virology Reviewer
Eric Donaldson, PhD, Virology Reviewer
Hanan Ghantous, PhD, Pharm/Tox Team Leader
John Dubinion, PhD, Pharm/Tox Reviewer
Suzanne Strayhorn, Sr. Regulatory Project Manager
Elizabeth Thompson, Chief Project Management

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)

Islam Younis, PhD, Clinical Pharmacology Team Leader
Vikram Arya PhD, Clinical Pharmacology Reviewer

OTS/OB/Division of Biometrics IV (DBIV)

Thamban Valappil, PhD, Statistical Team Leader
Wen Zeng, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)

Elizabeth Everhart, MSN, RN, ACNP, Risk Management Analyst
Naomi Redd, PhD, Epidemiologist

Office of Pharmaceutical Quality (OPQ)

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

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

Product Quality

At this time, the evaluation of the manufacturing facilities is in progress. We remind you to contact your contract manufacturers and DMF holders to confirm continued facilities adequacy/acceptability.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

A. **Introductory Comments** – 5 minutes (Suzanne Strayhorn, Wendy Carter)

- Welcome, Introductions, Ground rules, Objectives of the meeting

B. **Discussion of Substantive Review Issues** – 5 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Product Quality: The evaluation of the manufacturing facilities is in progress.

C. **Information Requests** – 5 minutes

- Product Quality

Please update the drug product specification to include the following shelf-life acceptance criteria as addressed in your amendment (SN 0016) dated October 18, 2017:

- NMT [REDACTED] (b) (4)
- NMT [REDACTED] (b) (4) for Total TAF-related degradation products

D. **Postmarketing Requirements/Postmarketing Commitments** – 5 minutes

The PREA PMR [REDACTED] (b) (4) are under internal review and discussion. We will send further communication after our internal meetings are completed.

E. **Labeling Issues** – 5 minutes

The Division is having internal discussion regarding the clinical recommendation for the use of BIKTARVY with antacids and supplements and have included comments as part of the labeling changes sent on November 16, 2017.

F. **Review Plans** – 5 minutes

- Complete application review by the Signatory Authority, Division Director, and Cross-Discipline Team Leader
- Await completion of CMC facility evaluation and address any issues that may arise
- Finalize labeling
- Finalize PMR/PMCs

G. **Wrap-up and Action Items** – 5 minutes

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/s/

DEBRA B BIRNKRANT
11/21/2017