

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205551Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205551

SUPPL # 0

HFD # 530

Trade Name TRIUMEQ

Generic Name abacavir sulfate, dolutegravir, and lamivudine

Applicant Name ViiV Healthcare Company

Approval Date, If Known 08/22/2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

Study ING114580 evaluated the bioequivalence of the fixed dose combination of abacavir/dolutegravir/lamivudine compared with the dolutegravir tablet and abacavir/lamivudine fixed dose tablets. In addition, the study evaluated of the effect of food on the bioavailability of the products. The study was conducted in healthy volunteers. The sponsor's request for exclusivity did not identify this study as the new clinical data essential for approval, so discussion regarding study ING114580 did not occur.

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

3

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 204790	TIVICAY (dolutegravir)
NDA# 20977	ZIAGEN tablet (Abacavir Sulfate)
NDA# 20978	ZIAGEN solution (Abacavir Sulfate)
NDA# 21652	EPZICOM (Abacavir Sulfate/Lamivudine)
NDA# 21205	TRIZVIR (Abacavir Sulfate/Lamivudine/Zidovudine)
NDA# 20857	COMBIVIR ((lamivudine/zidovudine)
NDA# 21004	EPIVIR-HBV (lamivudine) Oral Solution
NDA# 20596	EPIVIR Oral Solution (lamivudine oral solution)
NDA# 20564	EPIVIR Tablets (lamivudine tablets)
NDA# 21003	EPIVIR-HBV (lamivudine) Tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE

SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES NO

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

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

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

YES NO

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

The clinical studies to support the use of dolutegravir, single component product, in combination with abacavir and lamivudine were used to support the approval of NDA 204790. These studies were essential for that approval. To support the new fixed dose combination of these three drugs, the sponsor only needed to conduct a

bioavailability/bioequivalence study. All other studies would be supportive, but not essential to approval.

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously

approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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

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

Investigation #1 !
!

IND # YES ! NO ! Explain:

Investigation #2
IND # 114820 YES ! NO ! Explain:

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

Investigation #1
YES ! NO ! Explain:

Investigation #2
YES ! NO ! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Sohail Mosaddegh
Title: Regulatory Project Manager
Date: 08/20/2014

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

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

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

/s/

SOHAIL MOSADDEGH
08/22/2014

DEBRA B BIRNKRANT
08/22/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205551 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: TRIUMEQ Established/Proper Name: abacavir sulfate, dolutegravir, and lamivudine Dosage Form: fixed-dose combination tablets, 600/50/300 mg.		Applicant: ViiV Healthcare Company Agent for Applicant (if applicable):
RPM: Sohail Mosaddegh		Division: Division of Antiviral Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:
Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.		
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>08/22/2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 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 | |

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

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approved 08/22/2014
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 08/20/2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 10/22/2014
❖ 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> Warning Card
<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 08/20/2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 10/22/2014
❖ 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 08/20/2014
❖ Proprietary Name	Acceptability letter 01/19/2014 Review 01/16/2014
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None 12/20/2013 DMEPA: <input type="checkbox"/> None 04/22/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 07/02/2014 OPDP: <input type="checkbox"/> None 07/02/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM filing review: 12/20/2013 Memo:12/20/2013
❖ 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 only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<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 <input checked="" type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>06/25/2014</u> If PeRC review not necessary, explain: _____ 	PERC 06/25/2014 minutes
❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	11/15/2013, 12/31/2013, 1/3/2014, 1/23/2014 (x3), 1/30/2014, 2/20/2014, 2/24/2014, 2/28/2014, 3/7/2014, 3/21/2014 (x2), 4/22/2014, 4/24/2014, 5/8/2014, 5/22/2014, 6/6/2014, 6/19/2014, 7/14/2014, 8/7/2014
❖ 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)	
❖ Minutes of Meetings <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Mid-cycle Communication (<i>indicate date of mtg</i>) Late-cycle Meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 02/27/2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 07/14/2014 Filing review 12/30/2013 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Pages 43-44 of 07/14/2014 clinical review

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/06/2014 Filing review 12/17/2013
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/17/2014 Filing review 12/20/2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/16/2014 Filing review 12/18/2013
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 08/12/2014
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review <input checked="" type="checkbox"/> No separate review <input type="checkbox"/> None Filing review 12/19/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<input type="checkbox"/> None Product quality: 08/14/2014 amended 08/20/14 Biopharmaceutics: 07/08/2014, amended 08/15/2014 Filing review 12/19/2013
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed Microbiology Non-Sterile: 03/17/2014 filing review 12/11/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 81 of ONDQA review 07/14/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 04/04/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

SOHAIL MOSADDEGH
09/02/2014

**PeRC PREA Subcommittee Meeting Minutes
June 25, 2014**

PeRC Members Attending:

Robert Nelson
Rosemary Addy
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Peter Starke
Gregory Reaman
Lily Mulugeta
Kristiana Brugger
Rachel Witten

Agenda

NDA	21937	Atripla (efvirenz_emtricitabine_tenofovir) (b) (4)	Treatment of HIV-1 infection
NDA	205551	Triumeq (dolutegravir_abacavir_lamivudine) Partial Waiver_Deferral_Plan	Treatment of HIV-1 infection
IND BLA	(b) (4) 125160	Cimzia (certolizumab pegol) (b) (4)	Treatment of rheumatoid arthritis

Atripla (efvirenz emtricitabine tenofovir) (b) (4)

- NDA 21937 was approved on July 12, 2006, for Atripla (efvirenz_emtricitabine_tenofovir) for the treatment of HIV-1 infection.
- The current PREA PMR for this product requires studies for pediatric patients (b) (4)
- *PeRC Recommendations:*
 - (b) (4)
 - (b) (4)
 - The PeRC agreed to release the sponsor from the PMR for pediatric patients less than 2 years of age, (b) (4)

Triumeq (dolutegravir abacavir lamivudine) Partial Waiver Deferral Plan

- NDA 205551 seeks marketing approval for Triumeq (dolutegravir_abacavir_lamivudine) for the treatment of HIV-1 infection.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA a goal date of August 22, 2014.
- *PeRC Recommendations:*
 - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 4 weeks because studies would be impossible or highly impracticable for pediatric patients of this age.
 - The PeRC agreed with a partial waiver for pediatric patients aged 4 weeks to less than 2 years because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age, and is unlikely to be used in a substantial number of pediatric patients of this age.
 - The PeRC agreed with a deferral for pediatric patients aged 2 to 18 years because adult studies have been completed and the product is ready for approval. The deferred studies will be for PK and safety.
 - The PeRC recommended separate PMRs for pediatric patients aged 2-11 and 12-17 years. The PeRC noted that a PMR for 12-17 years may not be necessary based on review of the application.

Cimzia (certolizumab pegol) (b) (4)

- BLA 125160 was approved on May 13, 2009, for Cimzia (certolizumab pegol) for the treatment of rheumatoid arthritis.

(b) (4)

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/s/

JANE E INGLESE
07/07/2014



NDA 205551

INFORMATION REQUEST

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abacavir sulfate, dolutegravir, and lamivudine, fixed-dose combination tablets, 600/50/300 mg.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response by July 21, 2014, in order to continue our evaluation of your NDA.

1. Please be advised that approval of the NDA does not constitute approval of the process validation and sampling plans provided in the NDA. Process validation and sampling documents are evaluated during CGMP inspection of the manufacturing site.
2. It is our understanding that in the manufacturing process description in Section P.3.3, the word 'typical' refers to target operating conditions and the equipment referred to as 'for example' denote the equipment type where the ranges/set points are justified by development data provided in Module 2. In addition, it is our understanding that the process parameter ranges as provided in the MBR (Master Batch Record) in section 3.2.R supplements the drug product manufacturing process description provided in section 3.2.P.3.3, and that the MBR provides operating ranges/set points for the process parameters not included in section 3.2.P.3.3. The Agency's expectation is that the potential impact of changes to process parameters, including those with low criticality, be assessed under the firm's quality system at the time of the change. Confirm that as appropriate, changes with a potential to adversely affect product quality would be notified to the Agency in accordance with 21 CFR 314.70.

3. Section P.3.2 of the NDA indicates the commercial process scale is (b) (4) (coated tablet batch size) and is typically (b) (4) tablets. In the teleconference dated July 11, 2014, you indicated that the process is being (b) (4) (b) (4) would be validated subsequently. Please confirm that the (b) (4) process will be appropriately validated. Additionally, please confirm that as appropriate, changes to process parameters/ranges and equipment type with a potential to adversely affect product quality would be notified to the Agency in accordance with 21 CFR 314.70.
4. In section 3.2.P.2.2, you state that a (b) (4) type of microcrystalline cellulose (MCC) is need to (b) (4) (u) (v).” However, the MCC specification given in Section 3.2.P.4 is per USP. Indicate if the USP compendial specification is sufficient to accept MCC of desired (b) (4). If not, revise the MCC specification to include an acceptance criterion for (b) (4).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURawe
07/14/2014

From: Mosaddegh, Sohail
To: [Martha Anne Auld \(marthaanne.a.auld@gsk.com\)](mailto:marthaanne.a.auld@gsk.com)
Subject: Pediatric Certification for NDAs and sNDA that trigger PREA
Date: Thursday, June 19, 2014 2:19:00 PM

Hello:

During our review of your submission, we note that you have submitted a request for a pediatric waiver and or deferral. However, we could not locate the certification that is required under 21, CFR 314.55. If you have submitted this information, please provide the location. If not, please submit this information no later than July 02, 2014.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

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/s/

SOHAIL MOSADDEGH
06/19/2014

Cuff, Althea

From: Cuff, Althea
Sent: Thursday, May 22, 2014 2:29 PM
To: Martha Anne Auld (marthaanne.a.auld@gsk.com)
Subject: NDA 205551 - Information Request

Dear Martha Anne,

To support the image change (score, shape and debossing/color), provide the comparative dissolution data (raw data, mean, SD, full profiles/figures, f2 calculation) using the currently proposed dissolution method for the FDC drug product before the image change (used in trial ING114580), and after the image change (commercial to-be-marketed product).

Please send response by May 30, 2014.

Thanks, Althea

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/s/

ALTHEA CUFF
05/22/2014

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: May 8, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Comments on labeling

Please find the attached USPI for TRIUMEQ. In an effort to make the label more streamlined we have modified the Indications and Usage, Warning and Precaution, Adverse Reactions and Clinical Studies section. These changes were made to avoid redundancy throughout the label and refer to other sections or the individual drug labeling as appropriate. The focus of section 6 and 14 should be on trials that contain the components of TRIUMEQ. Therefore we have limited the sections to display of results from the SINGLE trial. Limited details from SAILING were retained in the label to support the broad indication. Additionally, references were included, where appropriate, to the Tivicay label. As a result the long-term data from SPRING and results from Flamingo will be included in the Tivicay label under supplement 002.

- **Indications and Usage Section**

This section should be concisely written to include the necessary information needed to clearly convey the use for which the drug has been shown safe and effective. Please note that the Agency is moving away from using terms such as 'points to consider'. Instead, any additional statements should be under the subheading of 'Limitation of Use'. We have also removed redundant information already included in other sections such as 'Dosage and Administration' or 'Contraindication'.

- **Information related to abacavir and lamivudine**

In an effort to streamline the label which contains labeling information for three ARV drugs, we have edited contents related to abacavir and lamivudine. Instead, references to the individual labels are included for additional details. We understand you also have proposals

to revise the [REDACTED] (b) (4). We welcome these changes to the TRIUMEQ label during this review to streamline this section. Similar changes can be made to [REDACTED] (b) (4) at a later date.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

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/s/

SOHAIL MOSADDEGH
05/08/2014

Please indicate on the revised immediate container and carton labels where the lot number and expiration date will appear.

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

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/s/

SOHAIL MOSADDEGH
04/24/2014

From: Mosaddegh, Sohail
To: [Martha Anne Auld \(marthaanne.a.auld@gsk.com\)](mailto:marthaanne.a.auld@gsk.com)
Subject: Triumeq NDA 205551
Date: Monday, April 21, 2014 1:48:00 PM

Hello:

For Triumeq (Abacavir, Dolutegravir, and Lamivudine) NDA 205551, We are currently reviewing the carton labeling for Triumeq (Abacavir, Dolutegravir, and Lamivudine) NDA 205551. We noticed a rectangular blue empty box on the principle display panel of the carton labeling. This box takes up $\frac{1}{4}$ of the principle display panel. What is the purpose of this box? Please respond by COB on Wednesday, April 23, 2014.

Sohail

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/s/

SOHAIL MOSADDEGH
04/22/2014



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: March 21, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Comments on labeling

Please specify the dose and AUC values for animal exposures used to generate the draft TRIUMEQ label, and indicate when those values differ from the EPZICOM label. Please provide justification for using data different from the values used to generate the approved EPZICOM label.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/21/2014

Cuff, Althea

From: Cuff, Althea
Sent: Friday, March 21, 2014 2:10 PM
To: Martha Anne Auld (marthaanne.a.auld@gsk.com)
Subject: NDA 205551 - Information Request

Dear Martha,

- We consider that the proposed dissolution medium with surfactant is not adequate for the dissolution testing of abacavir and lamivudine. Therefore, provide full dissolution profile data (individual, mean, SD, mean plots) for abacavir and lamivudine for your three registration stability batches (at the current stability time point), using USP App 2 with paddle rotation speeds of 60, 75, and 85 rpm, using the proposed dissolution medium without 0.5% SDS.
- Provide full dissolution profile data (individual, mean, SD, mean plots) for dolutegravir for your three registration stability batches (at the current stability time point) using the proposed dissolution method, but with a paddle rotation speed of 75 rpm instead of the proposed 85 rpm.

Thanks, Althea

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/s/

ALTHEA CUFF
03/21/2014

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: March 7, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Comments on labeling

Regarding Section 8.1 Pregnancy and Section 13. Nonclinical Toxicology, several discrepancies were noted between the draft TRIUMEQ product label and the approved EPZICOM (abacavir and lamivudine) label. Specifically, listed exposure margins for various toxicology studies do not agree (see Sections 8.1 and 13 of the draft TRIUMEQ label, portions excerpted below, with exposure margins from the EPZICOM label included in highlighted text). Please explain the discrepancies in exposure margins between the draft TRIUMEQ product label and the approved EPZICOM label.

8.1 Pregnancy

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 28 (35) times the human exposure for a dose of 600 mg based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 7(8.5) times the human exposure at the recommended dose based on AUC.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to

approximately 32 (35) times the human exposure for a dose of 300 mg. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at plasma levels up to 32 (35) times those in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Dolutegravir: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg/kg, and rats were administered doses of up to 50 mg/kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 26-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30-fold higher in males and females, respectively, than those in human at the recommended dose of 50 mg once daily.

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 7 (6) to 28 (32) times the human exposure at the recommended dose of 600 mg.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 (10) times (mice) and (b) (4) (58) times (rats) the human exposures at the recommended dose of 300 mg.

Impairment of Fertility: Dolutegravir, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, (b) (4) (8), or 112 (130) times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/07/2014



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: February 28, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Comments on food effect

Please provide the following food effect information:

- a) For the food effect evaluation in the ING114580 trial, the trial report states that a high fat meal was administered that consisted of 53% fat and 869 calories. However as recommended in the FDA's guidance document "Food-Effect Bioavailability and Fed Bioequivalence Studies", please provide the specific breakdown of the number of calories from carbohydrates, protein and fat, respectively, for the high fat meal.
- b) Similarly for the ING113674 trial that evaluated the effect of food on dolutegravir and the abacavir food effect trial from the original abacavir NDA, please provide the specific breakdown of the number of calories from carbohydrates, protein and fat, respectively. Additionally, please provide information regarding the percentage derived from fat and the total number of calories for the high fat meal for both food effect trials.
- c) Please clarify whether the abacavir, dolutegravir, and lamivudine fixed dose combination tablet that was administered in the ING114580 trial (product code (b) (4) is identical to the proposed U.S. commercially marketed formulation. Similarly, please provide specify how the dolutegravir 25 mg AW formulation that was administered in the ING113674 trial is linked to the U.S. commercially marketed dolutegravir 50 mg tablets and provide information on whether the abacavir formulation from the abacavir food effect trial is the U.S. commercially marketed abacavir formulation

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
02/28/2014



IND 114820

MEETING MINUTES

ViiV Healthcare
Attention: Brandy Muchanic
Manager, Regulatory Affairs
Five Moore Drive
P.O. Box 13398, Bldg 5.5219
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK2619619 (dolutegravir, abacavir sulfate, and lamivudine).

We also refer to the telecon between representatives of your firm and the FDA on February 27, 2013. The purpose of the meeting was to discuss the content and format of the proposed New Drug Application (NDA) for GSK2619619.

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

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
GSK/ViiV response to DAVP preliminary comments
Draft USPI



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 27, 2013, 12:00 pm to 1:00 pm
Meeting Location: 10903 New Hampshire Ave., Bldg. 22, Room 6201

Application Number: IND 114,820
Product Name: GSK2619619 (dolutegravir, abacavir sulfate, and lamivudine)
Indication: treatment of HIV-1 infection
Sponsor/Applicant Name: ViiV Healthcare Co (ViiV)

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Sohail Mosaddegh, PharmD

FDA ATTENDEES

1. Debra Birnkrant, MD, Director
2. Greg Soon, PhD, Statistical Team Lead
3. Jeffrey Murray, MD, MPH, Deputy Director
4. Julian O'Rear, PhD, Virology Team Lead
5. Karen Winestock, Chief, Project Management Staff, DAVP
6. Katherine Schumann, MS, Regulatory Project Manager
7. Kendall Marcus, MD, Associate Director of Safety
8. Kim Struble, PharmD, Medical Team Lead
9. Lisa Naeger, PhD, Virology Reviewer
10. Mark Seaton, PhD, Pharmacology/Toxicology Reviewer, DAVP
11. Shirley K Seo, PhD, Clinical Pharmacology Team Lead
12. Sohail Mosaddegh, PharmD, Regulatory Project Manager
13. Stephen Miller, PhD, CMC-Lead, ONDQA
14. Dave Roeder Assoc. Dir. Regulatory Affairs, OAP/CDER
15. Morgan Walker, Labeling Reviewer, OSE/DMPEA
16. Jamie Wilkins Parker, PharmD, Team Leader, OSE/DMEPA
17. Kim Taylor, MA, MBA. Operations Research Analyst
18. Deepika Arora Lakhani, PhD, Biopharmaceutics Reviewer
19. Tamika Greenwood, DAVP Intern

20. ^{(b) (4)} [REDACTED] **ATTENDEES**
^{(b) (4)} [REDACTED]

Meeting Minutes
Pre-NDA, type B

SPONSOR ATTENDEES

1. W. Garrett Nichols, MD, MS, Project Leader, ID MDC
2. Martha Anne Auld, RPh, Senior Director, Global Regulatory Affairs
3. Brandy Muchanic, Manager, Regulatory Affairs
4. Brian Wynne, MD, Physician Project Leader
5. Director, Clinical Development, ID MDC
6. Stephen Piscitelli, PharmD, Director, Clinical Pharmacology, ID MDC
7. Keith Pappa, PharmD, Director, Clinical Development, ID MDC
8. Lloyd Curtis, MA MRCP, Medical Director, Signal Evaluation & Risk Management, Global Clinical Safety and Pharmacovigilance
9. Mark Underwood, PhD, Lead Integrase Virologist
10. Catherine Granier, Manager Statistics, Projects Clinical Platforms and Sciences
11. Ella Jaczynska Vice President, ID GRA
12. Neil Shortman Vice President, Head of Regulatory
13. James Goodrich, PhD, MD, Vice President, Global Medical Strategy
14. Melody Courtney, Manager, CMC pre-approval

BACKGROUND

The purpose of this meeting is to confirm agreements between DAVP and the Sponsor on proposals for the content and format of the New Drug Application (NDA) to be submitted for GSK2619619. GSK2619619 is a fixed-dose combination (FDC) drug product consisting of dolutegravir (DTG), abacavir sulfate (abacavir, ABC) and lamivudine (3TC), DTG/ABC/3TC 50/600/300 mg. The proposed indication for GSK2619619 is for (b) (4) for the treatment of HIV infection in adults without resistance to its components.

The objectives of the meeting are to confirm agreements on proposals for the content and format of the NDA:

- Cross-reference strategy to applications for abacavir, lamivudine, and dolutegravir
- Proposed structure of clinical efficacy and safety datasets to be submitted for dolutegravir pivotal Phase III clinical studies
- Agree in principle that the data to be presented are adequate to support the submission and filing of the NDA for GSK2619619

Pre-IND discussions of the development program of GSK2619619 occurred between the Sponsor and DAVP on May 23, 2012. IND 114820 was submitted on June 07, 2012 in order for the Sponsor to conduct a study establishing the bioequivalence of GSK2619619 to co-administration of DTG 50 mg + ABC/3TC 600/300 mg.

ViiV submitted a New Drug Application (NDA) for DTG (NDA 204790), on December 17, 2012, that is currently under review with DAVP. The Sponsor intends to submit an NDA for GSK2619619 in July 2013. Information for DTG, ABC, and 3TC will be incorporated by reference to relevant historical nonclinical and clinical data found in applications submitted to the Agency for each of the actives; ABC and 3TC are approved individually (ZIAGEN and EPIVIR, respectively) and in combination (EPZICOM/KIVEXA).

To support this proposed indication, the Sponsor intends to show the efficacy of GSK2619619 in HIV-infected subjects through the following:

- By establishing the bioequivalence of the GSK2619619 tablet, pivotal bioequivalence study (ING114580)
- By demonstrating the efficacy of the DTG component in HIV-infected subjects based on data from the DTG single entity program
- By presenting the broad indications currently approved for ABC, 3TC and the ABC/3TC combination product EPZICOM/KIVEXA as evidence that clinical efficacy of the ABC and 3TC components have been established for HIV-infected subjects
- By summarizing the efficacy of the GSK2619619 dosing regimen through clinical data from subjects that were on a treatment arm of DTG 50 mg QD + ABC/3TC 600/300 mg in key relevant DTG studies:
 - Pivotal: ING114467 (n=414 through 48 weeks)
 - Supportive:

- ING113086 (n=169 through 96 weeks)
- ING112276 (n=17 through 96 weeks)
- ING111762 (n=7 through 48 weeks)

Protocols:

- **Pivotal Efficacy Study: ING114467 (SINGLE):** is a Phase III, randomized, double-blind study of the safety and efficacy of DTG plus ABC/3TC FDC therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy-naïve adult subjects
- **Supportive Efficacy Studies:**
 - ING113086 (**SPRING-2**) is a Phase III, randomized, double blind study of the safety and efficacy of DTG 50 mg once daily compared to raltegravir (RAL) 400 mg twice daily both administered with fixed-dose dual NRTI (either ABC/ 3TC or TDF/FTC FDCs) therapy over 96 weeks in HIV-1 infected antiretroviral therapy-naïve adult subjects.
 - **ING112276 (SPRING-1)** is a Phase IIb study to select a once daily oral dose of DTG administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected antiretroviral therapy-naïve adult subjects.
 - **ING111762 (SAILING)** is a Phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor naïve, antiretroviral therapy-experienced adults. SAILING evaluated the efficacy of DTG in highly treatment experienced (yet INSTI class-naïve) subjects.

DISCUSSION

The Sponsor notified DAVP at the beginning of the meeting that they wanted to concentrate on questions 1B, 2 and 4 in relation to the draft labeling, and 12; they accepted DAVP’s other comments.

Your questions from January 29, 2013 are in **bold** font followed by DAVP’s responses in *italic* font followed by your comments from February 26, 2013 in **bold** font. Meeting discussions follow in regular font.

Clinical Pharmacology

1. The Sponsor has conducted a bioequivalence (BE) study, ING114580, to establish a clinical bridge between the DTG/ABC/3TC 50/600/300 mg fixed-dose combination (FDC) single-tablet regimen (STR) (hereafter referred to as “(b) (4)”) and the co-administration of DTG 50 mg plus ABC/3TC 600/300 mg (EPZICOM/KIVEXA) in Phase III studies (ING113086 and ING114467). The results demonstrate that the (b) (4) tablet formulation was bioequivalent to the separate tablet formulations.

- A) Does the Agency agree that bioequivalence between (b) (4) and co-administration of DTG and ABC/3TC has been demonstrated, thereby establishing a clinical bridge?**
- B) Does the Agency agree that the results of BE study ING114580 are adequate to support submission of the application for the (b) (4) tablet?**

DAVP response to 1, 1A, and 1B:

- *An assessment regarding whether bioequivalence is achieved between dolutegravir/abacavir/lamivudine fixed dose combination tablets compared to dolutegravir tablets and abacavir and lamivudine fixed dose combination tablets will be a review issue. However, in general, a bioequivalence assessment appears to be reasonable for submission of a NDA for the dolutegravir/abacavir/lamivudine fixed dose combination tablets.*
- *In order to determine if the results of ING114580 are sufficient to support submission of the NDA for the dolutegravir/abacavir/lamivudine fixed dose combination tablet, please clarify the following issues:*
 - *Are the dolutegravir/abacavir/lamivudine fixed dose combination tablets (code (b) (4)) that were administered in ING114850 identical to the proposed U.S. commercially marketed dolutegravir/abacavir/lamivudine fixed dose combination tablets?*
 - *Are the dolutegravir tablets (code (b) (4)) and the fixed dose combination tablets of abacavir and lamivudine that were administered in ING114850 identical to the proposed U.S. commercially marketed dolutegravir tablets and the current U.S. commercially marketed abacavir and lamivudine fixed dose combination tablets?*
- *As part of the NDA, please submit all the relevant bioanalytical information, including the following for ING114580 and for any other trials where new pharmacokinetic data will be submitted:*
 - *method validation reports, including information on the anticoagulant used for methods that are validated in plasma*
 - *bioanalytical reports, including information on the anticoagulant used to collect blood samples from the clinical trials*
 - *incurred sample reanalysis data, if conducted*
 - *long term stability data, including information on the specific temperatures that were evaluated and the anticoagulant used for the QC plasma samples*
 - *sample storage conditions (specific temperatures) and the duration of storage (e.g. number of days) at the following locations: 1) trial sites (if multiple site are used for a trial, please specify the maximum overall duration of storage at the trial sites), 2) secondary storage facilities, and 3) the bioanalytical laboratory, covering the period from the day samples were first drawn until the day the last sample was analyzed, including any reanalysis*

Sponsor Response:

We would like to clarify that the formulations of (b) (4) DTG, and EPZ tablets used in the BE study are identical to the US commercial formulations for each.

All relevant bioanalytical information requested will be provided. Regarding your request for information concerning storage conditions and duration of storage of samples at the trial site: would this information need to be part of the bioanalytical report or could it be provided as part of m2.7.1, perhaps in tabular format?

Discussion:

DAVP stated that the inclusion of information regarding the storage conditions and the duration of storage for samples at the trial site in m2.7.1 is acceptable.

Clinical Efficacy

2. The Sponsor proposes the following indication for the (b) (4) tablet: (b) (4), a combination of 2 nucleoside analogue HIV reverse transcriptase inhibitors (abacavir and lamivudine) and 1 integrase strand transfer inhibitor (dolutegravir), is indicated for (b) (4) for the treatment of HIV infection in adults without resistance to its components.

To support this proposed indication, the Sponsor intends to show the efficacy of (b) (4) in HIV-infected subjects through the following:

- **By establishing the bioequivalence of the (b) (4) tablet (see previous question)**
- **By demonstrating the efficacy of the DTG component in HIV-infected subjects based on data from the DTG single entity program**
 - **ING114467 (SINGLE)**
 - **data for all subjects through 48 weeks of therapy to be provided**
 - **n=844 total ART-naive subjects randomized 1:1 to DTG 50 mg + ABC/3TC 600/300 mg once daily (QD) vs. efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) QD**
 - **ING113086 (SPRING-2)**
 - **data for all subjects through 96 weeks of therapy to be provided**
 - **n=827 total ART-naive subjects randomized 1:1 to DTG 50 mg QD vs. raltegravir (RAL) 400 mg twice daily (BID), both in combination with investigator-selected background therapy of ABC/3TC QD or TDF/FTC QD**
 - **ING112276 (SPRING-1)**
 - **data for all subjects through 96 weeks of therapy to be provided**
 - **n=205 total ART-naive subjects randomized 1:1:1:1 to DTG 10 mg QD, DTG 25 mg QD, DTG 50 mg QD, or EFV 600 mg QD, all in combination with investigator-selected background therapy of ABC/3TC QD or TDF/FTC QD**
 - **ING111762 (SAILING)**

- data for all subjects through 48 weeks of therapy to be provided
 - n=724 total subjects randomized 1:1 to DTG 50 mg QD vs. RAL 400 mg BID, both in combination with investigator-selected background therapy of at least one fully active agent but no more than 2 background agents
- By presenting the broad indications currently approved for ABC, 3TC and the ABC/3TC combination product EPZICOM/KIVEXA as evidence that clinical efficacy of the ABC and 3TC components have been established for HIV-infected subjects
 - By summarizing the efficacy of the (b) (4) dosing regimen through clinical data from subjects that were on a treatment arm of DTG 50 mg QD + ABC/3TC 600/300 mg in key relevant DTG studies:
 - Pivotal: ING114467 (n=414 through 48 weeks)
 - Supportive:
 - ING113086 (n=169 through 96 weeks)
 - ING112276 (n=17 through 96 weeks)
 - ING111762 (n=7 through 48 weeks)

Integrase inhibitor (INI)-naive subjects, both antiretroviral therapy (ART)-naive and ART-experienced, are the targeted population. (b) (4) is not intended for use in the INI-resistant population.

Does the Agency agree that the above proposals are sufficient to support the proposed indication of (b) (4) as outlined above?

DAVP response:

We are in general agreement with your proposed plan to support the efficacy of the FDC drug product using the single entity drug products. We note that the pivotal trial you will rely upon for support of the FDC drug product is the SINGLE trial. Please clarify how you plan to display efficacy results in your label with respect to SINGLE, SRPING-2 and SAILING. In addition, please clarify if you plan to include in the label the longer term efficacy (and virology) data for the two supportive studies- i.e. for ING113086, 96 Week data and for ING 111762 48 Week data. Please refer to Question 4 for similar comments with regards to safety data presentation in the label.

Please submit a draft label to the Division prior to the T-con in order to facilitate the meeting.

Sponsor Response:

Please refer to the draft USPI provided. We plan to present the efficacy data from SINGLE in tabular format and to describe the (b) (4) and SAILING efficacy data in the text of the USPI. We would like to discuss this further during the meeting.

Discussion for question 2 & 4:

DAVP stated the plan to present the safety data from SINGLE in tabular format and to describe the (b) (4) and SAILING safety data in the text of the USPI is acceptable. DAVP stated that section 14 should be similar to section 6 of the submitted draft USPI. DAVP wants a more concise section with statements that the overall efficacy results were similar to the overall population with a reference to the DTG (NDA 204790) label; as opposed to the detailed information from the limited number of patients receiving the background regimen of abacavir and lamivudine in (b) (4) and SAILING.

In the draft label submitted by ViiV, (b) (4) are discussed. DAVP requests that instead of the (b) (4) the USPI show treatment effect for each group and then the overall treatment difference with the confidence interval.

DAVP stated that minimal clinical data are presented in section 12.4 ((b) (4)) and with the submission of 96 week data from DTG this section may need to be expanded. ViiV stated the section is sparse as very little resistance has been observed on DTG so far.

ViiV concluded that they will incorporate DAVP's recommendations into the labeling prior to submission of the NDA.

Virology

3. The Sponsor plans to provide virology information from the current Summary of Product Characteristics (SmPC) / US Prescribing Information (USPI) submitted to the approved (ABC, 3TC, EPZICOM/KIVEXA) or pending (DTG) applications for the individual components. The Sponsor also will include relevant new nonclinical or clinical data or updates which have become available since the most recent update to the SmPC or USPI.

The nonclinical reports and data analyses to be provided include, but are not limited to: mechanism of action studies, in vitro passage studies, within class resistance analyses, broad clade activity, HIV-2 activity, and combination analyses.

The submission will also include a discussion of relevant existing and updated clinical study virology data and analyses from ART-naive and ART-experienced (INI-naïve) studies for the individual components, as well as where available for combined components. Studies that are not otherwise included as pivotal or supportive studies in the main efficacy discussion of ABC and 3TC may also be discussed. Virology for the raltegravir resistant clinical studies (ING112961 and ING112574) will not be discussed, except where it may inform on DTG resistance.

Does the Agency agree that the current (and draft, in the case of DTG) SmPC/USPI for the individual components are an appropriate reference to determine the relevant virology data to be presented in the (b) (4) submission?

DAVP response:

We agree. Additionally, if longer term efficacy data are submitted for the Phase 3 studies, updated resistance analysis datasets will also need to be submitted.

Sponsor Response:

Thank you.

Clinical Safety

(b) (4)

4. To support the safety of the (b) (4) product, the application will include pooled safety analyses from studies involving subjects who were exposed to a once-daily regimen of DTG+ABC/3TC. The studies in ART-naive subjects are: ING114467, ING113086, and ING112276. The safety data from subjects receiving DTG+ABC/3TC will be integrated. For ART-experienced (INI-naive) subjects, updated information on DTG from the Week 48 analysis of all subjects exposed to DTG in study ING111762 will be included in the submission; safety data from this study would not be integrated.

In addition, key safety information such as Serious Adverse Events (SAEs), deaths, and pregnancies from DTG single entity program studies ING114915 (FLAMINGO) and ING116070 (cerebrospinal fluid [CSF]) will be submitted. The estimated number of subjects as of 30 January 2013 who will have received a once-daily regimen of DTG+ABC/3TC in studies is approximately 700, which includes subjects from ART-naive and ART-experienced (INI-naive) populations.

Does the Agency agree with this approach to demonstrating the safety of (b) (4) DAVP response:

Please clarify how you plan to have the safety profile of the FDC drug product displayed in the label. Specifically, will the ADR table(s) in Section 6 of the PI only include those subjects who received ABC/3TC as background regimen? Do you plan to have two ADR tables, one for the naive and one for the treatment-experienced population? Do you envision including any descriptive safety data in the PI that would reflect safety profile of DTG when used with other background ARVs, especially for events such as renal AEs or other adverse events of special interest? Please refer to our request for submission of a draft label prior to the scheduled Tcon.

For the treatment naïve population, if your plan is to include only those who received ABC/3TC as background regimen, you may integrate the safety data from the Phase 3 trials. However, the P2b trial data should not be integrated with the P3 data.

For the treatment experienced population, the planned submission for the safety analysis differs from the treatment-naïve population in that you plan to include all subjects, regardless of the background regimen. This approach will lead to inconsistent labeling when compared to the naïve population, especially if you propose to have an ADR table for the treatment experienced population. However, if you plan to communicate the safety profile of DTG in treatment-experienced population (INSTI naïve) in a descriptive format (e.g. a paragraph), your proposed approach to include all subjects may be acceptable.

In summary, DAVP can provide you with additional advice after reviewing your draft label.

Sponsor Response:

Please refer to the draft USPI provided. We plan to present only SINGLE safety data in tabular ADR format.

We do not intend to present integrated data from the Phase III studies of the subjects who received DTG+ABC/3TC in tabular format.

Safety data from (b) (4) and SAILING subjects (treatment-naive and treatment-experienced, respectively) who received DTG with other background regimens will be described in the label text.

Please note, in relation to the Division’s comments to Question 4, that the analysis for the ISS is intended to support the USPI, the EU SmPC and the Canadian Product Monograph, as well other country-specific labeling. The presentation of data in the ISS (as indicated below) is not necessarily reflective of how the data would be presented in the USPI. We would like to discuss this further during the meeting.

SPRING-1		SPRING-2		SINGLE		Total
572/EPZ	EFV/ EPZ	572/ EPZ	RAL/ EPZ	572/ EPZ	Atripla	572/ EPZ

EPZ = EPZICOM

Discussion: Please see question 2.

DTG, ABC, and 3TC

5. The application will describe relevant safety information in high-level summaries to support the safety of each of the three active components of (b) (4) – DTG, ABC, and 3TC. The safety of (b) (4) reflects the safety of the individual actives without additive risk.

For DTG, safety information from clinical trials will support the safety of this component. This would include datasets from studies ING114467, ING113086, ING112276, and ING111762, as noted above.

For ABC and 3TC, the basis to support the safety of these components will be described by a review of post-marketing safety data, as well as updates from post-marketing safety monitoring. Because listed adverse events for ABC and 3TC have evolved over time, they will be described (and supported) by current approved labelling for ABC and 3TC. Much of this information will have been previously presented to the Agency via Development/Periodic Safety Update Reports and Risk Management Plans. The Sponsor believes this data will present the most contemporary overview of the clinical safety of these components and, hence, be relevant to the (b) (4) application.

Please note that data previously submitted to the approved applications for ABC and 3TC will not be resubmitted in this application but rather cross-referenced where appropriate.

Does the Agency agree with this approach to demonstrating the safety of each of the active components of (b) (4)

DAVP response: Yes

Sponsor Response:

Thank you.

General

6. Nonclinical, Clinical, and CMC (i.e., drug substance) information for DTG, ABC, and 3TC have been provided previously in applications submitted to and/or approved by the Agency, including ZIAGEN, EPIVIR, EPZICOM/KIVEXA, and most recently TIVICAY (dolutegravir). The Sponsor intends to cross-refer to the information in these applications where appropriate, and will capture our cross-reference strategy in m1.4.4, Cross Reference to Other Applications and Information Previously Submitted in Paper as follows:

Certain Nonclinical, Clinical, and CMC data for the active ingredients of (b) (4) – dolutegravir, abacavir sulfate (abacavir), and lamivudine – are incorporated by cross-reference into this application. The following applications and all amendments/supplements thereto are cross-referred for information related to the actives.

Application Number	Product	Submitted Approved/Active
NDA 020564	EPIVIR (lamivudine) Tablets	Submitted 29 Jun 1995 Approved 17 Nov 1995
NDA 020977	ZIAGEN (abacavir sulfate) Tablets	Submitted 24 Jun 1998 Approved 17 Dec 1998
NDA 021652	EPZICOM (abacavir sulfate and lamivudine) Tablets	Submitted 07 Oct 2003 Approved 02 Aug 2004
IND 075382	dolutegravir (GSK1349572), HIV Integrase Inhibitor	Submitted 24 Oct 2007 Active 13 Dec 2007
IND 114820	GSK2619619 (dolutegravir, abacavir sulfate, and lamivudine) Tablets	Submitted 07 Jun 2012 Active 02 Jul 2012
NDA 204790	TIVICAY (dolutegravir) Tablets	Submitted 16 Dec 2012 in review

References within various sections of this application to specific nonclinical and clinical study reports that were submitted to any of the above applications are linked to lists found in m2.4 and m2.5, as appropriate.

Does the Agency agree with this approach to cross-referencing?

DAVP response:

The approach is acceptable from the clinical and nonclinical perspective perspectives.

When cross-referencing CMC information from another IND or NDA, please specify the dates of the submissions which include the relevant information and clearly identify what information is being referenced (e.g., drug substance stability, manufacturing process for

a drug product intermediate, etc.). In addition, a cross-reference is not generally appropriate for the following information, which we recommend you included in the application:

- Physical or chemical attributes of the drug substance which are important for dosage form performance (e.g., characterization; justification of specification; etc.)
- The specification that is used for acceptance of the drug substance
- The analytical methods that will be used for acceptance of the drug substance
- Complete information on the manufacturing, release or stability testing, packaging, or labeling facilities for the drug substance

Sponsor Response:

We would like to discuss the Division's comments a bit more at the meeting to gain clarity on what is being requested with regard to CMC cross referencing.

Discussion: ViiV clarified that they are evaluating the NDAs that will be cross-referenced so that dates of submission can be provided for specific topics. DAVP stated this is very useful to avoid unnecessary questions where agreement has already been reached, or where the cross-referenced material was submitted in paper.

7. The (b) (4) NDA is currently targeted to be submitted in July 2013. It is our understanding from the regulations in PDUFA V that all new molecular entity (NME) applications submitted between 01 October 2012 and 30 September 2017 are subject to the new review program ("the Program"), whereby review of the application begins at the conclusion of a 60 calendar day filing review period. Non-NME applications are not subject to the Program; thus, review begins upon receipt of the application. The Sponsor considers (b) (4) to be a non-NME due to the following:

- The active ingredients ABC and 3TC are approved and marketed in the United States, both individually and in combination
- The application for the active ingredient DTG is currently under review with the Agency, and its action date will likely occur before the Agency has determined the fileability of the (b) (4) application. Therefore, DTG will also likely be an approved active by the time the (b) (4) application is filed.
- As all actives in (b) (4) may be approved by the time the (b) (4) application is filed, (b) (4) may be considered a new combination (chemical type 4) rather than a new chemical entity.

Therefore, the Sponsor believes that the (b) (4) NDA would not be subject to the 60 calendar day filing review period.

Based upon the information provided, would the Agency share its thoughts regarding the possibility of the (b) (4) NDA not being subject to the Program?

DAVP response:

The decision on whether or not an application is reviewed under the Program is made at the time of NDA submission. Therefore, if the NDA for abacavir/dolutegravir/lamivudine

arrives prior to the action date for DTG, it will likely be considered an NME and be subject to the 'Program'.

Sponsor Response:

Thank you for your comments. We have nothing further at this time.

8. The Sponsor is providing information to support its rationale regarding why the (b)(4) NDA submission should (b)(4)

Based upon the information provided, would the Agency share its thoughts regarding the possibility of the (b)(4) NDA (b)(4) ?

DAVP response:

We acknowledge your rationale for (b)(4). Please note that the determination whether to (b)(4) will be made (b)(4).

Sponsor Response:

Thank you for your comments. We have nothing further at this time.

9. The Sponsor's project team developing plans for a safety update to the NDA following the initial submission, plans which will in part depend upon the determination of the (b)(4) NDA's review status. The project team would like to discuss its safety update plans with the Agency's review team prior to the target July 2013 submission, most likely in May.

Does the Agency agree with this approach?

DAVP response: Yes, we agree to further discussions on the timing of the safety update in May.

Sponsor Response:

Thank you.

Pediatrics

10. The Sponsor intends to submit in the NDA for (b)(4) a request for a deferral from pediatric studies in subjects (b)(4), and a waiver from studies in subjects (b)(4). A brief summary of the justification will be provided in the briefing materials.

Does the Agency agree with this approach?

DAVP response: Yes

Sponsor Response:

Thank you.

CDISC, from 14 December 2012 submission (Serial No. 0007, Sequence No. 0009)

In addition to the questions above, the following questions were submitted 14 December 2012 (Serial No. 0007, Sequence No. 0009) as General Correspondence: Request for Comments and Advice on our proposed plan to provide suitable data

packages for a pivotal BE study and pivotal Phase III clinical studies in an acceptable format in the initial NDA submission of (b) (4)

11. For the GSK2619619 NDA submission, we intend to provide clinical efficacy, safety, and virology datasets for 3 dolutegravir pivotal Phase III studies and safety datasets for the Integrated Safety Summary (ISS). In addition, GSK intends to provide special efficacy datasets as outlined in the document “Efficacy Data Submission in ADaM Conversion for HIV Drugs”.

- **ING114467 48 Weeks**
 - **Datasets identical to those provided in NDA 204790**

- **ING113086 96 Weeks**
 - **Datasets updated from 48 Weeks provided in NDA 204790**

- **ING111762 48 Weeks**
 - **Datasets updated from 24 Weeks provided in NDA 204790**

- **ISS based on a February 2013 data cut-off**
 - **Updated from October 2012 data cut-off provided in NDA 204790**

GSK/ViiV Healthcare does not intend to provide clinical safety datasets for BE study ING114580 nor (b) (4)

Does the Agency agree with this proposal?

DAVP response:

We acknowledge your plan to submit your clinical datasets in the format identical to the DTG single drug entity NDA. We are also in agreement with your proposal to provide special efficacy datasets as outlined in the document “Efficacy Data Submission in ADaM Conversion for HIV Drugs”.

Sponsor Response:

Thank you.

12. The Phase III clinical data to be relied upon for GSK2619619 are similar to the data submitted in the dolutegravir NDA 204790 (see Question 2). The data structures that were provided in NDA 204790 for these Phase III clinical data are GSK standard (legacy) format with modifications in line with those requested by and agreed with the Agency during several conference call and correspondence exchanges post the 20 September 2012 pre-NDA meeting [for DTG single entity]. We propose to provide data structures in the NDA for GSK2619619 similar to those in the dolutegravir NDA 204790, i.e., GSK format (IDSL) with agreed modifications rather than the CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) structures as defined in the FDA's Study Data Specifications guidance document. This would include any updates to the NDA 204790 datasets during review of the application by the Agency.

This proposal will ensure consistency in data presentation across the two submissions, particularly with regard to study ING114467 48 Weeks, which is a key study for both applications.

A) Does the Agency agree with this proposal?

DAVP response: Yes

Sponsor Response:

Thank you. Please confirm that the response to the question around data formats is a commonly agreed response from both the clinical as well as statistical reviewers.

Discussion and post meeting comment:

DAVP stated the data format from NDA 204790 is acceptable for the clinical reviewers.

Post meeting comment: The data format is acceptable for the statistics reviewer as well.

B) Does the Agency foresee a need for including analysis programs (executable or non-executable), as part of the submission?

DAVP response:

Yes, please include the programs for the key efficacy outcomes, as well as outcome datasets.

Sponsor Response:

Thank you.

13. We intend to cross-refer to approved applications for abacavir and lamivudine for relevant study information and reports and do not intend to provide the reports again in the NDA for GSK2619619. Therefore, no datasets for abacavir and/or lamivudine-related studies will be provided in the GSK2619619 application.

Does the Agency agree with this proposal?

DAVP response: Yes

Sponsor Response:

Thank you.

ADDITIONAL COMMENTS:

1. We did not find any information regarding the dissolution method that you will be using for the FDC tablet (one method for all three APIs or separate ones for different APIs). Please note the following points regarding the development and validation of the dissolution method(s):

*a. **Dissolution Test:** The dissolution method report supporting the selection of the proposed dissolution test should be provided in the NDA. The dissolution report should include the following information:*

i. Solubility data for all the drug substances covering the pH range;

ii. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (i.e., 15, 20, 30, 45, & 60 minutes) and cover at least (b) (4) % of drug release of the label amount

- or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;*
- iii. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and*
 - iv. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test for each API, as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.)*
- b. Dissolution Acceptance Criterion(a): For the setting of the dissolution acceptance criterion(a) of your proposed drug product, the following points should be considered:*
- i. The dissolution profile data (i.e., 15, 20, 30, 45, & 60 minutes) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug product [i.e., specification sampling time point and specification value].*
 - ii. The in vitro dissolution profile should encompass the timeframe over which at least (b)(4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.*
 - iii. The selection of the specification time point should be where $Q = (b)(4)\%$ dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = (b)(4)\%$ dissolution occurs.*
 - iv. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).*

Sponsor Response:

We will provide the requested information in the NDA submission.

- 2. The general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when a protease or integrase inhibitor is boosted by including a cytochrome P450 inhibitor; in that case the cytochrome inhibitor will be listed directly after the drug that is being boosted. We recommend the following nomenclature for this product:*

*Tradename (abacavir, dolutegravir, and lamivudine) Tablets
600mg / 50mg / 300mg*

We recommend that you include an equivalency statement on the container labels such as, "Each film-coated tablet contains abacavir sulfate equivalent to 300 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine."

Sponsor Response:

Thank you, we will take this under advisement

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. To support this proposed indication, the Sponsor intends to show the efficacy of GSK2619619 in HIV-infected subjects through the following:
 - By establishing the bioequivalence of the GSK2619619 tablet, pivotal bioequivalence study (ING114580)
 - By demonstrating the efficacy of the DTG component in HIV-infected subjects based on data from the DTG single entity program
 - By presenting the broad indications currently approved for ABC, 3TC and the ABC/3TC combination product EPZICOM/KIVEXA as evidence that clinical efficacy of the ABC and 3TC components have been established for HIV-infected subjects
 - By summarizing the efficacy of the GSK2619619 dosing regimen through clinical data from subjects that were on a treatment arm of DTG 50 mg QD + ABC/3TC 600/300 mg in key relevant DTG studies:
 - Pivotal: ING114467 (n=414 through 48 weeks)
 - Supportive:
 - ING113086 (n=169 through 96 weeks)
 - ING112276 (n=17 through 96 weeks)
 - ING111762 (n=7 through 48 weeks)
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application
- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS was not needed.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In

any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

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

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

MANUFACTURING FACILITIES

To facilitate our inspectional process, 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.				

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

ViiV response to DAVP preliminary comments and the submitted Draft USPI

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

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/s/

DEBRA B BIRNKRANT
03/08/2013



NDA 205551

INFORMATION REQUEST

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abacavir sulfate, dolutegravir, and lamivudine, fixed-dose combination tablets, 600/50/300 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by March 14, 2014, in order to continue our evaluation of your NDA.

1. Provide the drug substance specifications that are used in the NDA for acceptance of each drug substance. We remind you that this information has been previously requested during the pre-NDA meeting.
2. Please provide data to demonstrate that the drug product is (b) (4)
3. We recommend that (b) (4) be included in the drug product specification until sufficient data from commercial batches are obtained. If the additional data definitely confirm that (b) (4) has no impact on the (b) (4) and the formation of the (b) (4), you may request elimination of the test for (b) (4). Please provide the updated drug product specifications.
4. Your proposal not to include the (b) (4) content in the drug product specification is acceptable. However, we recommend that you continue to monitor the (b) (4) content in tablet lots that are put on stability. At a minimum, we recommend testing at the initial time point and at expiry.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURawe
02/24/2014

From: Mosaddegh, Sohail
To: [Martha Anne Auld \(marthaanne.a.auld@gsk.com\)](mailto:marthaanne.a.auld@gsk.com)
Subject: : NDA 205551 - clarification needed for 23 Jan 2014 comment
Date: Thursday, February 20, 2014 1:04:00 PM
Attachments: [image001.png](#)
[image002.png](#)

Here is the clarification:

Question 3: Provide a summary table for the bioanalytical method validation for the bioanalytical method used in BE study ING114580 for each drug substance in the format provided below:

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

Sohail Mosaddegh, Pharm.D.
 Lieutenant Commander, USPHS
 Regulatory Health Project Manager
 FDA/CDER/OND/OAP/Division of Antiviral Products
 10903 New Hampshire Ave., Bldg. 22, Room 6223
 Silver Spring, MD 20993-0002
 Phone: (301) 796-4876

Fax: (301) 796-9883

Email: Sohail.Mosaddegh@FDA.HHS.GOV

From: Martha Anne Auld
Sent: Wednesday, January 29, 2014 4:35 PM
To: 'Mosaddegh, Sohail'
Subject: NDA 205551 - clarification needed for 23 Jan 2014 comment

Hi Sohail,

I hope all is well with you.

We would like to have clarification please on what the review team would like to receive for comment 3 from the 23 Jan 2014 communication for NDA 205551. Below please find the question that our team would like to ask.

To assist us in providing the appropriate response to the reviewer's question 3 (below), we respectfully request additional clarification. As part of the original submission (module 2.7.1, Appendix 15, Pgs 84-96), we provided a summary of the bioanalytical methods for each of the drug substances (dolutegravir, abacavir and lamivudine) that were validated in a variety of matrices. Additionally, section m2.7.1 details which studies the individual bioanalytical methods were used to support. We recognize that some, but not all, of the information being requested for the Table is detailed in this section, although links are provided to the respective method validation reports.

As multiple method validations are listed, it would be helpful to know which specific analytical methods the reviewer would like us to collate the additional information in the table format below.

Response to DAVP Comments of 23 January 2014
NDA 205551

Question 3 Provide a summary table for the bioanalytical method validation for each drug substance in the format provided below:

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

Thank you, Sohail, for your assistance. Have a good evening.

Kind regards,

Martha Anne

Martha Anne Auld, R.Ph.
Sr Dir Therapeutic Group
 US Therapeutic Groups
 RD Chief Regulatory Office

GSK
 5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States
Email marthaanne.a.auld@gsk.com
Internal 8/7 703 9347
Tel +1 919 483 9347
Mobile +1 919 928 6648



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/s/

SOHAIL MOSADDEGH
02/20/2014

From: Mosaddegh, Sohail
To: ["Martha Anne Auld"](#)
Subject: RE: NDA 205551 120D Safety Update Proposal of 16 Jan 2014
Date: Thursday, January 30, 2014 11:39:00 AM
Attachments: [image001.png](#)

Hello: your proposal is acceptable.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

From: Martha Anne Auld [mailto:marthaanne.a.auld@gsk.com]
Sent: Sunday, January 26, 2014 9:56 AM
To: Mosaddegh, Sohail
Subject: NDA 205551 120D Safety Update Proposal of 16 Jan 2014

Hi Sohail,

I hope that you are doing well.

We are in the process of generating the (b) (4) 120D safety update. We appreciate the feedback that you provided last week (23 Jan) regarding the update. In our 16 Jan response to 3 Jan FDA filing comments for (b) (4) we included a proposal for #3. The text is provided below (full response is attached; if a WORD document would be helpful, please let me know).

3. Postmarketing safety reports (line listing and case narratives for serious events) should be submitted in the Safety Update Report.

Company Response

The Sponsor wishes to propose that the requested information is limited to post marketing safety reports for TIVICAY only (i.e., not for EPZICOM®/KIVEXA® without TIVICAY, ZIAGEN® or EPIVIR®), received by the Sponsor from 01June2013 (the day after the data lock point [DLP] of 31 May 2013 for the ISS and m.2.7.4 for the NDA) to 20 Jan 2014 (DLP for the Day 120 Safety Update Report). We will also present as a separate subset any cases that involve DTG+ABC/3TC.

The Sponsor proposes not to include any post marketing safety reports for EPZICOM/KIVEXA, ZIAGEN or EPIVIR without TIVICAY because the Sponsor believes that these cases would be of no additional value in the evaluation of the NDA for the DTG/ABC/3TC FDC.

Please check with the review team regarding the acceptability of our proposal. We are progressing the update as proposed above and would like to ensure that our submission is acceptable to the

team.

Many thanks for your assistance with this, Sohail.

Kind regards,

Martha Anne

Martha Anne Auld, R.Ph.
Sr Dir Therapeutic Group
US Therapeutic Groups
RD Chief Regulatory Office

GSK

5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States

Email marthaanne.a.auld@gsk.com

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/s/

SOHAIL MOSADDEGH
01/30/2014

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: January 23, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Comments on proposed 120 day Safety Update

Your proposal for the “120 Day Safety Update” as you have outlined below is acceptable:

“Discussions regarding a safety update for NDA 205,551 were deferred at the time of the February 27, 2013 Type B, Pre-NDA Meeting. The following proposals are provided in order to reach agreement with review team members regarding the reporting period, submission timing and content of the 120 Day Safety update for NDA 205,551.

Reporting Period and Submission Timing for 120 Day Safety Update

The data cutoff for the 120 day safety update (January 20, 2014) is proposed to be 90 calendar days post submission of NDA 205,551 which was submitted on October 22, 2013. The reporting period for this 120 day update is May 31, 2013 through January 20, 2014. The submission date is proposed for February 19, 2014.

Content for 120 Day Safety Update

Please note at NDA submission, studies ING114580 (pivotal bioequivalence), (b) (4) and ING116898 (Ca/Fe DDI study) were complete with full study reports provided, there are no safety updates for these studies.

For the reporting period described above, we propose to submit the following:

- *Listings and a brief discussion of serious adverse events (SAEs), deaths and pregnancies will be provided. Data will be pulled from the GlaxoSmithKline's (GSK) GCSP's OCEANS safety database. These data will not have undergone a complete quality assurance review.*

Safety data as described above will be provided for the following ongoing studies included in the NDA submission:

- *ING114467 (SINGLE)*
- *ING112276 (SPRING-1)*
- *ING113086 (SPRING-2)*
- *ING111762 (SAILING)*
- *ING114915 (FLAMINGO)*
- *ING116070 (CSF)*
- *ING112578 (P1093)*
- *ING117172 (ARIA).*

Please note that we propose not to include case report tabulations (CRT) packages and case report forms (CRFs) for this safety update.”

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
01/23/2014



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: January 23, 2014

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: CMC, Biopharmaceutic, Product Quality Microbiology comments

CMC:

1. The general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when one active ingredient is boosted by including a cytochrome P450 inhibitor; in that case the cytochrome inhibitor will be listed directly after the drug that is being boosted. We recommend that this product be named: Trademark (abacavir, dolutegravir and lamivudine) Tablets 600mg / 50mg /300mg . Please submit revised container labels and prescribing information.

Biopharmaceutics:

2. Submit the following PK data from the BE Study (ING114580) in SAS Transport format in two separate files as described below:
 - a. SUBJ SEQ PER TRT C_{max} AUC_t AUC_{inf} T_{max} T_{1/2} K_{el}
 - b. SUBJ SEQ PER TRT C1 C2 C3 Cn
3. Provide a summary table for the bioanalytical method validation for each drug substance in the format provided below:

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

4. Product Quality Microbiology:

Your application provides a suitable approach and justification for microbial limits testing using a (b) (4) strategy. However, changes in drug product release specifications must be made by submitting a supplemental application for a post-approval manufacturing change. For your NDA, you should revise your list of release specifications to omit the footnote listed as Note #7, and plan to submit a supplemental application if you wish to remove the (b) (4) /microbial limits test from release specifications after 30 batches. For more information on post-approval changes, see FDA's Guidance for Industry: Changes to an Approved NDA or ANDA

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>).

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
01/23/2014

From: Mosaddegh, Sohail
To: [Martha Anne Auld \(marthaanne.a.auld@gsk.com\)](mailto:marthaanne.a.auld@gsk.com)
Subject: FW: Questions for Team - NDA 204790 and 205551
Date: Thursday, January 23, 2014 4:05:00 PM
Attachments: [image001.png](#)

Hello:
Your proposal is acceptable.
Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

From: Martha Anne Auld [<mailto:marthaanne.a.auld@gsk.com>]

Hi Sohail,
I hope that you are doing well today.
Apologies, but I wanted to provide a little more detail to the question I sent on 10 Jan. Please see added text to the first paragraph from my 10 Jan email (highlighted below).



I hope the additional detail is helpful to the review team. Thank you for your help, Sohail. Have a good afternoon.
kind regards,

Martha Anne

From: Martha Anne Auld

Subject: Questions for Team - NDA 204790 and 205551

Hi Sohail,

I hope that you are doing well & that you've had a good week.

Would you mind asking the review team about the following items for us? We need a little assistance to help with our responses.

NDA 204790

(b) (4)

NDA 205551

- You kindly provided labeling comments on 31 Dec and in the filing correspondence of 3 Jan?

Two questions:

- Will there be any additional labeling comments provided prior to 17 Jan?
- If the team would like revised labeling to be provided based upon responses to the 31 Dec & 3 Jan comments, would it be possible for us to provide revised labeling during the

week of 20 - 24 Jan rather than 17 Jan?

Your help is appreciated, Sohail. I hope that you have a nice weekend!

Kind regards,

Martha Anne

Martha Anne Auld, R.Ph.
Sr Dir Therapeutic Group
US Therapeutic Groups
RD Chief Regulatory Office

GSK

5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States

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/s/

SOHAIL MOSADDEGH
01/23/2014



NDA 205551

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

ViiV Healthcare Company
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

ATTENTION: Jeffrey S. Troughton, M.S., RAC
Director, Therapeutic Group, Global Regulatory Affairs

Dear Mr. Troughton:

Please refer to your New Drug Application (NDA) dated and received October 22, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dolutegravir, Abacavir Sulfate and Lamivudine Tablet, 50 mg/600 mg/300 mg.

We also refer to your correspondence dated and received October 23, 2013, requesting review of your proposed proprietary name, Triumeq. We have completed our review of the proposed proprietary name Triumeq, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your October 23, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Sohail Mosaddegh at (301) 796-4876.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
01/19/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/19/2014



NDA 205551

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

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated received October 22, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for abacavir sulfate, dolutegravir, and lamivudine, fixed-dose combination tablets, 600/50/300 mg.

We also refer to your amendments dated: October 22, 2013, October 23, 2013, and December 17, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 22, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 22, 2014.

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

We request that you submit the following information:

CLINICAL

1. Because the pivotal clinical trials have multinational sites, please provide a rationale for the applicability of foreign data to U.S. populations and practice of medicine.
2. Please submit a Coding Dictionary used for mapping investigator verbatim terms to preferred terms.
3. Postmarketing safety reports (line listing and case narratives for serious events) should be submitted in the Safety Update Report.
4. Case narratives for adverse events leading to discontinuations may be requested during the review cycle if deemed necessary.
5. Please refer to sections 6 and 14 of your proposed labeling. The tables under these sections should reflect the longest use data for DTG and its comparator, (b) (4). Please revise the tables accordingly. We do not agree with including (b) (4) and Week 96 data ((b) (4)).
6. Safety and efficacy results displayed in the label should not include subjects who were enrolled from sites that were excluded during the original NDA review (e.g. Russian sites). Please revise the tables accordingly.

Please respond only to the above requests for information, no later January 17, 2014. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
01/03/2014



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: December 31, 2013

NDA: 205,551

Drug: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine 600/50/300 mg) tablets

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Formatting comments for labeling

Please refer to your labeling submitted on October 22, 2013.

1. In the table of contents, delete the white space above the "FULL PRESCRIBING INFORMATION : CONTENTS*" this will align the text in right column with the text in the left column.
2. There should not be text between a section headings and a subsection heading. Please see 6 Adverse Reactions and 7 Drug Interactions.
3. White space should be present before each major heading in HL. The space between the product title and Initial U. S. approval date needs to be removed. White space should separate the Initial US approval information and the Boxed Warning.
4. In the Boxed Warning in Highlights: heading should be centered; the statement ""**See full prescribing information for complete boxed warning.**"" should be centered
5. The clinical microbiology review team has informed sponsor's that the following cross reference be used when referencing their section of the labeling, "see Microbiology 12.4, instead of CLINICAL PHARMACOLOGY 12.4.
6. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following

verbatim statement or appropriate modification should precede the presentation of adverse reactions:

- a. “The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
12/31/2013



NDA 205551

NDA ACKNOWLEDGMENT

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Auld:

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: GSK2619619 (abacavir sulfate, dolutegravir, and lamivudine
600/50/300 mg) tablets

Date of Application: October 22, 2013

Date of Receipt: October 22, 2013

Our Reference Number: NDA 205551

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 21, 2013, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SOHAIL MOSADDEGH
11/15/2013