CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210192Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 210192	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: JULUCA Established/Proper Name: dolutegravir and rilpivirine Dosage Form: Tablets; Fixed –Dose Combination		Applicant: ViiV Healthcare Company Agent for Applicant (if applicable):
RPM: Nina Mani		Division: Antiviral Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
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	
• Proposed action Date is November 21, 2017 • User Fee Goal Date is December 1, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 4- New Combination
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ 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	☒ No ☐ 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 11/21/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	August 24, 2017 August 23, 2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ July 6, 2017 & DMEPA: ☒ September 17, 2017 & October 16, 2017 DMPP/PLT (DRISK): 10/30/2017 ☒ OPDP: ☒ 10/31/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ In OPQ 11.12.17 Review Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	July 10, 2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC November 1, 2017 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	See the Action Package
❖ 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	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg March 22, 2017
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/20/17 (MDR)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/16/17 & 11/20/17
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/8/17 & 11/20/17
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 104 of the MDR/Division Director Summary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None DBRUP Consult Review: August 30, 2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 11/3/17
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 10/26/17 & 11/20/17
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 11/7/17 & 11/20/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/3/17 & 11/20/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 9/22/17

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/30/17 & 11/20/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 11/12/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/12/17
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

KAREN D WINESTOCK
11/22/2017

Winestock, Karen

From: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Sent: Monday, November 20, 2017 4:19 PM
To: Winestock, Karen; Martha Anne Auld
Subject: RE: NDA 210192 - FDA's 11/20/17 Labeling Proposal

Good afternoon Karen,

We agree with all of the Division's revisions, including the change you noted in your previous email regarding the pregnancy registry information in the PPI. Our labeling group is doing a final QC and I will forward a clean version once I receive it in case we do find any discrepancies. Should we formally submit this to the NDA?

We also note that the last revision date is 11/2017 (whereas the target action date is 12/1/2017). Can you share your thoughts on whether our team should be prepared for an action on NDA 210192 this week? This would assist us with planning and to ensure that appropriate staff are in the office during the holiday week if necessary.

Warm Regards,
Jeff

From: Winestock, Karen [mailto:Karen.Winestock@fda.hhs.gov]
Sent: Monday, November 20, 2017 3:07 PM
To: Martha Anne Auld <marthaanne.a.auld@gsk.com>; Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: NDA 210192 - FDA's 11/20/17 Labeling Proposal

EXTERNAL

Good afternoon,

The FDA's latest labeling proposal is attached. If you agree with the proposals, please send me your response via email as soon as possible, but no later than
8:00 am, Tuesday, November 21, 2017.

Thanks,
Karen

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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/s/

KAREN D WINESTOCK
11/20/2017

Winestock, Karen

From: Winestock, Karen
Sent: Monday, November 20, 2017 3:07 PM
To: Martha Anne Auld; jeffrey.s.troughton@gsk.com
Subject: NDA 210192 - FDA's 11/20/17 Labeling Proposal
Attachments: FDA's 11.20.17 PI and PPI revisions.2.docx

Good afternoon,

The FDA's latest labeling proposal is attached. If you agree with the proposals, please send me your response via email as soon as possible, but no later than
8:00 am, Tuesday, November 21, 2017.

Thanks,
Karen

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

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/s/

KAREN D WINESTOCK
11/20/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 8, 2017

Application Number: NDA 210192, NDA 205551/S-11, NDA 204790/S-14
Product Name: JULUCA, TRIUMEQ, and TIVICAY
Sponsor/Applicant Name: ViiV Healthcare Company

Subject: Hepatoxicity labeling proposal

FDA's Division of Antiviral Products Participants
1. Debra, Birnkrant, MD, Director
2. Jeffrey S. Murray, MD, MPH, Deputy Director
3. Poonam Mishra, MD, MPH, Deputy Director for Safety
4. Kim Struble, PharmD, Clinical Team Lead
5. Yodit Belew, MD, Clinical Reviewer
6. Karen Winestock, Chief, Project Management Staff

Applicant Participants
ViiV Healthcare Company/GlaxoSmithKline
1. Martha Anne Auld – Senior Director, Global Regulatory Affairs (GSK)
2. Karen Grainger – Head of Regulatory Affairs (ViiV)
3. Nassrin Payvandi PhD, PV Dip – Vice President, Safety and Pharmacovigilance, EU QPPV (ViiV)
4. Kimberly Y. Smith MD, MPH – Vice President and Head, Global Research and Medical Strategy (ViiV)
5. Jeffrey S. Troughton – Director, Global Regulatory Affairs (GSK)
6. Lloyd Curtis from Safety

1.0 BACKGROUND:

On November 7, 2017, the Agency sent ViiV Healthcare their proposed changes to the labeling for JULUCA, TRIUMEQ, and TIVICAY. The major proposal was related to revising or updating the WARNINGS AND PRECAUTIONS section for all dolutegravir-containing labels to reflect that "Hepatoxicity" has been observed with the use of dolutegravir-containing regimens; the proposal also included the following statement "Drug-induced liver injury leading to liver transplant has also been reported with dolutegravir use" based on a recently published case report. ViiV disagreed with the Agency's proposal and rationale for including this information in the labeling. ViiV requested this telephone conference to discuss their position.

Prior to the meeting ViiV, submitted additional information to support their rationale. Please see the attached documents.

2.0 DISCUSSION:

ViiV agreed with most of the Agency's proposed revisions. However, they wanted to discuss the liver transplant case. Based on their assessment, the patient in the published literature report

appeared to be the same patient ViiV had included in their safety report submitted to the FDA. The age, gender, race, location, and increase in ALT were the same. In addition, one of the co-authors of the literature article was involved in treating the patient and is listed in the safety report. ViiV provided additional information on the patient's prior HIV therapy. Prior to receiving TRIUMEQ, the patient's ALT and AST had increased while receiving another abacavir containing regimen. She was switched to another regimen and her ALT stabilized. She was switched to TRIUMEQ which led to an increase in her ALT. She eventually needed a liver transplant. ViiV believed the rechallenge with an abacavir containing regimen may have led to the need for a liver transplant.

Based upon the information obtained to date, ViiV did not want to include the liver transplant information in the JULUCA and TIVICAY prescribing information.

FDA discussed the discrepancies (i.e. two liver transplants, patient receiving TRIUMEQ before it was approved) they had identified in the information provided in the safety report. ViiV acknowledged that the safety reporting they had received contained several errors and confirmed that clear narratives had not been submitted by the physician; therefore, they could not confirm or clarify many of the discrepancies, including the statement that the patient had received TRIUMEQ in 2013.

The FDA pointed out that based on reviews of other postmarketing reports received, there is evidence that patients receiving a dolutegravir containing regimen have experienced serious hepatoxicity, so ViiV should not conclude the liver transplant event was related to abacavir use. The Agency further stated that unlike the event with TRIUMEQ, the patient's previous history of elevation in liver serum enzymes with abacavir or other ARV use appear to have improved once switching to a different regimen without leading to liver failure.

The Agency recommended ViiV try to obtain the patient's hospital records to clarify the discrepancies in the current information. ViiV agreed to revise the WARNINGS AND PRECAUTIONS language to indicate that the case under discussion occurred with use of TRIUMEQ, instead of dolutegravir. ViiV will submit a revised label for TIVICAY, JULUCA, and TRIUMEQ.

3.0 ACTION ITEMS:

1. ViiV will try to obtain the hospital records for the patient.
2 ViiV will submit a revised labeling proposal to the Agency on November 13, 2017.

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/s/

KAREN D WINESTOCK
11/17/2017

Winestock, Karen

From: Winestock, Karen
Sent: Thursday, November 16, 2017 10:56 AM
To: jeffrey.s.troughton@gsk.com
Subject: NDA 210192 FDA's 11.16.17 Proposed PI & PPI
Attachments: 210192.FDA's.11.16.17 PPI.doc; NDA 210192_FDA's.11.16.17.PI.docx

Hello Again,

The labeling for JULUCA is attached. We would like to receive your response by Friday, November 17, 2017. Yes, you may email me ViiV's proposal on Friday and submit the official version on Monday. If you have questions, please feel free to contact me.

Regards,

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

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/s/

KAREN D WINESTOCK
11/16/2017

Winestock, Karen

From: Winestock, Karen
Sent: Wednesday, November 08, 2017 1:11 PM
To: 'Jeff Troughton'
Subject: RE: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

Hello Jeff,

The following information is correct:

Corrected Output (1 Sept 2017 Info Amendment)
-0.6 (-1.7, 0.6)

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

From: Winestock, Karen
Sent: Tuesday, November 07, 2017 6:15 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: RE: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

Hello Jeff,

My response to questions 1 and 2 are below. I am waiting for the review team to provide a response for comment 3.

Thanksgiving is November 23, 2017, will GSK be closed prior to Thursday, November 23, 2017?

Karen

From: Jeff Troughton [mailto:jeffrey.s.troughton@gsk.com]
Sent: Tuesday, November 07, 2017 3:02 PM
To: Winestock, Karen <Karen.Winestock@fda.hhs.gov>
Subject: RE: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

Hi Karen,

Thank you for confirming. In addition, regarding the labeling a few questions for clarification:

- As November 12 is a Sunday is the Division amenable to receiving our revised labeling on Monday November 13? We will need it by 11:00 am.

- Can the Division confirm if revised labeling for Tivicay sNDA S-014 should also be updated for consistency as well? Please see my email for Tivicay.

(b) (4)

[redacted]

Comparison of Adjusted Difference in Proportion for Snapshot Virological Failure at Week 48 (Pooled Data) (Uncorrected values in original Submission vs. corrected values from 1 September 2017 Information Amendment)

	Adjusted Difference in Proportion (95% CI)	
Source Table	**Uncorrected Output (Original Submission)**	**Corrected Output (1 Sept 2017 Info Amendment)**
2.183 Pooled Data	(b) (4) [redacted]	**-0.6 (-1.7, 0.6)**

Best Regards,
Jeff

From: Winestock, Karen [mailto:Karen.Winestock@fda.hhs.gov]
Sent: Tuesday, November 07, 2017 1:41 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: RE: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

EXTERNAL

Hello Jeff,

At this time the Agency does not have any PMR or PMCs for JULUCA.

Best,
Karen
6-0834

From: Jeff Troughton [mailto:jeffrey.s.troughton@gsk.com]
Sent: Tuesday, November 07, 2017 1:20 PM
To: Winestock, Karen <Karen.Winestock@fda.hhs.gov>
Subject: RE: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

Thank you Karen –

I am confirming receipt. I have forwarded to the team.

I also noted that the filing communication indicated that if necessary, any postmarketing commitments / requirements would be communicated by 8 November. Are you able comment whether the Agency is planning to propose any postmarketing commitments?

Best Regards,
Jeff

From: Winestock, Karen [mailto:Karen.Winestock@fda.hhs.gov]
Sent: Tuesday, November 07, 2017 12:58 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale

EXTERNAL

Hello Jeff,

Attached are the FDA's latest PI and PPI revisions. We would like to receive your revised labeling no later than, November 12, 2017. If you have questions, please feel free to contact me.

Best

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

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/s/

KAREN D WINESTOCK
11/08/2017

Winestock, Karen

From: Winestock, Karen
Sent: Tuesday, November 07, 2017 12:58 PM
To: jeffrey.s.troughton@gsk.com
Subject: NDA 210192 Juluca - FDA's 11.7.17_PI and PPI Proposed Revisions and Hepatoxicity Rationale
Attachments: FDA's hepatoxicity rationale final for JULUCA.doc; FDAs. 11.7.17 JULUCA.proposed USPI.docx; JULUCA NDA 210192.FDA. PPI_11.7.17.docx

Hello Jeff,

Attached are the FDA's latest PI and PPI revisions. We would like to receive your revised labeling no later than, November 12, 2017. If you have questions, please feel free to contact me.

Best

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov

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/s/

KAREN D WINESTOCK
11/07/2017

From:	Jeff Troughton
To:	Mani, Nina
Cc:	Winestock, Karen
Subject:	RE: NDA 210192 JULUCA & NDA 204790 S14 TIVICAY: FDA Labeling Revisions
Date:	Monday, October 23, 2017 1:13:25 PM
Attachments:	image001.png

Hi Nina,

Thank you for the comments. I am confirming receipt.

Best Regards,
Jeff

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Monday, October 23, 2017 1:06 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Cc: Winestock, Karen <Karen.Winestock@fda.hhs.gov>
Subject: RE: NDA 210192 JULUCA & NDA 204790 S14 TIVICAY: FDA Labeling Revisions

EXTERNAL

Hi Jeff:

Kindly acknowledge receipt of the attached Word and PDF versions for your teams' review. For both labelings, please accept all revisions you agree with and only leave in track changes those that need further discussion.
Also, please ensure that you align the two labels unless otherwise noted.

Kindly submit your response to the NDAs by **October 31, 2017**.

Regards,
Nina

Nina Mani, PhD, MPH
Senior Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

NOTICE:

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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/s/

NINA MANI
10/23/2017

From: Jeff Troughton
To: Mani, Nina
Subject: RE: NDA 210192 JULUCA (dolutegravir and rilpivirine) - Labeling Revisions #1
Date: Thursday, October 05, 2017 2:15:57 PM

Hi Nina,

Thank you. I am confirming receipt.

Best Regards,
Jeff

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, October 05, 2017 2:10 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: RE: NDA 210192 JULUCA (dolutegravir and rilpivirine) - Labeling Revisions #1

EXTERNAL

Hi Jeff:

Kindly acknowledge receipt of the attached revisions (PDF and Word) to the USPI and Patient Information, and container label for your team's review.
Submit your response by **COB, Wednesday October 11, 2017,** and only include comments or edits that are new, accepting all other edits.

Regards,
Nina

From: Jeff Troughton [mailto:jeffrey.s.troughton@gsk.com]
Sent: Friday, September 29, 2017 4:34 PM
To: Mani, Nina
Subject: RE: NDA 210192 JULUCA (dolutegravir and rilpivirine) - Request for Review Status Update

Hi Nina –

Thank you for your helpful feedback. We will look forward to the labeling revisions next week.

Best Regards,
Jeff

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, September 29, 2017 4:08 PM
To: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: RE: NDA 210192 JULUCA (dolutegravir and rilpivirine) - Request for Review Status Update

EXTERNAL

Hi Jeff:

We have had our midcycle review and do not have any issues we'd like to discuss at the current time.
I did want to alert you that we will be sending Juluca labeling revisions beginning late next week, asking for a one week turnaround.
Comments on Tivicay will be forthcoming following the second round of Juluca comments.

Regards,
Nina

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/s/

NINA MANI
10/05/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/13/2017

TO: Office of New Drugs
Division of Clinical Pharmacology IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 210192

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Analytical		

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/s/

ANGEL S JOHNSON
09/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210192

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

ViiV Healthcare Company
Five Moore Drive, PO Box 13398
5.5100.5B
Research Triangle Park, NC 27709

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

Dear Mr. Troughton:

Please refer to your New Drug Application (NDA) dated and received June 1, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dolutegravir and Rilpivirine Tablets, 50 mg/25 mg.

We also refer to your correspondence dated and received June 7, 2017, requesting review of your proposed proprietary name, Juluca.

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

If any of the proposed product characteristics as stated in your June 7, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Nina Mani, Regulatory Project Manager in the Office of New Drugs, at 240-402-0333.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
08/23/2017

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210192

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

ViiV Healthcare Company
Attention: Jeffrey S. Troughton, MS, RAC
Director, Therapeutic Group, Global Regulatory Affairs
5 Moore Drive, PO Box 13398
5.5100.5B
Research Triangle Park, NC 27709

Dear Mr. Troughton:

Please refer to your New Drug Application (NDA) dated and received June 1, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for JULUCA (dolutegravir and rilpivirine), tablet (50 mg/25 mg).

We also refer to your amendments dated June 6, 2017, June 13, 2017, June 30, 2017 and July 6, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 1, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 8, 2017.

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

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Nina Mani, Senior Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{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
07/20/2017

From:	Martha Anne Auld
To:	Mani, Nina
Cc:	Jeff Troughton
Subject:	RE: NDA 210192 (JULUCA): CP IR
Date:	Friday, July 07, 2017 2:24:28 PM
Attachments:	image002.png

Hi Nina,
In Jeff's absence, I acknowledge receipt of the clin pharm information request. We will get back to you early next week if there are any questions from our clin pharm colleagues.
Thank you, Nina and have a nice weekend.

kind regards,

Martha Anne

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, July 07, 2017 1:16 PM
To: Martha Anne Auld <marthaanne.a.auld@gsk.com>
Cc: Jeff Troughton <jeffrey.s.troughton@gsk.com>
Subject: NDA 210192 (JULUCA): CP IR

EXTERNAL

Hi Jeff:

Kindly acknowledge receipt of the following Clinical Pharmacology request for information.

1. Please submit subject level pharmacokinetic data for study 201674.
2. Please submit bioanalytical method validation reports for efavirenz and nevirapine.
3. The bioanalytical report for study 201676 states that the validated method P1170.02 (issued 14 August 2013) was used for dolutegravir quantitation. Currently, you have submitted method validation reports for P1170.0 and P1170.01, but not P1170.02. Please clarify the differences between P1170.02 and the submitted methods.

Please submit the requested information by **July 21, 2017**.

Regards,
Nina

Nina Mani, PhD, MPH
Senior Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22

Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

NOTICE:
Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

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/s/

NINA MANI
07/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 123306

MEETING MINUTES

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Jeffrey S. Troughton, MS, RAC
Director, Infectious Disease, Global Regulatory Affairs
5 Moore Drive, P.O. Box 13398
5.5100.5B
Research Triangle Park, NC 27709

Dear Mr. Troughton:

Please refer to your Pre-Investigational New Drug Application (PIND) file for GSK3365791, dolutegravir and rilpivirine, fixed dose combination tablet, 50 mg/25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 22, 2017. The purpose of the teleconference was to discuss the content and format for a new drug application (NDA) for GSK3365791.

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

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 22, 2017
Meeting Location:	Teleconference
Application Number:	PIND 123306
Product Name:	GSK3365791, dolutegravir and rilpivirine
Proposed Indication:	treatment of human immunodeficiency virus-1 (HIV-1) infection in virologically-suppressed (HIV-1 RNA <50 copies/mL) (b) (4) (b) (4)
Sponsor/Applicant Name:	ViiV Healthcare Company
Meeting Chair:	Debra Birnkrant, MD
Meeting Recorder:	Linda C. Onaga, MPH

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
2. Poonam Mishra, MD, MPH, Deputy Director of Safety, DAVP
3. Kimberly Struble, PharmD, Clinical Team Lead, DAVP
4. Shirley Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology, Division of Clinical Pharmacology IV
5. Guoxing (Greg) Soon, PhD, Biometrics Team Lead Office of Biostatistics, Biometrics IV
6. Mushfiqur Rashid, PhD, Biometrics Reviewer
7. Karen Winestock, Chief, Project Management Staff, DAVP
8. Nina Mani, PhD, MPH, Senior Regulatory Project Manager, DAVP
9. Linda C. Onaga, MPH, Senior Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

ViiV Healthcare:

1. Martin Gartland, PhD – Vice President, Medicine Development
2. Karen Grainger – Director, Regulatory Affairs
3. Keith Pappa, PharmD – Director, Clinical Development
4. Kimberly Y. Smith MD, MPH – Vice President and Head, Global Research and Medical Strategy
5. Allen Tenorio, MD – Director, Clinical Development
6. Mark Underwood, PhD – Program Virologist, Clinical Virology and Immunology
7. Brian Wynne, MD – Project Physician Lead, Dolutegravir

GlaxoSmithKline
8. Martha Anne Auld – RPh, Senior Director, Global Regulatory Affairs
9. Lloyd Curtis, MA, BM, BCh, MRCP – Medical Director, Global Clinical Safety and Pharmacovigilance
10. Miles Dunn, MA, Manager of Statistical Programming
11. Naomi Givens, MSc – Director, Statistics Programming and Data Strategy
12. Rashmi Mehta, PhD – Director, Clinical Pharmacology Modeling Simulation
13. Jeffrey S. Troughton, MS, RAC – Director, Global Regulatory Affairs

Janssen Research and Development LLC
14. Kati Vandermeulen, MSc – Senior Director, Global Regulatory Affairs and Edurant Compound Development Team Leader

1.0 BACKGROUND

ViiV Healthcare, in partnership with Janssen, is developing GSK3365791, a fixed dose combination tablet containing dolutegravir and rilpivirine. Tivicay (dolutegravir) is an integrase inhibitor approved on August 13, 2013 for the treatment of HIV-1 infection. Edurant (rilpivirine) is a non-nucleoside reverse transcriptase inhibitor approved on May 20, 2011 for the treatment of HIV-1 infection. GSK3365791 is being developed as a complete regimen for the treatment of HIV-1 infection in virologically suppressed (b) (4) ViiV Healthcare will be the sponsor of the development program.

On March 3, 2017, ViiV submitted a Notification of Intent to the Agency to Submit an Application with Rare Pediatric Disease Priority Review Voucher. This submission is currently under review within the Agency.

The purpose of the meeting is to discuss the content and format of a planned new drug application (NDA) for GSK3365791.

FDA sent preliminary comments to ViiV on March 17, 2017. After reviewing the Division's preliminary comments, ViiV requested the face-to-face meeting be converted to a teleconference. At ViiV's request, the teleconference discussion focused on the Division's response to question 18, and the Division's Additional Clinical Comment.

2.0 DISCUSSION

2.1. Statistical/Datasets

Question 18: ***As with previous NDA submissions, the Sponsor proposes to not include SAS Programs in the planned submission.***

Does the Division agree?

FDA Response to Question 18: We do not agree. Please submit SAS programs with descriptions of input data sets.

ViiV's Response: *Thank you for your response. We propose to submit SAS programs in ASCII text format for the ADaM datasets and the primary and secondary analyses for Phase III studies 201636 and 201637, as well as pivotal bioequivalence study 201676 as per section 4.1.2.10 of the FDA Study Data Technical Conformance Guide (November 2016). Descriptions of all SDTM and ADaM datasets included in the submission will be provided as part of the CRT package. Does the Agency agree?*

Discussion: The Division agrees with ViiV's proposal to submit SAS programs. The Division stated that they are interested in the information presented in Tables 8-12 of the briefing package, because the Division needs to be able to reproduce this data.

Additional FDA Comment:

Clinical

- We noted that the reported AEs for psychiatric-related events, including suicidal ideation/behavior or thoughts were significantly higher than previously reported for the individual products including dolutegravir, rilpivirine and efavirenz. Please provide your planned analyses (sub-analyses and/or sensitivity analyses) to evaluate the various psychiatric-related AEs to further understand the apparent higher incidences reported during the SWORD trials. Please submit this information prior to the NDA submission.

ViiV's Response: *We have not observed that the reported AEs for psychiatric events are higher in the SWORD studies than for previous studies with the individual drugs. The incidence of psychiatric events in the pooled analysis for the SWORD studies was 12% for the DTG/RPV group compared with 6% in the CAR group. There were 3 (<1%) patients in the DTG/RPV group who reported suicidal ideation and 1 attempted suicide, compared with 2 (<1%) patients with suicidal ideation and 1 attempted suicide in the CAR group.*

These results are comparable to examples of switch studies with DTG or RPV. The incidence of events in STRIIVING (201147) is very similar (13% for the DTG arm and 3% for the CAR arm. Being an open-label switch study, STRIIVING is the most appropriate study for comparison of DTG.

In study GS-US-264-0106, a phase III, randomized, open-label switch study from a PI-based regimen to an RPV-based fixed dose combination the incidence of psychiatric disorders in the RPV group was 19.6%, compared with 6.3% in the 'Stay on background' (SBR) group. The incidence of these events in the previous Phase III studies of DTG or RPV is also higher than observed in SWORD studies (see attached tables).

Psychiatric events including suicidal ideation and behaviors are AEs of special interest for the DTG/RPV combination and will be analyzed for incidence, severity, relationship to drug and outcome in the individual CSRs. In the pooled datasets more detailed analysis of these events such as depression (including all preferred terms containing 'depression', 'depressed mood', 'depressive', 'hypomania' or 'bipolar'), suicidality (including all preferred terms containing 'suicide', 'suicidal' or 'intentional self-injury') as well as insomnia,

nightmare/abnormal dreams and anxiety events will be presented. These analyses will include onset and duration, seriousness, relationship to drug, maximum severity, whether leading to withdrawal, fatalities, number of occurrences and outcome. Subgroup analyses including gender and previous medical history will also be available.

Does this planned analysis address the Agency's concern?

Discussion: The Division reviewed the additional background material provided by ViiV. The Division referred to Appendix 3, page 42 of the briefing package, where suicidal ideation was 8% higher than seen in other clinical trials. The Division asked ViiV to comment on whether they analyzed the data using all cause adverse events or treatment related adverse events.

ViiV stated they used all cause adverse events. ViiV further explained that the data presented was collected using an electronic self-administered assessment tool, Columbia Suicide-Severity Rating Scale (C-SSRS), which has been recommended in an FDA guidance document. By accident, a subject could click "yes" and the response is coded as suicidal ideation. The answers selected are final and study participant cannot go back and change it. ViiV acknowledged the potential for false positives in the database, which contributed to the high rates noted in the background package. When participants completed the C-SSRS, ViiV received notification of their response. When a "yes" answer was selected, ViiV contacted the site to confirm the assessment was correct. If confirmed by the site that the event is in fact true, this would be indicated on the CRF as an AE. If the answer selected by the participant was incorrect, it would not be documented in source files.

The Division inquired about the frequency of this type of error with other reported adverse events, where the subject could check the wrong box. ViiV confirmed that this potential only existed with the self-assessment tool used for suicidal ideation. ViiV will outline how the tool is being used and the information will be submitted to the PIND and the NDA.

3.0 PREA REQUIREMENTS

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

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

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

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

5.0 SUBMISSION FORMAT REQUIREMENTS

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

6.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

7.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators

who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

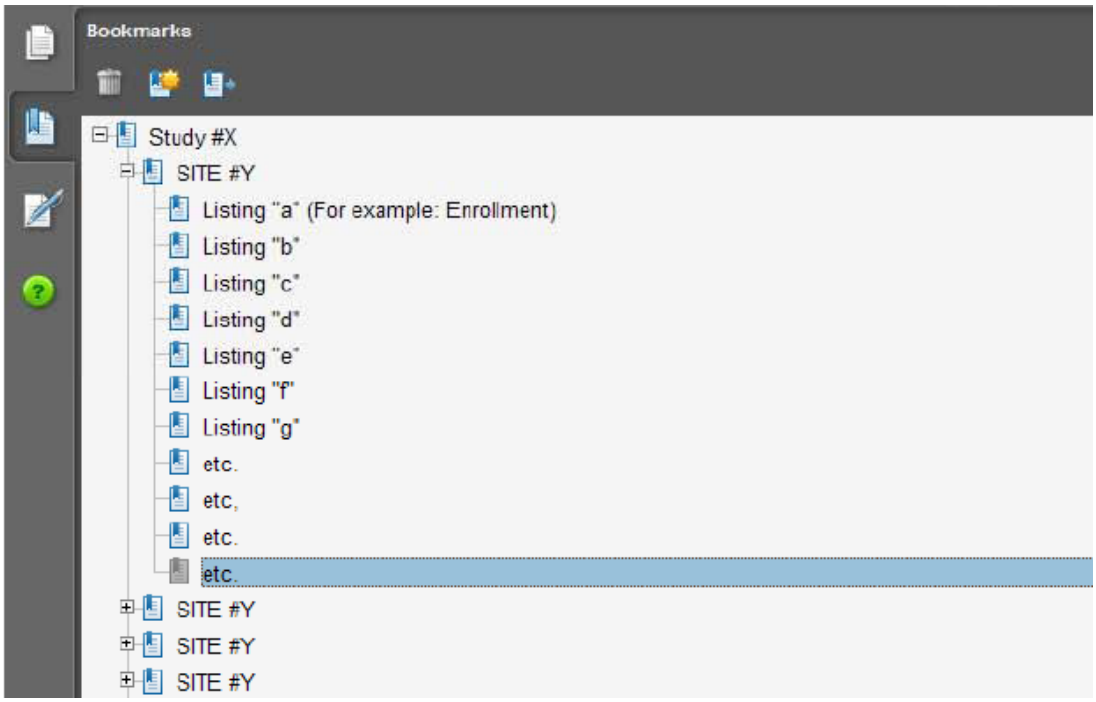
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

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

Attachment 1

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

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

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

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

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

References:

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

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

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

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

7.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
ViiV will submit to the PIND and NDA information regarding the C-SSRS tool to assess suicidal ideation	ViiV	Submit to the PreIND ASAP Include in the NDA submission

9.0 ATTACHMENTS AND HANDOUTS

Attached are the following:

1. ViiV's response to the Division's preliminary comments
2. Psychiatric Events from Clinical Trials rilpivirine
3. Psychiatric Events from Clinical Trials dolutegravir

ViiV’s response to the Division’s preliminary comments

Response to DAVP Meeting Preliminary Comments
IND 123306 (GSK3365791, Dolutegravir and Rilpivirine Fixed-Dose Combination Tablet)
Type B, Pre-NDA Meeting Scheduled for 22 March 2017

The following Meeting Preliminary Comments were conveyed via email on 17 March 2017 by FDA's Division of Antiviral Products (DAVP) to GlaxoSmithKline (GSK) on behalf of ViiV Healthcare Company (ViiV Healthcare), regarding the Type B, Pre-NDA Meeting for dolutegravir (DTG) and rilpivirine (RPV) fixed-dose combination (FDC) scheduled for 22 March 2017. The purpose of the meeting is to discuss ViiV Healthcare's plans for submitting a New Drug Application for the DTG/RPV FDC. After reviewing the Division's preliminary comments, the Sponsor determined that the format of the meeting could be changed from a face-to-face meeting to a teleconference.

The Agency's Meeting Preliminary Comments for Questions 1a, 1b, 2, 3, 4, 5a, 5b, 6, 7, 8, 9, 10, 11a, 11b, 12, 13, 14, 15, 16, 17, 19, 20, and 21 are sufficiently clear and therefore no further discussion is required for these questions. Therefore, during the teleconference we would like to focus the discussion on Question 18, as well as the additional Agency clinical comment.

The formatting of the FDA Meeting Preliminary Comments of 17 March 2017 has been retained with Sponsor's questions in ***bold italic*** text, followed by FDA preliminary responses in plain text. The Sponsor responses to DAVP's Meeting Preliminary Comments are provided in *italic* text.

2.1. Administrative / Regulatory

Question 1a: ***Does the Division agree with the proposed cross referencing strategy for the planned DTG/RPV FDC NDA?***

FDA Response to Question 1a: The Division agrees.

Sponsor Response: Thank you for your response.

Question 1b: ***Does the Division agree with the proposed table of contents of the planned DTG/RPV FDC NDA?***

FDA Response to Question 1b: Your TOC currently does not have the structured product labeling (SPL) under Draft Labeling in Module 1. Please ensure that the SPL will be under Module 1.14.1 Draft Labeling.

Sponsor Response: Thank you for your response. The SPL will be included in Module 1.14.1 Draft Labeling.

Question 2: ***Does the Division agree with the proposal to submit the planned DTG/RPV NDA under Section 505(b)(1) of the Act?***

FDA Response to Question 2: The Division agrees.

Sponsor Response: Thank you for your response.

Question 3: ***Does the Division agree with the planned DTG/RPV FDC NDA will be subjected to the traditional review timelines?***

FDA Response to Question 3: FDA has made a preliminary determination that the application for this product would not be reviewed as a new molecular entity (NME) and would not be subject to the Program under PDUFA V. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Sponsor Response: Thank you for your response.

Question 4: ***Does the Division agree with the provision of financial disclosure information in the planned DTG/RPV FDC NDA?***

FDA Response to Question 4: The Division agrees.

Sponsor Response: Thank you for your response.

Question 5a: ***If the Division files the planned DTG/RPV FDC NDA, the Sponsor is planning to submit a separate supplemental New Drug Application (sNDA) to NDA 204790 TIVICAY (dolutegravir) in order to include the combined use of DTG + RPV in the prescribing information for TIVICAY. Our current plan would be to submit the sNDA at approximately the time the Division files the NDA. The planned sNDA will include the proposed labeling while incorporating the supporting clinical information via cross reference to the DTG/RPV FDC NDA. As no additional clinical data will be submitted, the Sponsor's understanding is that that no additional user fee will be required for the planned sNDA.***

Does the Agency agree that the planned sNDA can be submitted at approximately the time the Division officially files the DTG/RPV FDC NDA?

FDA Response to Question 5a: The Division agrees with your proposed approach to submitting a sNDA to NDA 204790. In regards to the last statement regarding user fee assessment, without an annotated, red-lined proposed PI, it is difficult to determine whether the proposed sNDA to Tivicay will incur a user fee or not. However, in general, if the primary basis for approval of the changes to the Tivicay PI comes from clinical data that has

been previously reviewed under a fee-paying application/supplement and no re-review or reanalysis will be required, then a user fee will not be assessed. Please note that the final determination regarding user fees will be made when the supplement is submitted in its entirety to the Agency.

Sponsor Response: Thank you for your response. We do not anticipate that additional clinical data will be required for the planned sNDA for NDA 204790 TIVICAY (dolutegravir) tablets.

***Question 5b:** If acceptable, could the Division comment if the review of the NDA and sNDA could be aligned such that the action dates would occur in a similar timelines?*

FDA Response to Question 5b: This will be a review issue; however, the Division will make an effort to align the action timeline for the two applications.

Sponsor Response: Thank you for your response.

***Question 6:** The Sponsor is considering the use of a Rare Pediatric Priority Review Voucher for the planned DTG/RPV FDC NDA. Previously, per FDA feedback dated 31 October 2016 on the CMC End-of-Phase 2 package, an agreement was reached to include 9 months of drug product stability data in the planned NDA, and update with 12 months of drug product stability data during the review (within 2 months of original submission). We request confirmation that the agreed plan for providing 9 months of drug product stability data at the time of submission is acceptable under either a standard or a priority review condition. If a voucher is utilized, the sponsor will commit to notifying the Agency 90 days in advance of our intention to use the voucher, and to provide the 12-montyh drug product stability update within 4-6 weeks following the original NDA submission rather than 2 months as previously agreed with the Division.*

Is this proposal acceptable?

FDA Response to Question 6: Yes, submission of the 12-month stability update within 4-6 weeks following the original NDA submission is acceptable for this application.

Sponsor Response: Thank you for your response.

2.2. Clinical Pharmacology

***Question 7:** Does the Agency consider that the preliminary results of bioequivalence study 201676, if confirmed on final analysis, should be sufficient to demonstrate that a pharmacokinetic bridge has been established and are adequate to support the submission and filing of a marketing application for the DTG/RPV FDC tablet?*

FDA Response to Question 7: Yes, the preliminary results based on your analysis appear to support a PK bridge between DTG/RPV FDC tablets to the individual DTG or RPV agents.

However, a final determination on the acceptability of these study results will be made during the NDA review.

Sponsor Response: Thank you for your response. We acknowledge that the final determination of the acceptability of the study results is a review issue.

Question 8: ***Does the Agency consider that the outcome of Study 201674 should be sufficient to adequately characterize food effect and will support taking the DTG/RPV FDC tablet with a meal, as is currently recommended in the approved prescribing information for EDURANT?***

FDA Response to Question 8: Your preliminary analysis for food effect suggests that a moderate-fat meal has a similar effect on the FDC formulation AM as a high-fat meal, compared to fasted conditions, and also that the food effect on FDC formulation AM was similar as observed for individual DTG or RPV. Please submit data to support the similarity between formulations AW and AM, and thus support the extrapolation of food effect results from formulation AM to the to-be-marketed formulation AW.

Sponsor Response: Thank you for your response. The planned DTG/RPV NDA will include data to support the similarity of formulation used in the relative bioavailability study 201674 to the to-be-marketed formulation.

2.3. Clinical

Question 9: ***Does the Agency agree that the above-mentioned data should be sufficient to support the filing of a marketing application for the planned DTG/RPV FDC?***

FDA Response to Question 9: In principal, the data are sufficient to support a submission. However, the final determination will be made within the first 60 days after the NDA is received. Please note that although you have presented findings from the pooled studies, we generally evaluate the findings from each study.

Sponsor Response: Thank you for your response. As previously agreed during the End-of-Phase 2 interaction (09 January 2015, written responses only), the Sponsor's understanding is that the Division plans to pool the two trials and conduct an integrated efficacy analysis with a non-inferiority margin of 8%. In addition, the Division recommends for labeling that the pooled trial results be displayed. However, we acknowledge that the Division will also evaluate the findings from each study based on a non-inferiority margin of 10%. In the planned DTG/RPV NDA both individual study results as well as pooled study results will be presented.

Question 10: ***Does the Division agree with the proposal to submit the SCE in Module 2 and not to submit a separate ISE in Module 5?***

FDA Response to Question 10: The Division does not agree. Please submit an ISE in addition to SCE, as required by eCTD electronic submission guidance. The two reports may be similar but submission is required under modules 2.5 and 5.3.5.3. Additionally, the individual study reports for each trial should be submitted under 5.3.5.1.

According to FDA's April 2009 Guidance for Industry:
Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, Module 5 is the appropriate location for the ISE and ISS. The rare exception to include the ISE and ISS in Module 2 is reserved for applications that are small and consist of a single study or a number of small studies. The ISE and ISS are not intended as summaries but rather detailed integrated analyses of all relevant data (including tables and appendices) from the clinical study reports that belong in Module 5. Therefore, to be consistent with the guidance, the text for the ISE and ISS should be placed in Module 5, section 5.3.5.3 and appropriate SCE and SCS should be placed in Modules 2.7.3 and 2.7.4. Additionally, combining the text of the ISE and ISS into a single document with the supporting statistical outputs allows for easier navigation with hyperlinks. We are agreeable to allowing the same text to be used from the ISE and ISS as the Summary of Clinical Efficacy and Summary of Clinical Safety, respectively, if the text will be under the 400 page limit acceptable for Module 2.

Sponsor Response: Thank you for your response. A separate ISE will be provided in Module 5.

Question 11a: ***Does the Division agree that the size of the safety database will likely be sufficient to support the filing of the planned DTG/RPV FDC NDA?***

FDA Response to Question 11a: The Division agrees.

Sponsor Response: Thank you for your response.

Question 11b: ***Does the Division agree with the proposal to submit the SCS in Module 2 and not to submit a separate ISS in Module 5?***

FDA Response to Question 11b: The Division does not agree with your proposal. Please submit an ISS in addition to SCS, as required by eCTD electronic submission guidance. The two reports may be similar but submission is required under modules 2.5 and 5.3.5.3. Additionally, the individual study reports for each trial should be submitted under 5.3.5.1. Please see response to Question 10.

Sponsor Response: Thank you for your response. A separate ISS will be provided in Module 5. The Sponsor also plans to include a separate report for each trial.

Question 12: ***For the planned DTG/RPV FDC NDA, the Sponsor proposes to provide Case Report Forms (CRFs) for deaths, serious adverse events (SAEs), or any adverse events (AEs) leading to discontinuation. Case narratives will be included for deaths and SAEs, as well as for withdrawals due to AEs of special interest.***

Does the Division agree with the proposal for provision of CRFs and narratives?

FDA Response to Question 12: The Division agrees. Additional narratives may be requested if/when necessary during the NDA review.

Sponsor Response: Thank you for your response. We acknowledge that additional narratives may be requested during the review, and agree to provide these as necessary.

Question 13: ***The Sponsor proposes to submit the required Safety Update Report 120 days post submission of the planned NDA (or 60 days post-submission if Priority Review status is granted). The safety update report will include deaths, SAEs, AEs leading to withdrawal (including laboratory abnormalities), and pregnancies. As with previous NDAs and sNDAs sponsored by ViiV Healthcare, the data in the Safety Update Report will be in-stream and not quality assured.***

Does the Division agree?

FDA Response to Question 13: The Division agrees.

Sponsor Response: Thank you for your response.

Question 14: ***Because the planned DTG/RPV FDC NDA is for a fixed-dose combination of two currently approved active ingredients, the Sponsor proposes to not include eDISH datasets for this NDA.***

Does the Division agree?

FDA Response to Question 14: The Division agrees.

Sponsor Response: Thank you for your response.

Question 15: ***Postmarketing experience data for the individual components is reflected in the currently approved prescribing information for the single entities TIVICAY and EDURANT. Therefore, relevant data such as warnings and precautions, contraindications, and adverse events from postmarketing reports for each component will be incorporated via cross reference to the approved NDAs and reflected in the proposed DTG/RPV FDC label. We also propose to include a summary of reports of use of this combination from publications and spontaneous reports.***

Does the Division agree?

FDA Response to Question 15: The Division agrees.

Sponsor Response: Thank you for your response.

2.4. Statistical/Datasets

Question 16: ***For the planned DTG/RPV FDC NDA, we propose to include datasets for the Phase 3 studies 201636 and 201637, sub-study 202094 evaluating bone density using DEXA scanning, and the pivotal bioequivalence study 201676. The dataset package will be in standard CDISC-compliant format.***

Please note that data have been collected to GSK/ViiV Healthcare data standards and converted to SDTM. We propose to deliver only the SDTM and ADaM data. FDA-specific datasets for efficacy and virology will be created from the ADaM datasets as per the most recent dolutegravir-containing product NDA submission with dolutegravir (e.g. NDA 205551 TRIUMEQ [abacavir, dolutegravir, and lamivudine]).

Does the Division agree with the proposal?

FDA Response to Question 16:. Yes, we agree.

Sponsor Response: Thank you for your response.

Question 17: ***In addition to the Case Report Tabulations (CRT) package for the Phase 3 studies 201636 and 201637, the sub-study 202094, and the pivotal bioequivalence study 201676, virology SAS datasets will be provided in the format outlined in Draft Guidance, Attachment to Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency - Guidance for Submitting HIV-1 Resistance Data (February 2014). Virology datasets will not be provided in CDISC format.***

Does the Division agree with this approach?

FDA Response to Question 17: Yes, we agree.

Sponsor Response: Thank you for your response.

Question 18: ***As with previous NDA submissions, the Sponsor proposes to not include SAS Programs in the planned submission.***

Does the Division agree?

FDA Response to Question 18: We do not agree. Please submit SAS programs with descriptions of input data sets.

Sponsor Response: Thank you for your response. We propose to submit SAS programs in ASCII text format for the ADaM datasets and the primary and secondary analyses for Phase III studies 201636 and 201637, as well as pivotal bioequivalence study 201676 as per section 4.1.2.10 of the FDA Study Data Technical Conformance Guide (November 2016). Descriptions of all SDTM and ADaM datasets included in the submission will be provided as part of the CRT package. Does the Agency agree?

2.5. Virology

Question 19: ***Does the Agency agree that the current USPI for the individual components are appropriate reference to determine the relevant virology data to be presented in the planned DTG/RVP FDC NDA?***

FDA Response to Question 19: The Division agrees.

Sponsor Response: Thank you for your response.

Question 20: ***Does the Agency agree that this in vitro data adequately addresses the risk of antiviral antagonism for DTG + RPV?***

FDA Response to Question 20: The Division agrees.

Sponsor Response: Thank you for your response.

Question 21: ***Does the agency agree with this proposal to allow submission of the additional, more complete resistance data (for the one subject described above who met the CVW criteria) within 30 days of the NDA submission?***

FDA Response to Question 21: The Division agrees.

Sponsor Response: Thank you for your response.

Additional FDA Comment:

Clinical

- We noted that the reported AEs for psychiatric-related events, including suicidal ideation/behavior or thoughts were significantly higher than previously reported for the individual products including dolutegravir, rilpivirine and efavirenz. Please provide your planned analyses (sub-analyses and/or sensitivity analyses) to evaluate the various psychiatric-related AEs to further understand the apparent higher incidences reported during the SWORD trials. Please submit this information prior to the NDA submission.

Sponsor Response: We have not observed that the reported AEs for psychiatric events are higher in the SWORD studies than for previous studies with the individual drugs. The incidence of psychiatric events in the pooled analysis for the SWORD studies was 12% for the DTG/RPV group compared with 6% in the CAR group. There were 3 (<1%) patients in the DTG/RPV group who reported suicidal ideation and 1 attempted suicide, compared with 2 (<1%) patients with suicidal ideation and 1 attempted suicide in the CAR group.

These results are comparable to examples of switch studies with DTG or RPV. The incidence of events in STRIIVING (201147) is very similar (13% for the DTG arm and 3% for the CAR arm. Being an open-label switch study, STRIIVING is the most appropriate study for comparison of DTG.

In study GS-US-264-0106, a phase III, randomized, open-label switch study from a PI-based regimen to an RPV-based fixed dose combination the incidence of psychiatric disorders in the RPV group was 19.6%, compared with 6.3% in the 'Stay on background' (SBR) group. The incidence of these events in the previous Phase III studies of DTG or RPV is also higher than observed in SWORD studies (see attached tables).

Psychiatric events including suicidal ideation and behaviors are AEs of special interest for the DTG/RPV combination and will be analyzed for incidence, severity, relationship to drug and outcome in the individual CSRs. In the pooled datasets more detailed analysis of these events such as depression (including all preferred terms containing 'depression', 'depressed mood', 'depressive', 'hypomania' or 'bipolar'), suicidality (including all preferred terms containing 'suicide', 'suicidal' or 'intentional self-injury') as well as insomnia, nightmare/abnormal dreams and anxiety events will be presented. These analyses will include onset and duration, seriousness, relationship to drug, maximum severity, whether leading to withdrawal, fatalities, number of occurrences and outcome. Subgroup analyses including gender and previous medical history will also be available.

Does this planned analysis address the Agency's concern?

Psychiatric Events from Clinical Trials rilpivirine

Table 33: Psychiatric Events of Interest, Regardless of Severity and Causality (Phase III Week 48 Pooled Analysis)

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Psychiatric disorders	**81 (23.4)**	**112 (32.6)**	**83 (24.4)**	**86 (25.4)**	**164 (23.9)**	**198 (29.0)**
Insomnia	23 (6.6)	32 (9.3)	31 (9.1)	20 (5.9)	54 (7.9)	52 (7.6)
Abnormal dreams	28 (8.1)	41 (11.9)	18 (5.3)	25 (7.4)	46 (6.7)	66 (9.7)
Depression	22 (6.4)	17 (4.9)	18 (5.3)	15 (4.4)	40 (5.8)	32 (4.7)
Anxiety	4 (1.2)	21 (6.1)	12 (3.5)	14 (4.1)	16 (2.3)	35 (5.1)
Nightmare	8 (2.3)	11 (3.2)	8 (2.4)	15 (4.4)	16 (2.3)	26 (3.8)
Sleep disorder	4 (1.2)	12 (3.5)	7 (2.1)	12 (3.6)	11 (1.6)	24 (3.5)
Depressed mood	3 (0.9)	4 (1.2)	4 (1.2)	1 (0.3)	7 (1.0)	5 (0.7)
Libido decreased	3 (0.9)	3 (0.9)	1 (0.3)	3 (0.9)	4 (0.6)	6 (0.9)
Stress	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.4)	2 (0.3)
Delirium	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Drug dependence	2 (0.6)	0	0	0	2 (0.3)	0
Hallucination	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.3)	3 (0.4)
Initial insomnia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Major depression	2 (0.6)	0	0	2 (0.6)	2 (0.3)	2 (0.3)
Suicide attempt	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Adjustment disorder with anxiety	0	0	1 (0.3)	0	1 (0.1)	0
Affect lability	0	0	1 (0.3)	0	1 (0.1)	0
Alcoholism	1 (0.3)	0	0	0	1 (0.1)	0
Anxiety disorder	0	0	1 (0.3)	0	1 (0.1)	0
Attention deficit/hyperactivity disorder	1 (0.3)	0	0	0	1 (0.1)	0
Boredom	1 (0.3)	0	0	0	1 (0.1)	0
Bruxism	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Confusional state	0	3 (0.9)	1 (0.3)	0	1 (0.1)	3 (0.4)
Dysphoria	0	1 (0.3)	1 (0.3)	0	1 (0.1)	1 (0.1)
Early morning awakening	1 (0.3)	0	0	0	1 (0.1)	0
Emotional disorder	1 (0.3)	0	0	0	1 (0.1)	0
Hallucination, auditory	1 (0.3)	0	0	1 (0.3)	1 (0.1)	1 (0.1)
Hallucination, visual	1 (0.3)	0	0	0	1 (0.1)	0
Hallucinations, mixed	1 (0.3)	0	0	0	1 (0.1)	0
Euphoric mood	1 (0.3)	0	0	0	1 (0.1)	0
Libido increased	0	0	1 (0.3)	0	1 (0.1)	0
Loss of libido	0	0	1 (0.3)	0	1 (0.1)	0
Mania	1 (0.3)	0	0	0	1 (0.1)	0
Middle insomnia	0	0	1 (0.3)	0	1 (0.1)	0
Mood altered	0	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.1)	3 (0.4)
Mood swings	1 (0.3)	1 (0.3)	0	0	1 (0.1)	1 (0.1)
Negative thoughts	0	0	1 (0.3)	0	1 (0.1)	0
Nervousness	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	2 (0.3)
Psychogenic erectile dysfunction	1 (0.3)	0	0	0	1 (0.1)	0

Psychiatric Events from Clinical Trials dolutegravir

Table 8.4
Summary of All Adverse Events by System Organ Class – Randomized/Early Switch Phase

System Organ Class Preferred Term	ABC/DTG/3TC (N=276)		Current ART (N=277)	
Respiratory, thoracic and mediastinal disorders (cont.)				
Cough	14	(5%)	8	(3%)
Nasal congestion	9	(3%)	3	(1%)
Oropharyngeal pain	3	(1%)	4	(1%)
Sinus congestion	4	(1%)	0	
Rhinitis allergic	1	(<1%)	2	(<1%)
Respiratory tract congestion	1	(<1%)	1	(<1%)
Asthma	1	(<1%)	0	
Chronic obstructive pulmonary disease	0		1	(<1%)
Epistaxis	0		1	(<1%)
Lower respiratory tract congestion	1	(<1%)	0	
Rhinorrhoea	1	(<1%)	0	
Sleep apnoea syndrome	1	(<1%)	0	
Upper respiratory tract congestion	1	(<1%)	0	
Psychiatric disorders				
Any Event	35	(13%)	8	(3%)
Depression	8	(3%)	3	(1%)
Insomnia	10	(4%)	1	(<1%)
Anxiety	8	(3%)	1	(<1%)
Abnormal dreams	6	(2%)	1	(<1%)
Irritability	2	(<1%)	0	
Sleep disorder	1	(<1%)	1	(<1%)
Agitation	1	(<1%)	0	
Bipolar disorder	1	(<1%)	0	
Depressed mood	1	(<1%)	0	
Drug dependence	0		1	(<1%)
Euphoric mood	1	(<1%)	0	
Libido decreased	1	(<1%)	0	
Mood swings	1	(<1%)	0	
Nightmare	1	(<1%)	0	
Suicide attempt	1	(<1%)	0	
Nervous system disorders				
Any Event	32	(12%)	7	(3%)
Headache	13	(5%)	4	(1%)
Dizziness	8	(3%)	2	(<1%)
Hypoaesthesia	2	(<1%)	3	(1%)
Migraine	2	(<1%)	0	
Neuralgia	2	(<1%)	0	

Table is updated post Week 24 database lock due to noncompliance issues at site 209994. It includes the final safety data from all sites.
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Population: Safety (SPRING-1, SPRING-2, SINGLE, FLAMINGO, VIKING, VIKING-3, VIKING-4 and SAILING)

Table 2.905
Summary of All Adverse Events by System Organ Class and Maximum Toxicity
QD vs BID

Population: Total
Treatment: DTG QD (N=1606)

System Organ Class / Preferred Term	Maximum Toxicity				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Systemic inflammatory response syndrome	1 (<1%)	0	0	0	1 (<1%)
Thirst	1 (<1%)	0	0	0	1 (<1%)
Psychiatric disorders					
Any Event	220 (14%)	112 (7%)	23 (1%)	7 (<1%)	362 (23%)
Insomnia	96 (6%)	42 (3%)	4 (<1%)	0	142 (9%)
Depression	45 (3%)	33 (2%)	11 (<1%)	1 (<1%)	90 (6%)
Anxiety	36 (2%)	26 (2%)	1 (<1%)	0	63 (4%)
Abnormal dreams	47 (3%)	5 (<1%)	0	0	52 (3%)
Nightmare	15 (<1%)	4 (<1%)	2 (<1%)	0	21 (1%)
Sleep disorder	14 (<1%)	5 (<1%)	0	0	19 (1%)
Libido decreased	15 (<1%)	2 (<1%)	0	0	17 (1%)
Stress	7 (<1%)	4 (<1%)	0	0	11 (<1%)
Suicidal ideation	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)	8 (<1%)
Suicide attempt	1 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)	8 (<1%)
Depressed mood	5 (<1%)	2 (<1%)	0	0	7 (<1%)
Panic attack	3 (<1%)	1 (<1%)	1 (<1%)	0	5 (<1%)
Acute stress disorder	1 (<1%)	3 (<1%)	0	0	4 (<1%)
Drug abuse	2 (<1%)	1 (<1%)	0	1 (<1%)	4 (<1%)
Initial insomnia	4 (<1%)	0	0	0	4 (<1%)
Agitation	3 (<1%)	0	0	0	3 (<1%)
Bipolar disorder	1 (<1%)	2 (<1%)	0	0	3 (<1%)
Nervousness	3 (<1%)	0	0	0	3 (<1%)
Adjustment disorder	1 (<1%)	1 (<1%)	0	0	2 (<1%)
Alcohol withdrawal syndrome	1 (<1%)	0	1 (<1%)	0	2 (<1%)

Note: Summary does not include events with toxicity recorded as 'Not applicable'.
Note: DTG QD was taken in Spring-1, Spring-2, Viking cohort 1, Flamingo, Single and Sailing.
DTG BID was taken in Viking cohort 2, Viking 3 and Viking 4.
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Population: Safety (SPRING-1, SPRING-2, SINGLE, FLAMINGO, VIKING, VIKING-3, VIKING-4 and SAILING)

Table 2.905
Summary of All Adverse Events by System Organ Class and Maximum Toxicity
QD vs BID

Population: Total
Treatment: DTG QD (N=1606)

System Organ Class / Preferred Term	Maximum Toxicity				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Anxiety disorder	1 (<1%)	1 (<1%)	0	0	2 (<1%)
Dysthymic disorder	1 (<1%)	1 (<1%)	0	0	2 (<1%)
Euphoric mood	2 (<1%)	0	0	0	2 (<1%)
Libido increased	1 (<1%)	1 (<1%)	0	0	2 (<1%)
Mental disorder	0	2 (<1%)	0	0	2 (<1%)
Mood altered	2 (<1%)	0	0	0	2 (<1%)
Mood swings	1 (<1%)	1 (<1%)	0	0	2 (<1%)
Adjustment disorder with depressed mood	0	1 (<1%)	0	0	1 (<1%)
Affect lability	1 (<1%)	0	0	0	1 (<1%)
Aggression	1 (<1%)	0	0	0	1 (<1%)
Agoraphobia	0	1 (<1%)	0	0	1 (<1%)
Alcohol abuse	0	0	1 (<1%)	0	1 (<1%)
Alcoholic psychosis	0	0	1 (<1%)	0	1 (<1%)
Anger	0	1 (<1%)	0	0	1 (<1%)
Antisocial personality disorder	1 (<1%)	0	0	0	1 (<1%)
Binge eating	1 (<1%)	0	0	0	1 (<1%)
Bipolar II disorder	1 (<1%)	0	0	0	1 (<1%)
Bulimia nervosa	0	0	1 (<1%)	0	1 (<1%)
Burnout syndrome	1 (<1%)	0	0	0	1 (<1%)
Confusional state	0	1 (<1%)	0	0	1 (<1%)
Delusion	0	1 (<1%)	0	0	1 (<1%)
Depressive symptom	1 (<1%)	0	0	0	1 (<1%)
Emotional disorder	1 (<1%)	0	0	0	1 (<1%)
Homicidal ideation	0	0	0	1 (<1%)	1 (<1%)

Note: Summary does not include events with toxicity recorded as 'Not applicable'.
Note: DTG QD was taken in Spring-1, Spring-2, Viking cohort 1, Flamingo, Single and Sailing.
DTG BID was taken in Viking cohort 2, Viking 3 and Viking 4.
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Population: Safety (SPRING-1, SPRING-2, SINGLE, FLAMINGO, VIKING, VIKING-3, VIKING-4 and SAILING)

Table 2.905
Summary of All Adverse Events by System Organ Class and Maximum Toxicity
QD vs BID

Population: Total
Treatment: DTG QD (N=1606)

System Organ Class / Preferred Term	Maximum Toxicity				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Listless	1 (<1%)	0	0	0	1 (<1%)
Loss of libido	1 (<1%)	0	0	0	1 (<1%)
Mental status changes	0	0	1 (<1%)	0	1 (<1%)
Panic reaction	0	1 (<1%)	0	0	1 (<1%)
Premature ejaculation	1 (<1%)	0	0	0	1 (<1%)
Restlessness	0	1 (<1%)	0	0	1 (<1%)
Sleep-related eating disorder	1 (<1%)	0	0	0	1 (<1%)
Social phobia	0	1 (<1%)	0	0	1 (<1%)
Somnambulism	0	1 (<1%)	0	0	1 (<1%)
Substance abuse	0	1 (<1%)	0	0	1 (<1%)
Thinking abnormal	1 (<1%)	0	0	0	1 (<1%)
Tobacco abuse	0	1 (<1%)	0	0	1 (<1%)
Violence-related symptom	0	1 (<1%)	0	0	1 (<1%)
Withdrawal syndrome	1 (<1%)	0	0	0	1 (<1%)
Skin and subcutaneous tissue disorders					
Any Event	260 (16%)	73 (5%)	3 (<1%)	0	336 (21%)
Rash	66 (4%)	10 (<1%)	0	0	76 (5%)
Pruritus	42 (3%)	5 (<1%)	0	0	47 (3%)
Night sweats	23 (1%)	4 (<1%)	0	0	27 (2%)
Alopecia	20 (1%)	4 (<1%)	0	0	24 (1%)
Eczema	19 (1%)	2 (<1%)	0	0	21 (1%)
Acne	16 (<1%)	3 (<1%)	0	0	19 (1%)
Dermatitis	15 (<1%)	2 (<1%)	0	0	17 (1%)

Note: Summary does not include events with toxicity recorded as 'Not applicable'.
Note: DTG QD was taken in Spring-1, Spring-2, Viking cohort 1, Flamingo, Single and Sailing.
DTG BID was taken in Viking cohort 2, Viking 3 and Viking 4.
kxc1947: /arenv/arprod/gsk1349572/ing_psap/se_iss3/drivers/saf_taetox_qdbid1.sas 10OCT2013 18:33

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/s/

KAREN D WINESTOCK
04/19/2017