CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215499Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 109678

MEETING MINUTES

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

Dear Mr. Troughton:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cabotegravir (b) (4) injection (b) (4).

We also refer to the telecon between representatives of your firm and the FDA on February 19, 2021. The purpose of the meeting was to discuss ViiV Healthcare Company's proposed strategy for submission and filing of an original NDA for CAB LA for HIV-1 pre-exposure prophylaxis (PrEP).

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

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at 301-348-3926.

Sincerely,

{See appended electronic signature page}

London Harrison, MBEE
Regulatory Health Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- ViiV's Slide Presentation

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, Pre-NDA

Meeting Date and Time: February 19, 2021, 1:00 pm – 2:30 pm (EST)
Meeting Location: Telecon

Application Number: IND 109678
Product Name: cabotegravir [redacted (b) (4)] injection [redacted (b) (4)]
Indication: HIV-1 pre-exposure prophylaxis
Sponsor Name: ViiV Healthcare Company
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

FDA ATTENDEES

Office of Infectious Disease (OND/OID)
Adam Sherwat, MD, Deputy Director

OND/OID/Division of Antivirals (DAV)
Debra Birnkrant, MD, Director
Jeffrey Murray, MD, MPH, Deputy Director
Kimberly Struble, PharmD, Clinical Team Lead
Aimee Hodowanec, MD, Clinical Reviewer
Julian O'Rear, PhD, Clinical Virology Team Lead
Damon Deming, PhD, Clinical Virology Reviewer

OND/OID/Division of Pharmacology/Toxicology for Infectious Diseases
Hanan Ghantous, PhD, DABT, Director
David McMillan, PhD, Pharmacology/Toxicology Reviewer

Office of Regulatory Operations (ORO)/ Division of Regulatory Operations for Infectious Disease, Antivirals Group
Karen Winestock, Chief Project Management Staff
London Harrison, MBEE, Regulatory Project Manager

Office of Translational Sciences (OTS)/Office of Biostatistics (OB)/Division of Biometrics (DBIV)
Thamban Valappil, PhD, Biometrics Team Lead
Wen Zeng, PhD, Biometrics Reviewer

OTS/Office of Clinical Pharmacology (OCP)/Division of Infectious Disease Pharmacology (DIDP)

Vikram Arya, PhD, FCP, Clinical Pharmacology Team Lead
Mario Sampson, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)
Erika Englund, PhD, Product Quality Team Lead

Office of Program Operations (OND/OPO)
Hyo Sook Song, Lead Medical Editor
Pamela Hsieh, Assistant Medical Editor

SPONSOR ATTENDEES

ViiV Healthcare
Amy Cutrell, Director, Research Statistics
Karen Grainger, VP, Head of Regulatory
Scott McCallister, Clinical Development Lead
Nassrin Payvandi, VP, Safety & Pharmacovigilance
Alex Rinehart, Medicine Development Leader, Prevention
Kimberly Smith, SVP and Head of Research and Development
William Spreen, VP, Medicine Development Leader

GlaxoSmithKline
Yash Gandhi, Director, Clinical Pharmacology Modelling and Simulation
Susan Ford, Director, Clinical Pharmacology Modelling and Simulation
Karen Samms, Senior Director, Global Regulatory Affairs
Britt Stancil, Statistics Leader, Clinical Statistics
Shanker Thiagarajah, Medical Director, Safety Evaluation
Jeffrey Troughton, Director, Global Regulatory Affairs

1.0 BACKGROUND

Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor (INSTI) being developed by ViiV Healthcare as an oral and long-acting (LA) injectable formulation in combination (b) (4) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in high risk populations. Cabotegravir extended release injectable suspension and rilpivirine extended release injectable suspension was approved on January 21, 2021 under NDA 212888 as Cabenuva, a complete regimen for the treatment of HIV-1 infection in adults to replace their current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. For the Pre-exposure prophylaxis indication, cabotegravir extended release injectable suspension and the tablets are being developed as monotherapy.

The HIV Prevention Trials Network (HPTN) has conducted two double-blind randomized controlled phase 2/3 studies, HPTN 083 and HPTN 084, designed to compare injectable cabotegravir LA (CAB-LA) to daily, oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) PrEP in high risk populations of men who have sex with men, transgender women, and cisgender women. Based upon preliminary clinical data from studies HPTN083 and HPTN084, CAB LA was granted Breakthrough Therapy Designation for the prevention of HIV-1 infection in individuals at high risk for acquiring HIV-1.

ViiV submitted a Pre-NDA meeting request on December 23, 2020 to discuss their proposed strategy for submission and filing of an original NDA for CAB LA for PrEP. The meeting request was granted by the FDA on January 13, 2021 as a Type B Pre-NDA teleconference meeting scheduled for February 19, 2021. An informal teleconference was held on February 8, 2021 to clarify the NDA submission timeline and content prior to the scheduled Pre-NDA meeting.

FDA sent Preliminary Comments to ViiV Healthcare Company on February 17, 2021. Upon receipt of the Agency's preliminary comments, ViiV acknowledged the Agency's feedback and requested that the meeting focus on Questions 6, 10, 15 and 20. The Agency received a slide set which was used to support the discussion during the meeting.

2.0 DISCUSSION

2.1. Clinical

Question 6: As described in the CAB treatment program NDA submission, oral lead-in (OLI) has been used to evaluate the safety of oral CAB use prior to administration of CAB injections. The OLI was used in both the CAB treatment and the CAB prevention development programs, and the lack of clinically meaningful adverse reactions during OLI to preclude progression to LA treatment across both CAB development programs to date is encouraging. In order to reduce the risk that an OLI requirement becomes an impediment to use of CAB LA for PrEP and to reduce the risk of confusion for prescribers, the Sponsor intends to propose that the OLI be optional, at the discretion of the provider/participant, for PrEP (consistent with the OLI optional proposal for treatment).

Does the Division agree with this approach?

FDA Response to Question 6:
We are unable to determine if the OLI can be optional for an HIV PrEP indication at this time. Please provide an update on the timing of the availability of data from the FLAIR extension study. In addition, please propose potential language that could be used to describe an optional OLI in the CAB LA label.

Discussion:
ViiV acknowledged that the OLI requirement would be a review issue. They noted that safety data from the FLAIR extension study (Week 124 CSR) was submitted to IND 109678 in September 2020 and that the findings support an optional OLI. ViiV plans to submit an sNDA to NDA 212888 (Cabenuva) in May 2021 to revise labeling to reflect an optional OLI for the treatment indication. They also intend to include proposed labeling in a pre-sNDA briefing document to IND 109678. ViiV anticipates that similar labeling language will be used for the treatment and prevention indications.

The FDA noted that this approach seems reasonable. ViiV was advised to provide a formal justification for the optional OLI and to cross-reference the FLAIR results in the PrEP NDA.

2.2. Statistical/Datasets

Question 10: For the planned NDA, we propose to include data packages based on CDISC standards for the following studies (Table 1). Each study will include both SDTM & ADaM CRT packages. The Study Data Standardization Plan (SDSP) will be provided as an appendix to the Briefing Document if the meeting is granted. Please note that the Sponsor plans to include SAS Programs for studies with CSR in the planned NDA for the analysis of primary and safety (AE) endpoints as well as the additional safety (AE) analysis for HPTN 083 and HPTN 084 (m2.7.4).

Does the Division agree with this approach?

FDA Response to Question 10:
The proposed Study Data Standardization Plan (SDSP) is acceptable. Please submit SAS programs used to generate ADaM datasets from the SDTM datasets in addition to the SAS programs used for the primary and safety endpoints in the CSRs. Please also provide the analysis data reviewer's guide (ADRG) to facilitate the review process.

Discussion:
ViiV requested that the Division clarify whether SAS programs were required for the tables in m2.7.4 (clinical summary tables). The FDA strongly recommended that ViiV submit all SAS programs, including those for HPTN 084 (m2.7.4). ViiV agreed.

Question 15: Given the subsequent data acquisition in supplemental analyses, we propose that these emerging data packages (e.g. supplemental resistance and viral load from extensive testing for seroconverters) are to be submitted as separate submission data package(s). Furthermore, the limited phenotype results are available in individual reports alone rather than databased as well.

Does the Division agree with the proposal to submit the main submission data package (including the primary endpoint) and a separate submission data package (including the supplemental results)?

FDA Response to Question 15:
Please clarify whether the supplemental resistance and viral load information will change the primary results. In addition, please indicate the number of subjects that will be contributing to these supplemental data packages.

Discussion:
ViiV provided updates on virology data from HPTN 083 based on further supplemental virology analyses and characterization of seroconversions. These supplemental analyses revealed that during HPTN 083, a total of 58 infections occurred; 16 in the CAB LA group (4 prevalent infections (i.e., infection that was present at baseline) and 12 incident infections) and 42 in the Truvada group (3 prevalent infections and 39 incident infections). These updated figures reflect the reclassification of a CAB infection from an incident infection to a prevalent infection as well as the identification of an additional prevalent infection. These supplemental virology analyses do not impact the overall conclusion of statistical superiority of CAB over TDF/FTC, in fact, the treatment effect of CAB LA is slightly increased from prior based on these new analyses. These results will be presented at CROI via DAIDS.

Updated HPTN 084 virology data is to be submitted in the future and will further characterize all seroconversions in this trial. As of this meeting, 4 seroconversions had been identified in HPTN 084.

2.3. Administrative/Regulatory

Question 20: In accordance with the Pediatric Research Equity Act (PREA), ViiV Healthcare intends to meet the agreed terms of the Agreed Initial Pediatric Study Plan for CAB PrEP. Based on the Division's responses of the Type C Guidance Meeting (Written Responses) of 25 November 2020 under the CAB treatment program, the Sponsor proposes that PK and safety data from the MOCHA study that support the CAB treatment program could support every 2 months (Q8W) dosing of CAB LA for PrEP in adolescents weighing at least 35 kg.

Does the Division Agree that this proposal could provide sufficient evidence to support dosing information in the adolescent population weighing at least 35 kg?

FDA Response to Question 20:
We agree with your intention to include adolescents in the initial CAB LA PrEP indication and your proposal could potentially provide sufficient evidence to support dosing information in adolescents. However, this is a review issue and depends on several factors. We note that observed adolescent PK data from the MOCHA trial and modeling and simulation analyses to support CAB LA PrEP adolescent Q8W dosing will be included in the NDA. Please provide an update on what data from the MOCHA study and from HPTN 083-01 and HPTN 084-01 are expected to be available by July 2021.

Additionally, you will need to submit data to support safety in adolescents and to assess adherence/usage in adolescents. Per the FDA Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Product for Pre-Exposure Prophylaxis, "adherence data are important because lack of adherence could undermine the efficacy and safety of a systemic drug product in adolescents. Collection of usage data in adolescents is desirable until adolescent adherence is better understood for a given prevention modality."

We look forward to regular updates from MOCHA and the HPTN sub-studies in adolescents to determine if sufficient information is available to include adolescents in labeling.

Discussion:
ViiV stated that COVID-19 has impacted enrollment for adolescent studies. Currently, only 6 subjects have been enrolled in HPTN 083-01 and HPTN 084-01. Therefore, ViiV was not planning on any datasets from HPTN 083-01 and 084-01 being available in July. ViiV reiterated that these results were never intended to be part of the original NDA submission. The FDA acknowledged the impact of COVID-19 on enrollment and agreed to work with ViiV on solutions. Safety data from the 8 MOCHA study patients matching the adolescent weight requirement can be leveraged to support an adolescent indication. In addition, FDA requested that topline data (i.e., safety and adherence data) from the 6 patients enrolled in HPTN 083-01 and HPTN 084-01 be included in the NDA. FDA offered to provide an IR to facilitate obtaining these desired adolescent data from DAIDS and ViiV indicated that this would be helpful.

3.0 ADDITIONAL MEETING INFOMATION

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*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial

period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no items that require further discussion.

[6] https://www fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide extensive documentation justifying optional OLI for PrEP	ViiV Healthcare Company	
Submit appropriate cross referencing for FLAIR study dataset	ViiV Healthcare Company	
Submit all SAS programs and data (including those for m2.7.4)	ViiV Healthcare Company	
Provide any available topline, safety, and/or adherence data from HPTN 083-01 and 084-01 (for adolescents)	ViiV Healthcare Company	
Information Request to DAIDS for HPTN 083-01 and 084-01 data	FDA	

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slides that were discussed during this meeting have been attached.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LONDON F HARRISON
03/20/2021 04:54:06 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 109678
Request Receipt Date	September 18, 2020
Product	cabotegravir (b) (4) injection
Indication	For the prevention of HIV-1 infection in individuals at high risk for acquiring HIV-1 (HIV PrEP)
Drug Class/Mechanism of Action	Integrase strand transfer inhibitor
Sponsor	ViiV Healthcare Company
ODE/Division	OID/DAV
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	November 17, 2020

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Cabotegravir extended-release injectable suspension (CAB LA) is intended to be indicated in (b) (4) pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in individuals at high risk.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.**

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Although there have been tremendous advancements in the treatment of HIV in the past several decades, there remains no cure for HIV and HIV infection continues to have significant long-term health sequalae. According to the Centers for Disease Control and Prevention (CDC), in 2018 there were 37,968 new HIV diagnoses in the United States. According to the Department of Health and Human Services Ending the HIV Epidemic (EHE) and the US National HIV/AIDS Strategies (NHAS) initiatives, pre-exposure prophylaxis (PrEP) is an important means of reducing new HIV infections in the US.

Currently, there are two therapies approved for HIV PrEP: emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada) and emtricitabine/tenofovir alafenamide (FTC/TAF, Descovy). Both of these therapies are oral regimens that are administered once daily. In order to be effective in preventing HIV acquisition, they must be used correctly and consistently. Uptake of these available HIV PrEP regimens in the US has been increasing over recent years, but remains suboptimal. According to www.prepwatch.org, in 2020 there are 200,000-205,000 current PrEP users in the US. According to the CDC, in 2015 there were 1.2 million Americans eligible for HIV PrEP. Further, among those who initiate PrEP, usage may be intermittent and/or short-lived. As noted, adherence is vital to the effectiveness of PrEP. A metanalysis of HIV PrEP trials found that treatment adherence >70% was associated with 73% effectiveness in the reduction of new infections. Comparatively, the metanalyses found that trials with >40% to <70% adherence or <40% adherence showed effectiveness rates of 49% and 7%, respectively.[3]

Cabotegravir is an integrase inhibitor that has both a tablet and a long-acting injectable (CAB-LA) formulation. CAB LA is being developed for both the treatment and prevention of HIV. Neither the tablet or injectable form of cabotegravir are currently FDA-approved for any indication. In December 2019, NDA 212888 for CAB LA in combination with rilpivirine and NDA 212887 for cabotegravir tablets for the treatment of HIV received a Complete Response due to manufacturing deficiencies. Both of these HIV treatment NDAs were resubmitted in July 2020 and are currently under review. This Breakthrough Therapy Designation Request pertains to the HIV PrEP indication. For HIV PrEP, 600 mg CAB LA is administered via injection every 8 weeks. It is hoped that this will offer an alternative HIV prevention modality for those persons for whom consistent use of a daily oral medication is not possible or acceptable. The CAB LA NDA submission for HIV prevention is anticipated sometime in early 2021.

8. Information related to endpoints used in the available clinical data:

The primary endpoint for the Phase 3 trials supporting this BTDR (HPTN 083 and HPTN 084) is the number of documented incident HIV infections. This is a clinical endpoint that directly measures the clinical benefit of the drug. This is the preferred endpoint for HIV PrEP trials (see the FDA Guidance: Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis).

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

As noted above, FTC/TDF and FTC/TAF are currently approved for HIV PrEP. Both therapies come as a fixed dose tablet that is taken orally once daily. Of note, TAF and TDF are both prodrugs of tenofovir (TFV). Please see the table below for a summary of each of these approved therapies.

[3] Chou R, et al. Pre-Exposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review for the U.S. Preventive Services Task Force: Evidence Synthesis No. 178. Rockville, MD: Agency for Healthcare Research and Quality; 2018. AHRQ publication 18-05247-EF-1.

Table 1. Therapies Currently Approved for HIV PrEP

Therapy	Approved PrEP Indication	Efficacy Endpoint	Comments
FTC/TDF (TRUVADA)	(b) (4) for HIV-1 PrEP to reduce the risk of sexually acquired HIV-1 in at-risk[a] adults and adolescents weighing at least 35 kg	The incidence of documented HIV seroconversion: • iPrEx Trial: Among high risk MSM and TGW, TRUVADA resulted in a 42% (95% CI: 18-60%) reduction in risk compared to PBO • Partners PrEP Trial: Among HIV serodiscordant heterosexual couples, TRUVADA resulted in a risk reduction of 75% (95% CI: 55-87%) compared to PBO	In iPrEx, based on a post-hoc case control study of plasma and intracellular drug levels, efficacy appeared to strongly correlate with adherence.
FTC /TAF (DESCOVY)	For use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex.	The incidence of documented HIV-1 infection per 100 PYs • DISCOVER Trial: Among MSM and TGW, DESCOVY was noninferior to TRUVADA in reducing the risk of acquiring HIV infection (rate of HIV infection per 100 PYs was 0.16 and 0.34 in the DESCOVY and TRUVADA arms, respectively; rate ratio = 0.468 (95% CI: 0.19-1.15)).	Label includes the following Limitation of Use: The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

Abbreviations: FTC, emtricitabine; MSM, men who have sex with men; PBO, placebo; PrEP, pre-exposure prophylaxis; PY, person years; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TGW, transgender women

[a] Factors that help to identify individuals at risk may include: has partner(s) known to be HIV-1 infected, or engages in sexual activity within a high prevalence area or social network and has additional risk factors for HIV-1 acquisition, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections, exchange of sex for commodities (such as money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, or partner(s) of unknown HIV-1 status with any of the factors listed above.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

(b) (4)

[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

(b) (4)

11. Information related to the preliminary clinical evidence:

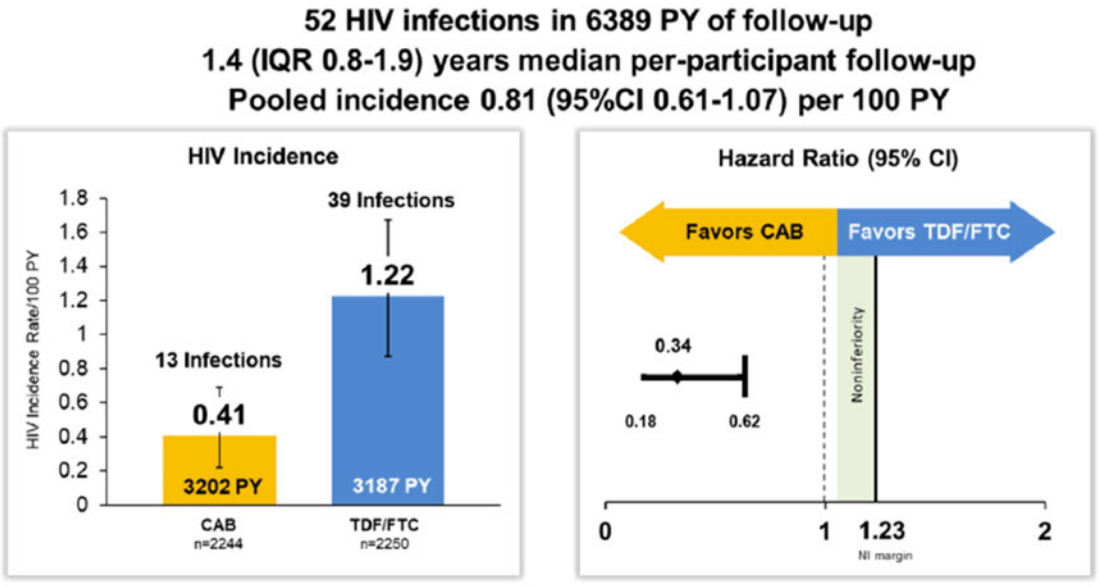
The preliminary clinical evidence that the Sponsor proposes to support this BTDR come from clinical trials HPTN 083 and HPTN 084.

HPTN 083

This is an ongoing Phase 3, double-blind, randomized, controlled trial in which HIV uninfected men who have sex with men (MSM) and transgender women (TGW) were randomized 1:1 to receive oral FTC/TDF daily or CAB LA every 8 weeks for HIV prevention. Overall 4,570 subjects were randomized across sites in the US, South America, Asia, and South Africa.

This was designed as a non-inferiority trial with a non-inferiority margin of 1.23. A multinational Data and Safety Monitoring Board (MDSMB) reviewed safety and efficacy data biannually and interim analyses were pre-specified at 25%, 50%, and 75% of total endpoint target (172 HIV seroconversions). On May 14, 2020 at a pre-planned interim review of trial data, the MDSMB recommended that the blinded phase of HPTN 083 be stopped due to the demonstration of superior efficacy of CAB LA when compared to daily, oral FTC/TDF (HR 0.345, two-sided p = 0.0005) and that participants randomized to the active FTC/TDF group be offered CAB LA. At the time of the interim review, there were a total of 52 incident HIV infections in 3689 person years of follow-up, distributed across arms as shown in the figure below. The hazard ratio in the CAB LA versus FTC/TDF arms is 0.345 (bias-corrected point estimate; 95% adjusted CI 0.181-0.617), this represents an approximate two-thirds reduction in the number of incident infections relative to oral FTC/TDF.

Figure 1. HIV Incidence in Trial HPTN 083



Source: Sponsor's BTDR package

Notably, adherence to FTC/TDF appeared high in this trial (protective drug levels were achieved in 83% of participants and drug levels correlating with daily use were detected in 74% of participants), suggesting that the observed superior efficacy of CAB LA is not attributable only to the improved adherence associated with an every 8-week dosing regimen. In addition, the rate of STIs among participants was high overall, suggesting that the study population was at high risk for HIV acquisition as intended.

Preliminary safety data from HPTN 083, as summarized by the Sponsor, suggest that CAB LA is generally well-tolerated. Injection site reactions (ISRs) were common, occurring in 81% of participants in the CAB LA arm. The majority (79%) of participants reported ISRs that were categorized as mild or moderate in severity. Approximately 2% of CAB LA participants permanently discontinued study drug because of an injection-related adverse event. There were no differences in Grade 3 or higher adverse event rates between CAB LA and oral FTC/TDF. There were 4 deaths (0.2%) in the CAB LA arm, none of which were determined to be attributable to study product.

HPTN 084

HPTN 084 is an ongoing Phase 3, double-blind, randomized, controlled trial of CAB LA vs FTC/TDF among cisgender African women. In May 2020, the MDSMB also reviewed data from HPTN 084 and at that time recommended that the trial continue. The MDSMB reviewed HPTN 084 data again on November 5, 2020 and concluded that the trial had met its objective of superiority over FTC/TDF and recommended that the blinded phase of the trial be stopped. At the time of this interim analysis, there were 3808 person-years of follow-up with a total of 38 incident HIV infections reported, 4 among participants receiving CAB LA and 34 among participants receiving FTC/TDF. The HIV incidence rates were 0.21 and 1.79 in the CAB LA and FTC/TDF arms, respectively, with a hazard ratio (95% CI) of 0.11 (0.04, 0.32).

In addition to demonstrating superior efficacy, the available safety data suggest that CAB LA was well-tolerated among cisgender women. ISRs were common, occurring in 32% of CAB-LA participants. Most ISRs were Grade 1 in severity and none lead to treatment discontinuation.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

BTD should be granted for CAB LA for HIV PrEP for individuals at high risk of HIV acquisition. In HPTN 083, CAB LA was shown to be superior to FTC/TDF for the prevention of HIV in MSM and TGW. Subsequently, in HPTN 084, CAB LA was found to be superior to FTC/TDF for the prevention of HIV in cisgender women.

In addition to demonstrating improved efficacy over FTC/TDF (the only approved therapy at the time Trials HPTN 083 and HPTN 084 were initiated), CAB LA offers a much-needed alternative approach to HIV PrEP for patients who aren't willing or able to take an oral medication daily. It is hoped that the availability of a long-acting therapy for HIV prevention will result in an increase in utilization of PrEP and will be associated with high rates of adherence, which has historically been a key driver of PrEP effectiveness.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

The Sponsor intends to submit an NDA for CAB LA for HIV PrEP in early-mid 2021. The Division has been and will continue to work closely with the Sponsor to determine the best path forward for the NDA. Both parties are committed to bringing the drug to the market as expeditiously as possible given the superiority finding in both HPTN 083 and HPTN 084.

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AIMEE C HODOWANEC
12/01/2020 01:38:22 PM

KIMBERLY A STRUBLE
12/01/2020 01:41:39 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109678

MEETING MINUTES

Viiv Healthcare Company
c/o GlaxoSmithKline
Attention: Beth Austin, PhD
Senior Director, Global Regulatory Affairs
5 Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Austin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK 1265744, cabotegravir (CAB).

We also refer to the face-to-face meeting between representatives of your firm and the FDA on June 14, 2017. The purpose of this meeting was to discuss the HIV pre-exposure prophylaxis (PrEP) development program for CAB.

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

If you have any questions, call me at (240) 402-5708.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: June 14, 2017, 11:00 AM – 12:30 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1311
Silver Spring, Maryland 20903

Application Number: 109678
Product Name: GSK 1265744, cabotegravir
Indication: Prevention of HIV-1 infection
Sponsor/Applicant Name: Viiv Healthcare Company

FDA ATTENDEES

Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, MPH, Deputy Director for Safety, DAVP
Kimberly Struble, PharmD, Clinical Team Lead, DAVP
Yodit Belew, MD, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Laine Peyton Myers, PhD, Acting Pharmacology/Toxicology Team Lead, DAVP
David McMillan, PhD, Pharmacology/Toxicology Reviewer, DAVP
Julian O'Rear, PhD, Lead Clinical Virology, DAVP
Damon Deming, PhD, Clinical Virology Reviewer, DAVP
Anamaris Colberg Poley, PhD, Clinical Virology Reviewer, DAVP
Islam Younis, PharmD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV), Office of Translational Science (OTS)
Lana Almansour, PharmD Candidate, DCP IV
Vikram Arya, PhD, Clinical Pharmacology Reviewer, DCP IV
Wen Zeng, PhD, Biometric Reviewer, Division of Biometrics IV (DBIV)
Tamara Johnson, MD, Maternal Health Team Lead, Division of Pediatric and Maternal Health
Ingrid Chapman, PharmD, BCPS, Office of Surveillance and Epidemiology (OSE), Division of Risk Management

SPONSOR ATTENDEES

ViiV Healthcare Participants

Kimberly Smith, M.D., MPH Vice President, Global Medical Strategy
Karen Grainger Head, Regulatory Affairs
William Spreen, Pharm. D. Vice President, Medicines Development Leader
David Margolis, M.D., MPH, Project Physician Leader

Parul Patel, Pharm. D. Director, Clinical Pharmacology
Alex Rinehart, Ph.D. Director, Global HIV Prevention Strategy
Amy Cutrell, M.S. Director, Research Statistics
Marty St. Clair Director, Clinical Virology
Beth Romach, Ph.D., D.A.B.T., Global Head of Nonclinical Safety

GlaxoSmithKline (GSK) Participants
Beth Austin, Ph.D. Senior Director, Global Regulatory Affairs
Shanker Thiagarajah, BSc Medical Science, MB ChB; Medical Director SERM, GCSP, Infectious Diseases
Chris Brook, Ph.D, CMC Project Leader, Medicine and Process Delivery

(b) (4)

HPTN/Division of Acquired Immunodeficiency Syndrome (DAIDS) Participants
Melissa Kin, M.S., MBA IND Manager, Regulatory Affairs Branch
Division of AIDS/NIAID/NIH/DHHS
Myron Cohen, M.D, Yeargan-Bate Professor of Medicine, Microbiology and Epidemiology Associate Vice Chancellor for Medical Affairs and Global Health
Director, Institute for Global Health and Infectious Diseases Chief, Division of Infectious Diseases
University Of North Carolina, Chapel Hill
Sheryl Zwerski, MSN, CRNP Acting Program Director, Prevention Sciences Program
DAIDS/NIAID/NIH/DHHS

1.0 BACKGROUND

GSK1265744 (cabotegravir, CAB) is an HIV integrase strand transfer inhibitor that is being developed by ViiV Healthcare as an oral and long-acting (LA) formulation for the treatment and pre-exposure prophylaxis (PrEP) of HIV-1 infection. The Division of Acquired Immunodeficiency Syndrome (DAIDS) is conducting most of the Phase 2 and 3 studies for the PrEP indication under IND 122744. Phase 2 study, (b) (4), HPTN 077, and Phase 2b/3 study 201738, HPTN 083, are currently ongoing. Phase 3 study 201739, HPTN 084, is pending. The purpose of this meeting was to discuss the Phase 2 studies and the Phase 3 development program for the CAB HIV PrEP indication. The sponsor sent a copy of their final slides *(see attached)* to the FDA to support a discussion of questions 2 (Vaccine Challenge Study), 5 (NDA Submission based on Phase 3 PrEP study), 6 (Optional CAB Oral Lead-in), 7 (PK tail and potential risk for development of resistance) and 8 (Safety monitoring of pregnancy in HPTN).

The FDA sent ViiV preliminary comments and ViiV requested that the meeting discussion focus on questions, 2, 7, 8, 6, and 5. Below are the questions ViiV wanted to discuss, FDA's preliminary comments, and the discussions during the meeting.

2.0 DISCUSSION

After introductory remarks, the sponsor acknowledged the FDA's feedback in the preliminary comments and proceeded to update the FDA on their Phase 3 development program of CAB for both HIV treatment and HIV PrEP indications. In the HIV treatment indication, sponsor indicated they had completed enrollment in both the FLAIR (n=615) and ATLAS (n=614) studies with good participation in females of 22% and 32% respectively. With these studies, sponsor anticipates there will be NDA/MAA filings in the first half of 2019. In their Phase 2 study, sponsor indicated they now have week 96 analysis from the LATTE-2 and these results will be presented at the IAS in July and the results support progression of Q8W dosing for an HIV treatment indication. The sponsor plans to submit a proposal to FDA in the upcoming weeks to obtain additional feedback on the Q8W dosing regimen for HIV treatment indication. For an HIV PrEP indication, the sponsor indicated that HPTN 077 primary results will be presented at IAS July 2017, HPTN 083 enrollment is still ongoing at US sites and HPTN 084 is on target for 4th quarter of 2017.

Question 2: Does the Division agree that the proposed clinical study is appropriately designed? Based on this design, does the Division agree that a lower limit of the 95% CI of the ratio for Anti-HAV GMC antibody response in the CAB group compared to the placebo group of at least 0.5 would provide adequate support that CAB does not pose a clinically relevant risk of immunotoxicity for subjects receiving oral or long-acting CAB for HIV prevention?

FDA Response to Question 2: We do not agree with the design of your proposed vaccine challenge study. It remains unclear, based on your study design, what effect cabotegravir will have on the booster immune response induced by the second vaccine challenge on Day 180. Therefore, subjects who received drug at the beginning of the study should also receive drug and be at steady state prior to the second challenge, and should continue treatment up to the collection of the final blood sample. Daily dosing throughout the entire duration of the study is not necessary – A drug holiday between the primary and secondary phases of the study would be acceptable.

Please provide the following in your protocol for this trial: justification of blood collection times for IgM and IgM responses using historical patient data with the hepatitis A vaccine, historical data or data from the scientific literature to support antibody response, and data to support use of the planned hepatitis A antibody assays. Please also confirm that detection of both IgG and IgM will be included as part of your immunogenicity analyses.

Statistical comment: According to the submission, the winning criteria is that if the lower limit of the two-sided 95% confidence interval for the ratio of anti-HAV antibody geometric mean concentration (GMC) 1 month after the first vaccine dose between the CAB group and the placebo group is greater than or equal to 0.5, this will provide sufficient evidence that CAB exposure does not attenuate the immunological response of the hepatitis A vaccine. The rationale for 0.5 is unclear. Please provide the full protocol with additional details concerning the analytical method used to meet the objective of the challenge study. Details should include whether the test criteria coincides with a non-inferiority, bioequivalence, or other testing strategy. The Division may have additional comments after review of the full protocol.

Discussion: The Sponsor agreed to add an identical six week period of CAB/placebo treatment in order to evaluate the potential impact of CAB on the immune response due to the second HAVRIX (booster) vaccination with an intervening drug holiday between the first and second vaccine dose as recommended. Furthermore, the Sponsor indicated that they would treat evaluation of antibody response after the booster as a secondary endpoint because they believed the best opportunity to evaluate immune response is with the first vaccine challenge.

Justification of IgM and IgM responses using historical patient data with the hepatitis A vaccine to support antibody response and data to support the use of the planned hepatitis A antibody assays.

The Sponsor acknowledged the FDA's recommendation but responded that documentation of IgM antibody response following vaccination is rarely performed given the primary objective of vaccine studies is to assess long-term humoral immune response. Consistent with HAVRIX studies, the Sponsor proposed to measure total antibody response which is a composite of Ig (M, G, A). The Sponsor also noted that the assay does not distinguish between the three classes.

The FDA expressed concern on the potential impact CAB may have on immunoglobulin class switching based on results of nonclinical studies that have been performed. Furthermore, the FDA asked the Sponsor if there is a possibility of evaluating specifically IgG in addition to all immunoglobulins (A, G and M) in the composite assay to assess any class switching. Possible interference with class switching was the original concern from the FDA from the nonclinical study with KLH. The Sponsor indicated that the IgG assay mentioned in the backgrounder was not currently validated. The Sponsor did not prefer to use an unvalidated assay. FDA asked the Sponsor if they had any historical data in their vaccine trials that measure just IgG or did they also look at total antibody response. The Sponsor further responded that the majority of their historical data measured total antibody response and that the challenge is using a validated assay in these trials.

FDA recommended that if the Sponsor could not address the safety concern with the vaccine challenge trial, then it may be preferable to investigate other antigens (e.g., KLH) instead. The Sponsor indicated concerns with using KLH as a challenge antigen due to assay validation issues. The Sponsor also indicated that that they thought about influenza vaccine but indicated the challenges with using a trivalent or quadrivalent vaccine.

FDA acknowledged the Sponsor's feedback and indicated they would discuss this issue internally to determine how much assay validation is needed. The Sponsor stated they would follow-up with the vaccine group on whether IgM and or IgG specific assays are available.

Statistical Comments:
The Sponsor clarified that the primary analyses will test for non-inferiority (NI) comparing CAB + HAVRIX and HAVRIX groups at day 29. The NI will be established if the lower bound of the two-sided 95% CI for anti- HAV antibody geometric mean concentration (GMC) ratio is equal to or greater than the NI margin of 0.5. The primary analysis will be performed in the per-protocol population but additional sensitivity analyses will be done using a modified intent-to-treat

population. The Sponsor also explained their rationale for using 0.5 as the NI margin in their study.

FDA indicated this will be discussed with their CBER colleagues along with the draft guidances that were cited by the Sponsor.

FDA pointed out that part of the justification for 0.5 as the NI margin seems inaccurate, i.e., the GMC on placebo would be zero. Because the titer value of the antibody would be zero in the placebo arm.

Question 7: Does the Division agree that although TDF/FTC will be used for CAB PK tail coverage in Phase 3 studies, based on current data limitations and study design considerations, future product labeling may recommend risk counseling in combination with appropriate use of HIV prevention methods, where clinically indicated, to cover the PK tail? Specifically, TDF/DTC use would be one of several risk-based options, but not mandatory. If not, can the Division elaborate on the expectation of evidence to support such an approach?

FDA Response to Question 7: The concern with CAB LA PK tail is that, unlike TDF/FTC for PrEP use, after the last dose of CAB LA, the duration of exposure to CAB is expected to be significantly longer, potentially longer than 52 weeks. Thus, the risk of development of resistance in patients who discontinue use of CAB for PrEP may be significantly higher (though theoretical). We agree that the counseling and selection of prevention methods for patients who discontinue CAB PrEP should occur between the patient and the provider. However, it is also important to quantify the theoretical risk of development of resistance to justify the optional use of TDF/FTC post discontinuation. Please provide your proposal for postmarketing plans to establish the incidence (or risk of) development of resistance.

Discussion: The Sponsor acknowledged the theoretical risk for development of resistance to CAB during waning plasma concentrations in the 'PK tail' but provided additional rationale for why they believed this risk is low. The Sponsor discussed data from nonclinical and clinical observations that suggest that CAB has a high barrier to the development of resistance. In addition, the Sponsor evaluated the susceptibilities of site-directed mutants expressing integrase substitutions, including Q148K and Q148R, to dolutegravir (DTG), CAB, raltegravir (RAL), and elvitegravir (EVG). The fold change (FC) reductions in susceptibility of the site-directed mutants to DTG and CAB were smaller than those to RAL and EVG. The Sponsor also discussed findings where INSTI resistance-associated substitutions were observed in viruses from 2 subjects from the LATTE and 1 subject from LATTE-2 trials. In virus from one of the LATTE subjects, the INSTI resistance-associated substitution Q148R and NNRTI resistance-associated substitution E138Q were selected at Week 48 and conferred a slight reduction in RPV susceptibility; there was a 3.08 FC reduction in susceptibility to CAB. In virus from the second LATTE subject, INSTI resistance-associated substitutions E138K, G140A, and Q148R, and the NNRTI resistance-associated substitution K101E were selected at Week 180 after 60 weeks of low level viremia. This virus had a 21 FC reduction to RPV and 116 FC reduction to CAB. In LATTE-2, virus selected from a subject at Week 48 of maintenance expressed the INSTI resistance-associated substitution Q148R and the NNRTI resistance-associated substitutions

K103N, E138G, and K238T. This virus had a 3.34 FC reduction in susceptibility to RPV and a 5.06 FC reduction to CAB.

Questions for Understanding the Risk of Developing CAB Resistance during PrEP

The Sponsor indicated that to better understand what proportion of individuals and for how long detectable levels persist in plasma beyond 52 weeks, a modification was made to HPTN 077 to add an additional 24 weeks of follow-up in the tail phase for a total of 76 weeks post final injection. The Sponsor indicated that long term follow-up data for HPTN 077 Cohort 1 will be due at the end of 2017 and Cohort 2 (mid-2018). In order to determine at what plasma concentration is protection from HIV infection lost and whether or not CAB can select for resistant mutants following infection with wild–type virus when plasma concentrations are subtherapeutic, the Sponsor indicated that results from HPTN 083/084 will help address these questions but that is dependent on adherence to oral TDF/FTC in step 3.

Considerations for Post-Marketing Resistance

The Sponsor indicated that they believe that the risk of developing resistant virus will be low for subjects at low risk of infection. The Sponsor also expressed the need to explore more "real-world" settings/trial designs in which the majority of participants will discontinue CAB LA after they are (perceived to be) no longer at risk of infection. This would mean exploring trial designs that do not provide TDF/FTC coverage in the PK tail in various populations and varying geographic settings. This would more likely occur in a demonstration setting and would the Sponsor would welcome the FDA's feedback. The Sponsor indicated that they would like to undertake more modeling work to understand the potential to develop resistance relative to varying levels of efficacy. As efficacy increases, the tolerance to accept any resistance that would develop could possible increase as well. From a public health perspective, the Sponsor indicated that they will be in collaboration with external groups to aid in surveillance of CAB resistance.

FDA indicated that they did not have any comments and would discuss this closer to the NDA submission. FDA asked Sponsor what would happen if a trial patient did get HIV infected? Are they started on an integrase inhibitor regimen? The Sponsor indicated that each case would be evaluated by the primary healthcare provider on a case by case basis after considering the results of resistance testing.

Question 8: Does the Division agree that the current level of monitoring for women of child-bearing potential and on-study pregnancies in HPTN 084, both during CAB LA therapy and following discontinuation of dosing is sufficient?

FDA Response to Question 8: Your proposed monitoring plan for women of child-bearing potential and on-study pregnancies is reasonable. In the event of pregnancies, we strongly recommend you collect outcomes of pregnancies, gestational age at delivery, birth weight of newborns, as well as on the presence of any congenital anomalies. Please clarify your plans to collect PK data in subjects who prematurely discontinue CAB during HPTN083 and HPTN084,

including in women who discontinue due to pregnancy. Collection of PK data on the neonates born to mothers exposed to CAB should also be considered.

In addition, when submitting safety reporting as INDSR or as part of the NDA safety assessment, please include country-specific background rates for pregnancy outcomes including still births, miscarriages, pre-term labor and congenital anomalies to help with the assessment of pregnancy outcomes during the clinical trials.

In light of the planned treatment discontinuation in case of pregnancies, please comment if you have future plans to further investigate the potential use of CAB during pregnancy. As you know, availability of safe and effective PrEP is important for pregnant women.

Discussion: The Sponsor presented slides on the current plans for managing and evaluating pregnancy outcomes in HPTN 084. It was stated that a pregnancy sub-study is being discussed with DAIDS and HPTN and that the sub-study design will be shared with the FDA when available. It was also stated that obtaining data in pregnancy with CAB will be valuable and that a stepwise approach to study CAB PrEP during pregnancy will be considered, following review of pregnancy data from HPTN 084 and the ongoing Phase 3 treatment studies.

FDA expressed concern that it appears no unblinding will occur in women who become pregnant during HPTN 084, and that perhaps women who become pregnant should be unblinded, or be permitted to unblind upon request. It was noted that still births and early postnatal deaths observed in the nonclinical rat pre- and post-natal studies are important data of concern that require appropriate patient consent and clinical evaluation to understand the relevance of the pre-clinical findings.

The Sponsor discussed the PPN results with respect to the CAB concentrations in rats being higher than those seen in the clinical setting.

FDA indicated that the relevance of the rat study results to human pregnancy and delivery are unknown and that the PPN results should be included in the informed consent form. FDA also recommended that increased monitoring during pregnancy be considered. It was communicated to the Sponsor that the HPTN 084 pregnancy substudy under discussion will provide important information on these safety concerns.

The Sponsor clarified there is no final timeline yet for the proposed HPTN 084 pregnancy substudy, but that it is being actively designed, and further details will be made available to the FDA. The Sponsor also stated that they will discuss/consider the FDA's recommendation to unblind women who become pregnant or offer the choice to women to have study drug unblinded to allow them to make informed decisions.

Question 6: Does the Division agree that lack of significant findings following analyses of the adverse event data during the mandatory oral lead-in throughout the treatment and PrEP clinical development programs, may be sufficient for labeling to indicate optional use of the oral lead-in for CAB for the PrEP indication at the time of NDA submission?

FDA Response to Question 6: While we agree that lack of significant safety findings during the oral lead-in dosing period during the Phase 3 trials will be encouraging and the absence of an oral lead in period is not anticipated to have a significant impact on the steady state exposures of CAB, the Division remains concerned that the proposed 'optional use of the oral lead-in' has not been evaluated during the pivotal Phase 3 trials. As recommended for your HIV-treatment development program, in order to support your proposed alternative dosing recommendations, we encourage you to consider modifying your Phase 3 PrEP trial(s) to allow a subset of subjects to be dosed without an oral lead-in.

Discussion: Sponsor acknowledged the need to study subjects who do not receive CAB oral lead-in (OLI) prior to transitioning to CAB LA. This is being discussed internally by the Sponsor.FDA inquired about feedback received in the field on OLI and the Sponsor shared that reactions have been mixed with end-users supporting no OLI and investigators having mixed reactions with some favoring OLI and others (e.g., the New York City Health Department) favoring no OLI as a simple path to CAB LA in participants at high risk.
The point was made that generally, product labeling reflects the clinical trials and dosing that have been studied clinically.

The Sponsor asked whether data with and without OLI generated in the HIV treatment program could be extrapolated to PrEP. It was acknowledged that clinical data without use of OLI could potentially be extrapolated from the HIV-infected population. It was also noted that the benefit/risk in the HIV-infected population may differ from that in the otherwise healthy PrEP population, and therefore, the overall available safety package would be a review issue.

Question 5: In the event that one study completes before the other and meets its primary objective of non-inferiority (HPTN 083) or superiority (HPTN 084), would a single Phase 3 study(once complete, and in conjunction with Phase 1 and Phase 2 data and supportive information from the treatment program) be sufficient to support an NDA submission of CAB for HIV PrEP in the studied population (male/TGW or female)?

FDA Response to Question 5: While the Division prefers that the submission for the original NDA contains both HPTN 083 and 084, if the time gap for study completions between the two trials is too wide, you may file the NDA based on results from HPTN 083; however, this will be further discussed at the preNDA meeting. If HPTN 084 is not part of the original NDA, submission of clinical trial data from HPTN 084 will be requested as a postmarketing commitment (PMC) or postmarketing requirement (PMR) as indicated, during the review cycle of the original NDA.

Discussion: The Sponsor indicated that HPTN 084 may complete in advance of HPTN 083. The sponsor asked if an NDA could be supported by HPTN 084. Ideally, the FDA would like to have data from two studies. However, if superiority is met with HPTN 084, the Agency could discuss allowing the NDA to be submitted with data from a single trial.

Question 10: Does the Division agree with the proposed plan for evaluation and cross reporting by ViiV of 'blinded' INDSRs issued by DAIDS during the conduct of PrEP studies? Does the Division have any additional advice with regard to the appropriate handling of blinded INDSRs?

FDA Response to Question 10: We are in general agreement with your proposal but have following requests:

- NIH should submit any INDSR electronically to minimize delay in reviewing the events.
- After ViiV/GSK reviews the INDSR and submits the assessment of the event to DAVP, please clearly reference the INDSR submitted by NIH so that the review team can cross-reference the two INDSR.
- In the event that the assessment of the AE by GSK/ViiV differs from the assessment of NIH, please describe how you plan to designate final coding of the event in the dataset. For example, if NIH finds the event not to be treatment-related, and the investigator finds the event to be possibly treatment-related and ViiV views the event to be definitely treatment-related, what will the final coding of the event reflect? Do you plan to have 3 different causality assessment columns?
    - We also have general comment with regards to your safety datasets. Please discuss how adverse events will be coded. It is the reviewer's experience that NIH uses a different AE assessment methodology compared to sponsors. Please provide a discussion on methodology to be used for coding AEs.

Discussion: The Sponsor sought clarification on whether confirmation that HTPN and ViiV/GSK use MedDRA coding for adverse events provided in advance of the meeting, addressed the FDA comments.

The FDA clarified that DAIDS AE entry and grading systems sometimes differ, with some events entered as a diagnosis vs. the individual AE symptoms, and that it would be best to collect AEs in the same manner and to use the same grading systems. As an example, DAIDS uses an AE grading scale of 1-5, with Grade 5 used for death. This grading scale is inconsistent with that used by sponsor (Grades 1-4). In addition, the FDA expressed concerns with causality assessments being provided by multiple sources (i.e., investigator, Sponsor).

The Sponsor acknowledged the FDA's recommendations and clarified that the intent within the data sets used as part of the submission, was to report causality as assigned by the Investigator. Individual case narratives may have additional contextual information and provide causality assessment from the Sponsor. The sponsor and DAIDS representative stated that they will review

the coding and data entry plans to ensure that AEs will be captured using MedDRA and using industry standard.

Summary of Action Items

1. Sponsor intends to follow-up with the vaccine group to address questions regarding the Vaccine Challenge Study and relay their findings back to the FDA.
    a. Sponsor intends to submit a copy of the protocol to the FDA in order for the agency to have an internal discussion with their CBER colleagues.
2. Sponsor summarized risk of developing CAB resistance if patient seroconverts during the PK tail and indicated their hopes in looking at HPTN 083 and 084 to provide data that will address these questions. However this is dependent on the level of adherence to TDF/FTC in Step 3.
3. Sponsor will provide a response to the Agency's question about the type of ARV regimen that will be used if a patient seroconverts.
4. Sponsor indicated they are conducting a pregnancy substudy and pursuing this strategy for HPTN 084 while also taking a stepwise approach to starting PrEP in pregnancy. The final study design is under active review and FDA recommended that the Sponsor submit a preliminary draft when available.

SECURE EMAIL COMMUNICATIONS

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

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

---

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

/s/

ANDREW A GENTLES
07/13/2017