CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212887Orig1s000
212888Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109678

MEETING MINUTES

ViiV Healthcare Company
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) LA and rilpivirine (RPV) LA.

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2019. The purpose of the meeting was to discuss proposals for the content and format of the two New Drug Applications (NDAs), one for oral CAB and the other for the co-pack of CAB LA + RPV LA injectable regimen as well as the results of the Phase 3 studies (ATLAS and FLAIR).

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 or the mainline at (301) 796-1500.

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: Pre-NDA

Meeting Date and Time: January 28, 2019 3:00-4:30 PM
Meeting Location: White Oak Building 22, Rm 1415

Application Number: 109678
Product Name: GSK 1265744, cabotegravir

Indication: Treatment and Prevention of HIV-1 infection
Sponsor/Applicant Name: ViiV Healthcare Company

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Andrew Gentles, PharmD, BCPS AQ-ID

FDA ATTENDEES
John Farley, MD, MPH Deputy Director, OAP
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, Deputy Director for Safety, DAVP
Sarah Connelly, MD, Associate Director of Biomedical Informatics
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, Pharmacology/Toxicology Team Lead (Acting), DAVP
David McMillan, PhD, Pharmacology/Toxicology Reviewer, DAVP
Julian O'Rear, PhD, Lead Clinical Virology, DAVP
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
Vikram Arya, PhD, Clinical Pharmacology Reviewer Team Lead (Acting), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV), Office of Translational Science (OTS)
Mario Sampson, PharmD, Clinical Pharmacology Reviewer, OTS/OCP/DCP IV
Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)
Wen Zeng, PhD, Biometric Reviewer, DBIV
Kathleen Fitzgerald, Nurse Consultant/Lead Reviewer, Office of Device Evaluation (ODE)

Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices (DAGRID)
Elizabeth Everhart, MSN, RN, ACNP, Team Lead, Division of Risk Management (DRISK)
Till Olickal, Ph.D., PharmD, Senior Risk Management Analyst, DRISK
Wen-Hung Chen, PhD, Team Leader, Clinical Outcome Assessments (COA) Staff

SPONSOR ATTENDEES
ViiV Healthcare Participants
William Spreen, Pharm.D, Vice President, Medicines Development Leader
David Margolis, M.D., MPH, Project Physician Leader, Director, Clinical Development
Amy Cutrell, M.S, Director, Research Statistics
Parul Patel, Pharm.D, Clinical Pharmacology Lead, Scientific and Medical Office
Krischan Hudson, Director, Clinical Development
Sandy Griffith, Director, Clinical Development
Christine Talarico, Clinical Development Manager
Christine Lampkin; Regulatory Affairs Director

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
Susan Ford, Pharm.D., Director, Clinical Pharmacology, Modeling and Simulation
Jeremy Roberts, M.Sc., Manager, Statistics

Janssen Participants
Peter Williams, Senior Director, Compound Development Team Leader RPV LA
Kati Vandermeulen, Senior Director, Global Regulatory Affairs ID&V
Karen Gerry, North American Regulatory Liaison
Rodica Van Solingen, Medical Lead
Eileen Birmingham, Medical Safety Officer
Veerle Van Eygen, Senior Scientist, Clinical Virology
Sophie Lauchau-Durand, Scientific Director, Preclinical
Herta Crauwels, Ph.D, Associate Scientific Director, Clinical Pharmacology
Simon Vanveggel, M.Sc, Qualitative Sciences

1.0 BACKGROUND

Cabotegravir (CAB) is an HIV integrase strand transfer inhibitor being developed by ViiV Healthcare as an oral and long-acting (LA) injectable formulation for the treatment and prevention of HIV-1 infection. Rilpivirine (Edurant, RPV) is a non-nucleoside reverse transcriptase inhibitor that is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL. Currently, ViiV/GSK/Janssen are developing a co-packaged product, CAB LA + RPV LA intramuscular injections as a complete regimen to maintain virologic suppression (HIV-1 RNA <50 copies/mL) in HIV-1 infected, virologically suppressed patients. A short-term oral lead-in using CAB and RPV tablets will be initiated prior to initiating the LA regimen.

Under this agreement, ViiV Healthcare will submit two NDAs, one for oral CAB tablet and a second for the co-pack (2 mL and 3 mL vials) of the LA regimen of CAB + RPV. Janssen will submit an efficacy supplement for RPV to update the approved EDURANT label for use as an oral lead-in prior to the CAB LA + RPV LA regimen.

ViiV submitted a Type B Pre-NDA meeting request on November 30, 2018, to obtain feedback from the FDA on key aspects related to submitting two New Drug Applications (NDAs), one for oral CAB and the other for the co-pack of CAB LA + RPV LA injectable regimen, as well as the results of the Phase 3 studies (ATLAS and FLAIR). The meeting request was granted by the FDA on December 10, 2018, with a Type B face-to-face (FTF) meeting scheduled for January 28, 2019.

FDA sent Preliminary Comments to ViiV on January 24, 2019. Upon receipt of the Agency's preliminary comments, ViiV acknowledged the Agency's feedback and requested that the meeting focus on Questions 10 (Evaluation of Drug Induced Serious Hepatotoxicity), 12 (Risk Management Plan (RMP) for the CAB + RPV program), 14 (Plan for submission of clinical trial datasets), 17 (Structure of Mock ISS datasets), 19 (Health Outcome Measures) and the additional comments pertaining to request for protocol and clinical pharmacology summaries. The Agency received a slide set from ViiV on January 28, 2019 which was used to support the discussion during the meeting.

2.0 DISCUSSION

In opening remarks, the Agency welcomed ViiV as well as their colleagues from GSK and Janssen and stated the Agency's goal is to reach consensus on key areas related to the planned NDA submissions for the oral CAB and co-pack of the CAB LA + RPV LA injectable regimen. ViiV acknowledged the Agency's feedback communicated in the Preliminary Comments dated January 24, 2019 and notified the Agency that the planned NDA submissions were scheduled for April 29, 2019. The Sponsor also summarized the pooled analyses of the Phase 3 study results for studies ALTAS and FLAIR using their slide set (refer to the appendix). During the discussion of Confirmed Virologic Failures in the CAB LA + RPV LA arm of the FLAIR trial, the Agency asked the Sponsor to provide information in the upcoming NDA submissions on the frequency of the L74I substitution among HIV-treatment naïve subjects in the US population. The Agency also requested the Sponsor provide information on whether there were any individuals who had L74I at baseline and responded to treatment using the CAB LA + RPV LA regimen.

ViiV also provided responses to the Agency's preliminary comments that were provided for Questions 10, 12, 14, 17 and 19. The following is a summary of the issues discussed at the meeting.

Evaluation of Drug Induced Serious Hepatotoxicity (eDISH)
In response to the Agency's preliminary comments for question 10, the Sponsor proposed to submit a comprehensive hepatotoxicity signal assessment as part of the NDA submission as per the FDA's *2009 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Considerations*. There was a noted higher incidence of acute viral hepatitis in the CAB + RPV group and the Sponsor plans to discuss these cases in the NDA submissions as requested.

The Agency agreed with the Sponsor's proposal to submit a comprehensive hepatoxicity signal assessment as part of the planned NDA submission along with a discussion of cases where acute viral hepatitis was observed in the CAB +RPV group.

Risk Management Plan for the CAB + RPV program

In response to the Agency's preliminary comments for question 12, the Sponsor proposed to submit a single integrated risk management plan for CAB + RPV program that would include relevant elements of the co-packaged (CAB LA + RPV LA) injectable regimen and oral CAB + oral RPV in the planned NDA submission. The Sponsor indicated that this proposal would avoid repetition, facilitate reviews, and make it easier to address overlapping risks for the various formulations.

The Agency agreed with the Sponsor's rationale and proposal to provide a single integrated risk management plan for the CAB + RPV regimen as mentioned above.

Plan for submission of clinical trial datasets

In response to the Agency's preliminary comments for question 14, the Sponsor proposed to divide the pooled laboratory dataset into 4 folders and submit the individual studies with the full laboratory datasets not divided. The folders proposed were as follows:

1. Hematology
2. Chemistry
3. Hepatic/Hepatobiliary
4. Other (will include immunology data)

The hepatic folder will contain the hepatic parameters of: prothrombin international normalized ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, direct bilirubin and total bilirubin.

The Agency agreed with the Sponsor's proposal on dividing the pooled laboratory dataset folders while submitting individual studies with full datasets not divided.

Structure of Mock ISS datasets

In response to the Agency's preliminary comments for question 17, the Sponsor provided the Agency with the requested sample application number (#901398) and date of submission (January 28, 2019) of the mock ISS datasets.

Post-Meeting Note: *The Agency has received the submission and it is currently under evaluation by the eDATA team. Evaluation results will be shared with the Sponsor once the evaluation has been completed.*

Health Outcome Measures

In response to the Agency's preliminary comments for question 19, the Sponsor acknowledged the comments from the COA staff and indicated that they will submit written responses ahead of the NDA submissions.

The Agency acknowledged the Sponsor's feedback and indicated that a future teleconference with the Sponsor was available to answer any additional questions regarding the health outcome measures.

Additional Comments – Clinical and Clinical Pharmacology Request for specific templates
In response to the Agency's request for providing information using a CDER generated template for clinical and clinical pharmacology, the Sponsor agreed to provide summaries of final study reports of clinical and clinical pharmacology trials as a MS Word document file using the template provided by DAVP. The applicant cited technical challenges with including hyperlinks to clinical pharmacology study reports in the word document.

The Agency indicated that hyperlinks were not required and concurred with the Sponsor that these summaries can be submitted within 30 days of the planned NDA submissions.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was not discussed during the January 28, 2019 meeting.

  Post-Meeting Note: *The Agency reviewed the Table of Contents for Planned NDA in Appendix 6 of the meeting package submitted on December 19, 2018 and has determined that this will be a complete application.*

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

  Post-Meeting Note: *At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary. We will make a final determination for the need for a REMS during the review of your application.*

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  1. *CDER generated summary templates for clinical and clinical pharmacology.*

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT-CLINICAL
  NDA NUMBER: LATE COMPONENT – CLINICAL PHARMACOLOGY

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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

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* (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.

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.				

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 (February 2018) and the associated 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor to provide information in the upcoming NDA submissions on the frequency of L74I substitution among HIV-treatment naïve subjects in the US population.	Sponsor	April 2019
Sponsor to provide information on whether there were any individuals who had L74I at baseline and responded to treatment using the CAB LA + RPV LA regimen	Sponsor	April 2019

5.0 ATTACHMENTS AND HANDOUTS

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

40 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

ANDREW A GENTLES
02/20/2019 02:12:46 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109678

MEETING MINUTES

ViiV Healthcare Company
Attention: Beth Austin, PhD
Senior Director, Global Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Austin:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1265744 (cabotegravir) injectable solution.

We also refer to the telecon between representatives of your firm and the FDA on August 19, 2016; 9:00 am to 10:00 am. The purpose of the meeting was to discuss the phase 3 clinical development program for cabotegravir long-acting in combination with rilpivirine long acting for the treatment of HIV-1.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 19, 2016; 9:00 am to 10:00 am
Meeting Location:	teleconference
Application Number:	IND 109,678
Product Name:	GSK1265744 injectable solution
Indication:	Treatment of HIV-1
Sponsor/Applicant Name:	ViiV Healthcare Company
Meeting Chair:	Debra Birnkrant, MD
Meeting Recorder:	Sohail Mosaddegh, PharmD

FDA ATTENDEES

Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Kim Struble, PharmD, Medical Team Lead, DAVP
Yodit Belew, MD, Clinical Reviewer, DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/ Toxicology Team Lead
Islam Younis, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP)
Vikram Arya, PhD, Clinical Pharmacology Reviewer, (OCP)
Julian O'Rear, PhD, Virology Team Lead, DAVP
Lisa Naeger, PhD, Virology Reviewer, DAVP
Thamban Valappil, PhD, Statistical Team Lead, Division of Biometric
Karen Winestock, Chief, Project Management Staff, DAVP
Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP
Erin South, PharmD, Risk Management Analyst, Division of Risk Management (DRISK)
Yasmin Choudhry, MD, Clinical Outcome Assessments

SPONSOR ATTENDEES

ViiV Attendees:
Kimberly Smith, MD, MPH, Vice President, Global Medical Strategy, Head, Research and Development

Karen Grainger, Director, Regulatory Affairs
William Spreen, Pharm D, Medicines Development Leader
David Margolis, MD, MPH, Project Physician Leader, Global Medical Strategy
Parul Patel, PharmD, Clinical Pharmacology Lead, Scientific and Medical Office
Paul Wannamaker, Director, Clinical Development
Amy Cutrell, MS, Director, Research Statistics
Marty St. Clair, Director, Clinical Virology
Miranda Murray, Head, Global Health Outcomes

GSK Attendees:
Beth Austin, PhD, Senior Director, Global Regulatory Affairs
David Dorey, M. Math, Principal Statistician
Shanker Thiagarajah, MD, Director, Safety Evaluation and Risk Management, Global Clinical Safety and Pharmacovigilance
Mark Pace, Regulatory Project Manager, Global Regulatory Affairs
Debbie Thomas, PhD, Director, Labeling, Global Regulatory Affairs

(b) (4) Attendee:
(b) (4), PharmD, Clinical Pharmacology, Modeling and Simulation

Janssen Attendees:
Peter Williams, PhD, Senior Director, Compound Development Team Leader
Kati Vandermeulen, Senior Director, Global Regulatory Affairs ID&V
Rodica Van Solingen, MD, Global Medical Leader
Simon Vanveggel, MSc, Assoc. Director, Quantitative Sciences
Herta Crauwels, PhD, Associate Director, Clinical Pharmacology

BACKGROUND

GSK1265744 (cabotegravir, CAB) long-acting injectable and oral tablet is an investigational HIV-1 integrase inhibitor. It is proposed in combination with injectable rilpivirine long-acting (RPV) for the treatment of human immunodeficiency virus type 1 (HIV-1).

The purpose of this meeting is to discuss the overall development program for the combination of cabotegravir oral, cabotegravir long-acting and rilpivirine long-acting for the maintenance of viral suppression of HIV-1.

FDA sent Preliminary Comments to ViiV Healthcare Company (ViiV) on August 12, 2016.

DISCUSSION

Questions from the July 15, 2016 meeting background package are in **bolded** font followed by FDA's preliminary responses in *italicized* font, meeting discussions follow in regular font. The meeting focused on questions 6, 7, 9, and 11.

6. CAB Oral Tablet: Indication and Intended Use

For the treatment of HIV infection, ViiV is developing oral CAB 30mg tablets for the following uses:

a. oral lead-in use in virologically suppressed subjects prior to transitioning to maintenance therapy with long-acting CAB LA + RPV LA. This would permit individual patient-level evaluation of safety and tolerability prior to administration of LA injection;

b. injection-free periods (bridging) for subjects on injectable LA maintenance therapy (e.g., due to travel plans or for a identified, short-term injection-free period).

Key sections of draft labeling will be provided as an appendix to the briefing document.

Does the Division agree that existing Phase 2b data and planned Phase 3 data generated with the oral tablet can provide sufficient data to allow approval of oral CAB 30 mg with the following limited use indication statements?

"TRADENAME is indicated in combination with EDURANT fora short-term oral lead-in dosing for at least 4 weeks to assess tolerability of oral cabotegravir and rilpivirine prior to monthly maintenance administration of TRADENAME CAB/RPV LA for the treatment of HIV-1 infection?"

"TRADENAME is indicated in combination with EDURANT for short-term oral therapy for patients who will miss planned maintenance dosing with TRADENAME CAB/RPV LA."

(b) (4)

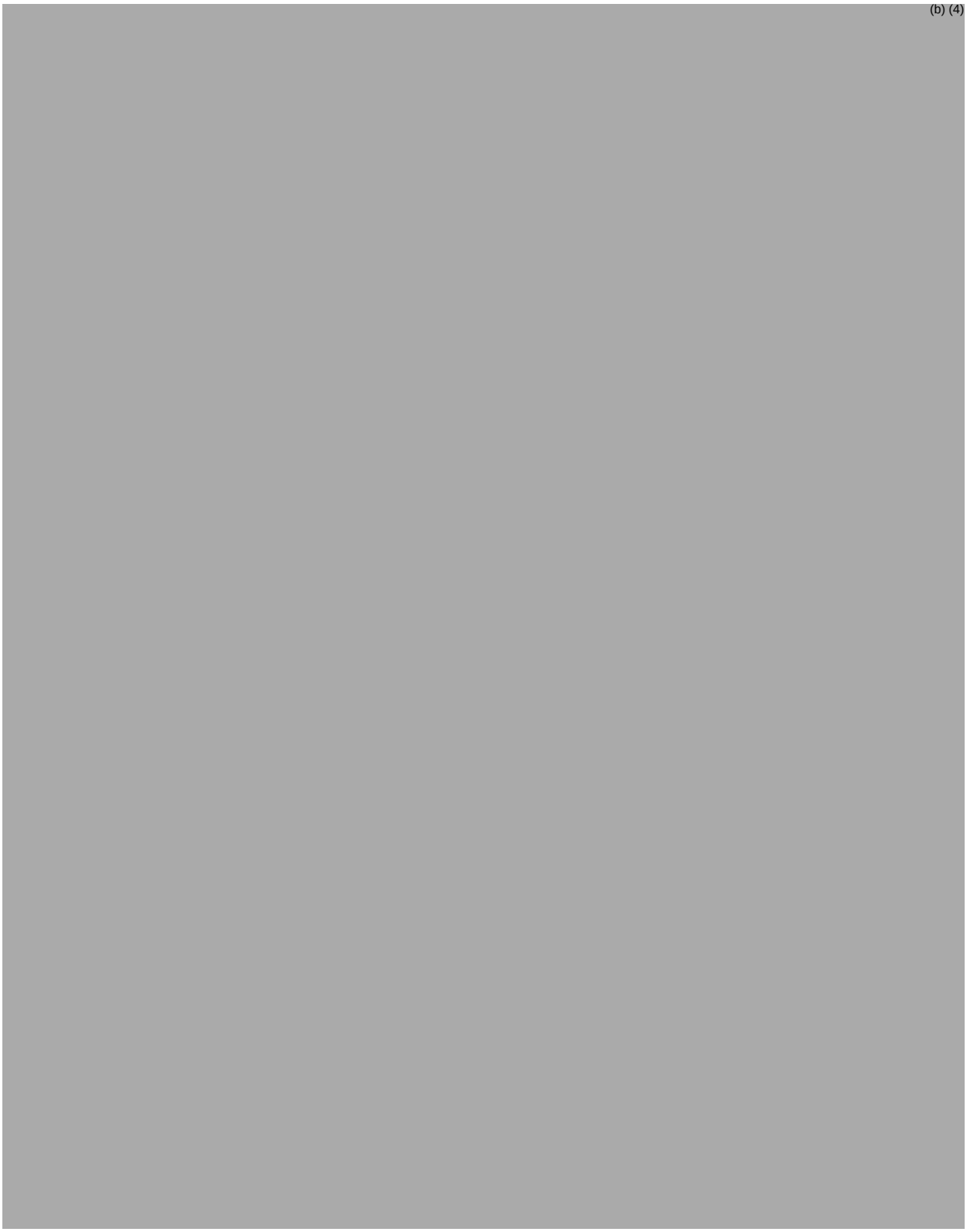
While your proposal appears reasonable, we cannot agree until we have reviewed the Phase 3 clinical trial data. You should also consider qualifying the maximum time allowed for use of the oral tablet while patients are unable to access the injectable form.

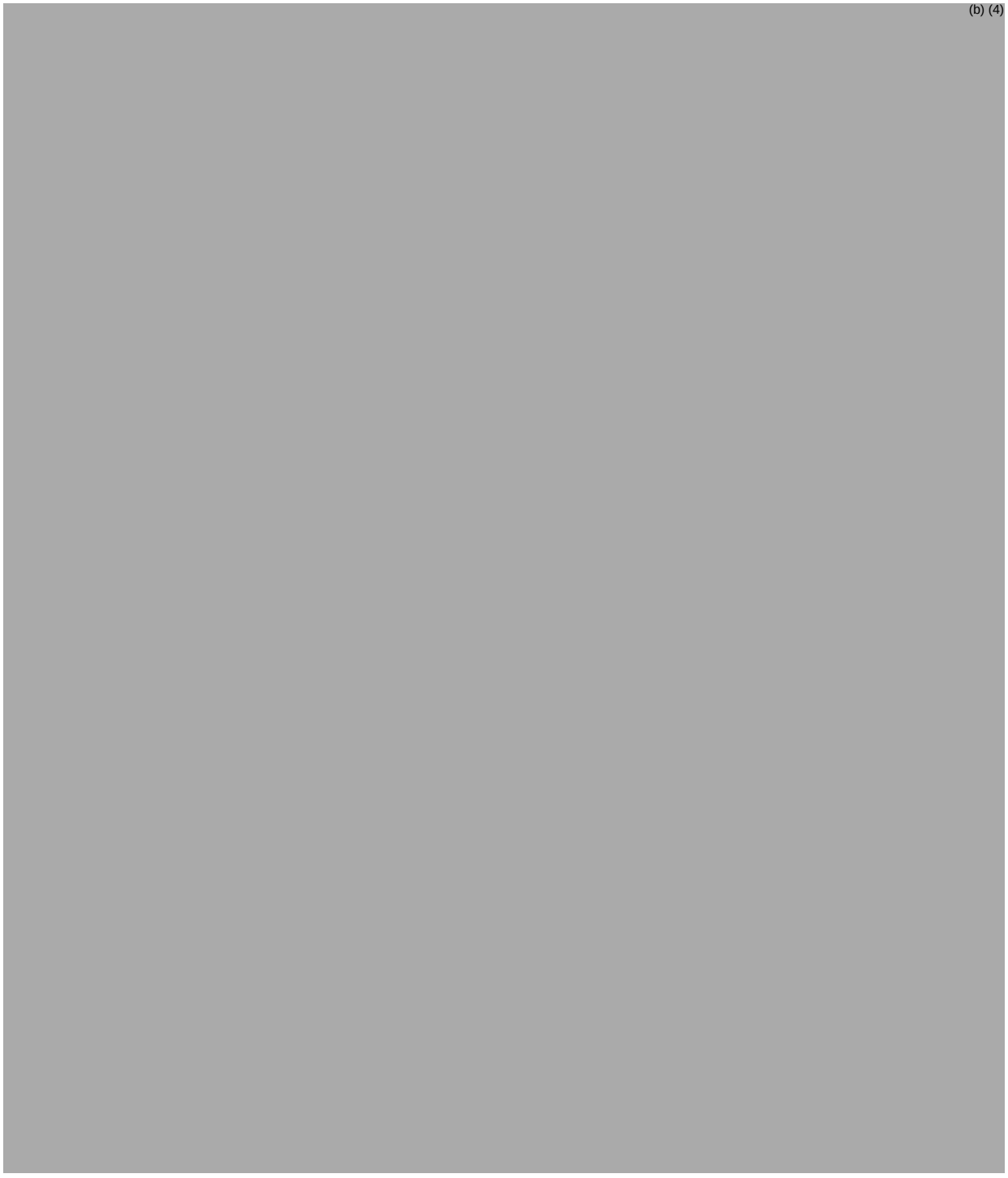
Meeting Discussion:
Viiv gave a summary of the bridging within the development program:

- Based on use of oral bridging in LATTE-2 (~4/230 subjects in LATTE-2), it is anticipated that oral bridging will not be commonly used. However, there is a need to provide guidance on maximum duration of use to support limited treatment indication.
- It is anticipated that oral bridging in Phaseb3 will not exceed 8-12 weeks and that participants who desire/require oral dosing beyond that point would be instructed to transition to approved HAART regimens.

FDA stated that 8 to 12 weeks may be reasonable for oral bridging; however, a final decision will be a review issue.

7. (b) (4)





9. CDISC Question

The clinical pharmacology development program spans a number of years. With the first clinical pharmacology studies initiated in 2008, the dataset standards pre-dated the initiative for reporting via CDISC standards. As a result, eight of these studies have completed the reporting process (finalized and signed off) using legacy dataset standards (namely, SI dataset standard).

Rather than revising finalized and signed-off clinical pharmacology study reports, the sponsor proposes to retrospectively convert study datasets to SDTM and ADAM while retaining the original statistical package and source tables from the legacy datasets. In general, clinical pharmacology study reports are transitioning to CDISC standards and several studies have already been finalized and signed off with fully traceable CDISC reporting processes. The status of existing studies is provided in Table 2.

SDTM and ADAM CDISC datasets, with the corresponding CRT packages, will be submitted with the NDA for all studies in the development program (Phase 1 – Phase 3). For the eight clinical pharmacology study reports which have been previously finalized, the datasets and CRT packages included in the submission will differ from those used to generate statistical displays. For all other study reports (clinical pharmacology and clinical), the CDISC datasets and CRT packages will be those used for generating the statistical displays.

Does the Division agree with this proposal for the NDA submission?

DAVP response: You will need to submit legacy data including legacy aCRF, CRF data and analysis data for traceability. The tables were created using the legacy datasets and the medical and stat reviewers need the data for their review. The Agency's Data Standards Group may have additional recommendation to share with you.

Study ID	Formulation	Description	Dataset Standard
ITZ111451	Oral suspension and oral tablet	First in human single and multiple dose escalation in healthy subjects, and 10 day monotherapy in HIV-infected subjects	SI*
ITZ111682	Oral tablet	Oral relative bioavailability study	SI
ITZ111839	Oral tablet	Drug interaction with etravirine	SI
ITZ112929	Oral tablet	10 day monotherapy in HIV-infected subjects (low dose)	SI
LAI114433	LA parenteral	Single dose escalation in healthy subjects and assessment of genital tract concentrations	SI
LAI115428	Oral tablet and LA parenteral	Multiple dose administration in healthy subjects	SI
LAI116181	Oral tablet	Drug interaction with rilpivirine	SI
LAI116585	Oral free acid and sodium salt	Oral relative bioavailability study	SI
LAI116815	Oral tablet and LA parenteral	LA relative bioavailability with midazolam probe	SI + CDISC
LAI117008	Oral tablet	Mass balance (ADME)	CDISC
LAI117009	Oral tablet	Thorough QT study	CDISC
LAI117010	Oral tablet	Rifampin DDI	CDISC
LAI117011	Oral tablet	Oral contraceptive DDI	CDISC
LAI117020	Oral tablet	Oral relative bioavailability study	CDISC
201103	LA parenteral	Phase 2a PrEP in low risk men & women (HPTN077)	HPTN** + CDISC
201120	LA parenteral	Phase 2a PrEP in low risk men (ECLAIR)	CDISC
201479 (ongoing)	Oral tablet	Moderate Hepatic impairment study	CDISC
201480 (ongoing)	Oral tablet	Severe Renal impairment study	CDISC
201741	Oral tablet	Oral relative bioavailability study with candidate Phase 3 formulation	CDISC
201767 (planned)	LA parenteral	Multicompartment PK study in healthy volunteers	CDISC
205696 (planned)	Oral tablet	Food effect study with high fat/high calorie meal	CDISC
205712 (planned)	Oral tablet	Rifabutin DDI study	CDISC

*SI: system independent, the GSK legacy dataset standard

**HPTN: the dataset standard applied by HPTN

Meeting Discussion:
ViiV stated that based on FDA's preliminary comments, they we now propose to submit only legacy packages for the first eight studies listed in Table 1 (i.e., non-CDISC). These legacy packages will consist of a define.pdf that links the aCRF and the analysis datasets. They

proposed a test transfer of a CRT package to illustrate traceability. FDA agreed that with the proposed test transfer.

FDA stated that recommendations from the FDA Data Standards Group were pending.

11. CDISC - Phase 2b/3 Studies

Given that the Phase 2b/3 studies (LATTE, LATTE-2, FLAIR, ATLAS) will be reported in CDISC, the Applicant proposes that additional efficacy datasets for these studies (i.e., ADEffOUT, 7 separate lab datasets and ADAEOUT) will not be submitted as part of the NDA.

Does the Division agree with this proposal? Are there specific virology / resistance datasets required for these studies?

DAVP Response: We strongly recommend you continue to submit the ADEffOUT, ADAEOUT and 7 separate lab datasets in your NDA submission.

Meeting Discussion:
ViiV will submit these additional datasets for the four identified studies. FDA requested that the laboratory datasets be submitted as separate files. When submitted as a single file, the file is too large.

Additional Topic:

FDA recommended a future meeting/discussion on the planned commercial co-pack for the US and that this topic could be addressed in a CMC End of Phase 2 meeting.

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

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

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

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

Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

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.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

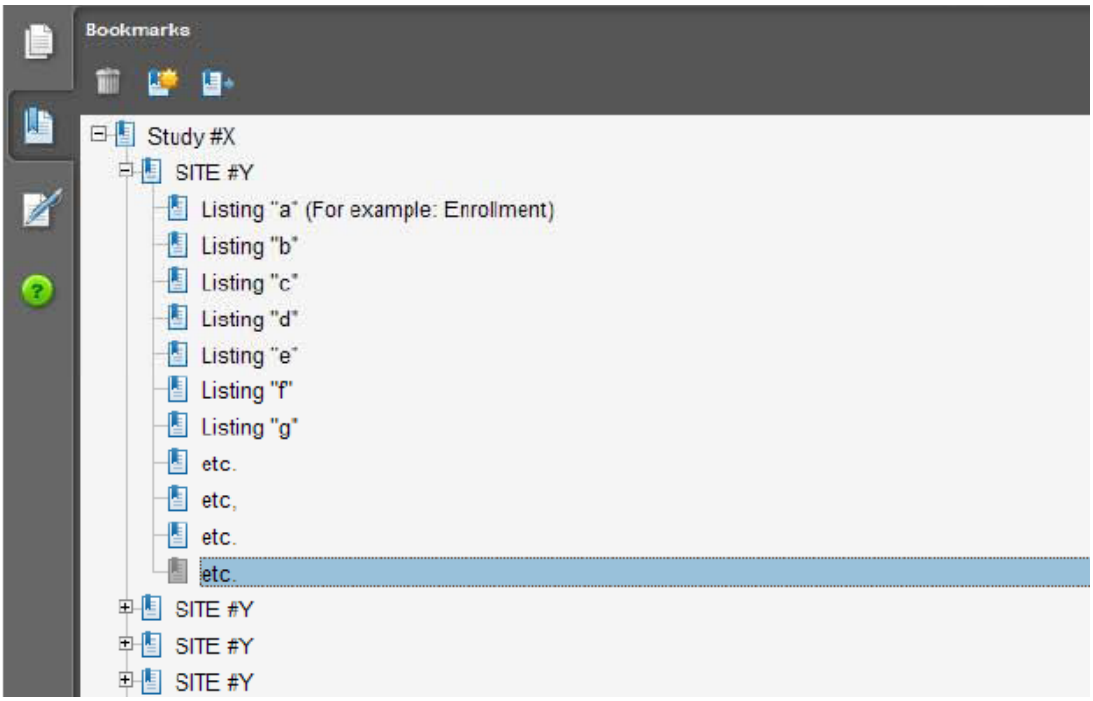
a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents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

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

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

References:

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Respond to questions regarding Patient Reported Outcome with advice from the Agency's Clinical Outcome Assessments Staff.	FDA	When possible

Respond to questions regarding data standards.	FDA	When possible
Submit iPSP	Sponsor	October 18, 2016

ATTACHMENTS AND HANDOUTS
Viiv's slide set used during the telecon.

6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SOHAIL MOSADDEGH
09/21/2016