CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210455Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113456

MEETING PRELIMINARY COMMENTS

Janssen Research & Development, LLC.
Attention: Karen Gerry, BSc
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Gerry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed dose combination tablet.

We also refer to your December 20, 2016, correspondence requesting a pre-NDA meeting to discuss and seek concurrence from the Agency regarding the proposed content and format of the NDA submission in support of the registration of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-NDA

Meeting Date and Time: February 14, 2017, 1 - 2 PM
Meeting Location: Teleconference

Application Number: IND 113456
Product Name: darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed dose combination tablet
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Janssen Research & Development, LLC.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 14, 2017, 1 PM, between Janssen Research & Development, LLC. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Due to an unmet medical need for a protease inhibitor (PI)-based single-tablet regimen, Janssen (Sponsor) and Gilead Sciences, Inc. (Gilead) have co-formulated the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TFV)-prodrug tenofovir alafenamide (TAF, 10 mg) with the PI darunavir (DRV, D; 800 mg), the pharmacokinetic (PK) enhancer cobicistat (COBI, C; 150 mg), and the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC, F; 200 mg) to form the first PI-based fixed-dose combination (FDC) single-tablet option for oral once daily use (D/C/F/TAF). The D/C/F/TAF tablet offers the additional advantage of including an N(t)RTI backbone that has an improved renal and bone safety profile compared with a tenofovir disoproxil fumarate (TDF)-containing backbone. The development program of the D/C/F/TAF FDC product is based on six clinical studies conducted with the FDC tablet in adults:

- Two pivotal Phase 3 studies (TMC114IFD3013 and TMC114FD2HTX3001), which are still ongoing;
    - Study TMC114FD2HTX3001 in HIV-infected, ART-naïve adult subjects
    - Study TMC114IFD3013 in HIV-infected, virologically-suppressed adult subjects
- One completed Phase 2 study conducted by Gilead; and
- Three completed Phase 1 studies, of which two were conducted by the Sponsor and one by Gilead.

This program is complemented, as appropriate, by studies from the development programs of the individual compounds, i.e., studies conducted in adolescents, studies to assess the QT effects, studies in special populations such as subjects with renal impairment, hepatic impairment and subjects co-infected with hepatitis B, and drug-drug interaction studies.

Gilead has transferred further development of the FDC tablet to Janssen and, subject to regulatory approval, the manufacturing, registration, distribution and commercialization of the product worldwide.

The primary purpose of the meeting is to discuss and seek concurrence from the Agency regarding the proposed content and format of the NDA submission in support of the registration of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection.

The proposed NDA submission is targeted for September 2017.

2.0 DISCUSSION

Your questions are in ***bold italics*** and DAVP comments are in standard font.

2.1. Pharmacology/Toxicology

Q1: As there are no new non-clinical studies included in this NDA, the Sponsor will only provide a non-clinical overview in Module 2.4. Does the Division agree with this approach?

FDA Response: Yes, we agree with your proposal.

2.2. Clinical Pharmacology

Q2: The Sponsor plans to align the drug-drug interaction information and recommendations for the D/C/F/TAF FDC with the approved Prescribing Information for the respective separate agents. Additional drug-drug interactions based on an up-to-date status of new drug approvals and/or Prescribing Information updates for relevant concomitant drugs will be included, as applicable. Since D/C/F/TAF is a complete treatment regimen for HIV-infection, drug-drug interaction data with other HIV antiretrovirals (ARVs) will however not be included in the D/C/F/TAF FDC Prescribing Information. Does the Division agree with this approach?

FDA Response: In general the proposed approach for addressing drug-drug interactions is acceptable. The need for additional drug-drug interaction studies will be a review issue.

2.3 Clinical

Q3: The Sponsor proposes to discuss and submit the analysis of the individual Phase 2/3 studies, and will not perform an integrated analysis of these studies. Does the Division agree with this proposal?

FDA Response: Yes, we agree with your proposal.

Q4: The Sponsor proposes to submit narratives and case report forms (CRFs) as outlined in the Sponsor Position. Does the Division agree with this strategy for inclusion of narratives and CRFs?

FDA Response: No, we do not agree. Narratives and CRFs should be submitted for all deaths, SAEs, and AEs leading to discontinuation of study drug, regardless of causality. With respect to adverse events (AEs) of special interest, given that the Phase 3 trials are comparing TAF to TDF, please submit narratives for all events of bone fractures, proximal renal tubulopathy and uveitis, regardless of severity or causality. Your analysis plan should include the list of terms used to identify these cases. In addition, an analysis of subclinical proximal renal tubulopathy cases, based on objective laboratory abnormalities, should be included in your reports, as has been done for recent submissions of clinical trial data involving TAF- and TDF-containing drug products. For the other listed events, which reflect safety concerns associated with darunavir, i.e., skin reactions/rash, hepatotoxicity, lipid abnormalities and coronary artery events, we concur with your strategy to submit narratives only for Grade 3 or 4 events that are at least possibly related to study drug; however, given that all subjects will be exposed to darunavir or a PI, we suggest that these cases not be limited to the D/C/F/TAF FDC arms.

Q5: The Sponsor proposes to submit the safety data of the 2 ongoing Phase 3 studies as follows:

- ***A primary safety analysis up to the individual subjects' Week 48 (or earlier in case of discontinuations) visits as cut-off date;***

- ***Safety data 'as available in the database' after the individual Week 48 visit up to a maximum of 90 days prior to the US NDA submission date, focusing on deaths, SAEs and discontinuations.***

Does the Division agree with the proposed safety reporting periods at the time of NDA submission?

FDA Response: Yes, we agree with your proposal.

Q6: The Sponsor proposes to use the NDA filing date as the data cut-off date for an NDA safety update. Does the Division agree with the proposed NDA safety update cut-off date and content?

FDA Response: Yes, we agree with your proposal.

2.4 Data Sets/Other

Q7: For the planned NDA, the Sponsor proposes to:

Submit Clinical Data Interchange Standards Consortium (CDISC)-compliant Study Data Tabulation Model (SDTM)/Analysis Data Model (ADaM) data set packages for the Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001 and Phase 1 studies TMC114FD2HTX1001 and TMC114FD2HTX1002. The CDISC package will contain the following:

- ***Four SDTMs (one for each of the 2 Phase 3 studies and 2 Phase 1 studies)***
- ***Four ADaMs (one for each of the 2 Phase 3 studies and 2 Phase 1 studies)***

- ***Generate Statistical Analysis Plan (SAS) transport files containing patient, endpoint, genotypic and phenotypic data as outlined in Draft Guidance, Attachment to Guidance on Antiviral Product Development –Conducting and Submitting Virology Studies to the Agency - Guidance for Submitting HIV-1 Resistance Data (February 2014) for the 2 Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001 that collect resistance data. Virology data sets will also be provided in CDISC format. A preliminary resistance data structure will be shared before assembling formal clinical trial resistance data sets.***

- ***Not include SAS Programs.***

Does the Division agree with the above proposals?

FDA Response: Please include SAS programs in the NDA submission. The programs should include those to generate ADaM datasets from the raw datasets as well as those to generate the main efficacy and safety results in the clinical reports. In addition to the datasets in CDISC format, we also request specifications for the efficacy outcomes dataset, i.e., ADEFFOUT.XPT. Please see the attached appendix (Attachment 2) for the details.

2.5 Regulatory

Q8: The Sponsor proposes to provide Financial Disclosure information for the 2 Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001 in the D/C/F/TAF NDA. Does the Division agree with this approach?

FDA Response: Yes, we agree with your proposal.

Additional Comments:

Chemistry, Manufacturing and Controls

- Please indicate how much stability data will be provided at the time of NDA submission. We note that different formulations have been used during the development process. If you are going to rely, in whole or in part, on stability data for slightly different developmental batches please indicate how these tablets differ from the marketed tablets. Please also discuss any plans to bridge between different tablets (e.g., Phase 3 to commercial, supportive stability to primary stability).

Clinical Pharmacology

- You proposed the use of D/C/F/TAF in adolescents based on prior pediatric studies including E/C/F/TAF Study GS-US-292-0106. D/C/F/TAF results in lower TAF exposure compared to F/TAF 200/25 mg, which has similar TAF exposure as E/C/F/TAF. Study GS-US-292-0106 alone, therefore, will not be sufficient to establish similar TAF exposures from D/C/F/TAF in adolescents compared to adults. In your NDA submission, you should provide data and/or a detailed justification to support the prediction of similar TAF exposures from D/C/F/TAF in adolescents compared to adults.

PREA REQUIREMENTS

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

We acknowledge your Agreed iPSP dated June 30, 2015. Your Agreed iPSP, along with any requests for waivers or deferrals, should be included in your New Drug Application.

PRESCRIBING INFORMATION

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

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

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

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

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

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 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).

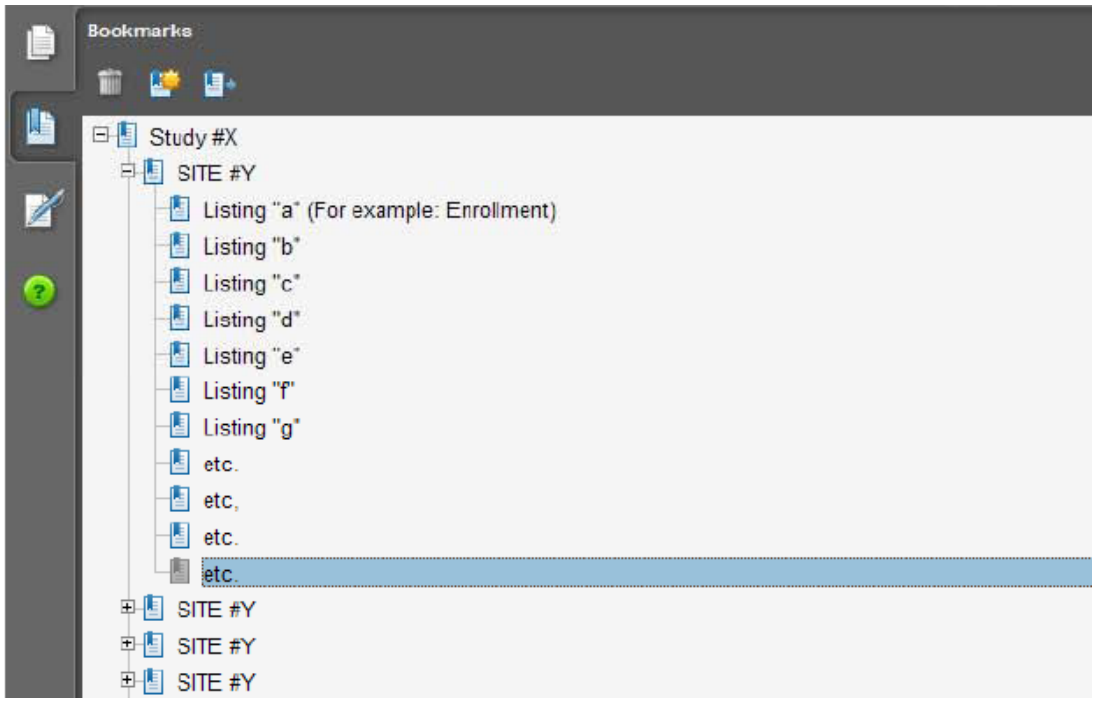
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

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.

Appendix:

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

Attachment 2

Specifications for Efficacy Outcomes Dataset

The dataset should have only one record per subject and should include information as outlined in detail in the table below for the following:

- Demographic variables
- Baseline characteristics (e.g., baseline genotypic and phenotypic data, stratification factors)
- Exposure variables (e.g., first and last dosing date)
- Population flags (e.g., intent to treat, per-protocol)
- Efficacy outcomes (e.g., primary, secondary)
- Covariates and subgroup variables
- Subject disposition variables

The table below includes recommendations for variable name, variable label, and codes and provides comments.[2]

Table 1. Efficacy Outcomes and Related Covariates (ADEFFOUT)[3]

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GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADaM	Analysis Data Model
AE	adverse event
ART	antiretroviral therapy
BLCF	baseline carried forward
BOCF	baseline observation carried forward
$CD4^+$	cluster of differentiation 4 positive
CDC	Centers for Disease Control and Prevention
CRF	case report file
FI	fusion inhibitor
GSS	genotypic sensitivity score
INSTI	integrase strand transfer inhibitor
ISE	integrated summary of effectiveness
ISO	International Organization for Standardization
ITT	intent to treat
LOCF	last observation carried forward
LVCF	last value carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MIX	multiple investigational agents
mL	milliliter
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OBT	optimized background treatment
PI	protease inhibitor
PSS	phenotypic sensitivity score
SAP	statistical analysis plan
SAE	serious adverse event
uL	microliter

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

/s/

MYUNG JOO P HONG
02/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113456

MEETING MINUTES

Janssen Research and Development, L.L.C.
Attention: Karen Gerry, BSc
Manager, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Gerry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (D/C/F/TAF) fixed-dose combination tablet.

We also refer to the teleconference between representatives of your firm and the FDA on October 22, 2014. The purpose of the meeting was to discuss the design of the proposed Phase 3 study and the suitability of the study to serve as the pivotal study to support the submission of the planned New Drug Application (NDA).

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

If you have any questions, call Stacey Min, Pharm.D., Senior Regulatory Project Manager at (301) 796-4253 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 22, 2014; 2:30 -3:30 pm, EST
Meeting Location:	Teleconference
Application Number:	113456
Product Name:	Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (D/C/F/TAF) fixed-dose combination tablet
Indication:	Treatment of HIV-1 Infection
Sponsor/Applicant Name:	Janssen Research and Development, L.L.C.
Meeting Chair:	Linda Lewis, M.D., Medical Team Leader
Meeting Recorder:	Stacey Min, Pharm.D., Senior Regulatory Project Manager

FDA ATTENDEES
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Linda Lewis, M.D., Medical Team Leader, DAVP
William Tauber, M.D., Medical Officer, DAVP
Adam Sherwat, M.D., Acting Medical Team Leader, DAVP
Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
Takashi Komatsu, Ph.D., RAC, Clinical Virology Reviewer, DAVP
Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
Julian O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
Mario Sampson, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCP IV)
Islam Younis, Ph.D., Clinical Pharmacology Team Leader, DCP IV
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DB IV)
Guoixing Soon, Ph.D., Biometrics Team Leader, DB IV
Karen Winestock, Chief Project Management Staff, DAVP
Stacey Min, Pharm.D., Senior Regulatory Project Manager, DAVP
Felicia Duffy, RN, BSN, MSEd, Risk Management Analyst, Division of Risk Management (DRISK)
Naomi Redd, Pharm.D., Acting Team Leader, DRISK

SPONSOR ATTENDEES (Janssen)
Katia Boven, MD, Senior Director, Global Clinical Development

Herta Crauwels, PhD, Associate Scientific Director, Clinical Pharmacology
Goedele De Smedt, MD, Senior Director, Compound Development Team Leader
Karen Gerry, BSc, Manager, North American Regulatory Liaison
Rhonda Hatfield, MBA, DHA, Manager, Global Regulatory
Erkki Lathouwers, MSc, Scientist, Clinical Virology
Magda Opsomer, MD, Medical Leader, Clinical Development
Simon Vanveggel, MSc, Associate Director, Biostatistics
Charles Zezza, PhD, MBA, Director, Global Regulatory Leader

SPONSOR ATTENDEES (Gilead)
Christophe Beraud, PhD, Director Regulatory Affairs
Scott McAllister, MD, Senior Director, Clinical Research
Brian Kearney, PharmD, Sr. Director, Clinical Pharmacology

1.0 BACKGROUND

On August 11, 2014, Gilead Sciences, Inc. on behalf of Janssen Research and Development L.L.C. submitted an End of Phase 2 (EOP2) meeting request for IND 113456, fixed-dose combination tablet of darunavir, cobicistat, emtricitabine and tenofovir alafenamide (E/C/F/TAF). Janssen is the sponsor for darunavir and Gilead is the sponsor for cobicistat, emtricitabine and tenofovir alafenamide. Gilead was the original sponsor of IND 113456 but the IND was transferred from Gilead to Janssen on October 8, 2014 after the meeting request and background package was submitted to the IND. In the October 7, 2014 and October 14, 2014 transfer of IND submission, both Gilead and Janssen have agreed to transfer the IND to Janssen and Janssen has requested to continue with the requested meeting as the new IND sponsor.

Darunavir is an HIV protease inhibitor currently used in combination with ritonavir and other antiretroviral agents for the treatment of HIV-1 in adults and pediatric patients 3 years and older. Cobicistat is a CYP3A4 inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection. Emtricitabine is an NRTI used in combination with other antiretroviral drugs for the treatment of HIV-1 in adults and pediatric patients aged 3 months and older. Tenofovir alafenamide is an investigational oral prodrug of TFV. It is an NtRTI used in combination with other antiretroviral drugs for the treatment of HIV-1 infection in adults.

Janssen, in collaboration with Gilead, is developing the D/C/F/TAF FDC tablet, combining DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg for oral once-daily use for the treatment of HIV-1 infection in adults. The following studies have been completed:

- Study GS-US-299-0101: A Phase 1, adaptive-design, multiple-dose study evaluating the bioavailability of 3 formulations of darunavir/cobicistat/emtricitabine/tenofovir alafenamide single tablet regimen relative to the administration of individual components cobicistat-boosted darunavir, emtricitabine, and tenofovir alafenamide.

- Study GS-US-299-0102: A Phase 2b, randomized, double-blinded study of the safety and efficacy of darunavir/cobicistat/emtricitabine/tenofovir alafenamide single tablet regimen

versus cobicistat-boosted darunavir plus emtricitabine/tenofovir disoproxil fumarate fixed-dose combination in HIV-1 infected, antiretroviral treatment-naïve adults.

The Sponsor plans to conduct the following phase 3 study:

- Study TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF)-containing once-daily tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) fixed-dose combination (FDC) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects.

The Sponsor plans to submit the original NDA for D/C/F/TAF during the first half of 2016. The purpose of the meeting is to discuss the development plan for the D/C/F/TAF FDC for the treatment of HIV-1 infection in adults. The meeting request was submitted on August 11, 2014 and the background package was submitted on September 22, 2014. FDA provided preliminary comments on October 21, 2014. After receiving the preliminary comments from FDA, Janssen submitted additional follow-up questions for Question 2, 3 and 6 and additional clinical virology and clinical pharmacology comments on October 22, 2014. Janssen's questions are **bolded**, followed by the preliminary comments in regular font, Janssen's clarifying questions (dated October 22, 2014) are underlined and the discussions are *italicized.*

2. DISCUSSION

2.1. Non-clinical

Question 1: The comprehensive non-clinical packages available for the individual components suggest that the combination of DRV, COBI, FTC and TAF is unlikely to cause additive or synergistic toxicity. Therefore, the Company does not plan to conduct non-clinical combination toxicity studies in support of a future NDA for the D/C/F/TAC FDC. Does the Agency agree that nonclinical combination toxicity studies are not required to support submitting a future NDA for the D/C/F/TAF FDC?

FDA Response to Question 1:
We agree.

Discussion:
No additional discussion.

2.2. Clinical and Biostatistics

Question 2: Does the Agency agree that a primary analysis at Week 24 (b) (4) **in the proposed Phase 3 study (TMC114IFD3013) is adequate to support the approval of an NDA for the D/C/F/TAF FDC?**

FDA Response to Question 2:
No, we do not agree. Switch studies do not allow an evaluation of a drug (or regimen) to induce treatment suppression and only allow an examination of maintenance of suppression. In order to assess the new regimen's ability in maintaining suppression, we recommend subjects remain on the randomized regimen for similar duration and for a minimum of 48 weeks to allow a more robust assessment of loss of viral suppression in patients who were otherwise suppressed on a regimen at trial enrollment. We recommend a primary efficacy analysis timepoint at Week 48, not Week 24.

Janssen's Follow-Up Questions and Discussions:

Janssen Clarifications:

Does the Agency consider that D/C/F/TAF could be approvable based on the following elements:
1/ in treatment-naive and treatment-experienced patients w/o DRV RAMs based on:
- a bioavailability study in healthy volunteers (Study GS-US-299-0101);
- a Phase 2b randomized, double-blind, multicenter, active-controlled study in HIV-1 infected, ARV treatment-naïve adult subjects (Study GS-US-299-0102);
- a bioequivalence study in healthy volunteers
- Is a single dose BE study in fed conditions with [DRV + COBI + F/TAF(10mg)] as the reference acceptable?
  Therefore, the switch study TMC114IFD3013 would not be required.
  Week-24 safety and efficacy analyses of the study as proposed could be suitable as supportive evidence for the approval of D/C/F/TAF

Yes, a single dose BE study can be used for approval but with the caveat that D/C/F/TAF fixed-dose combination (FDC) tablet drug exposure is bioequivalent to approved reference drugs components of the drug for which we have safety and efficacy data. The results of Study -0101 summarized in the meeting background package did not show that drug exposures of all components of D/C/F/TAF were similar to the reference products of the study. TAF is currently not approved as a stand-alone drug but E/C/F/TAF could be used as the comparator for TAF once that FDC is approved because there will be safety and efficacy data applicable to TAF. Darunavir exposures of D/C/F/TAF will need to be similar to exposures of the approved darunavir.

Janssen also inquired if F/TAF FDC tablet is approved to be used in combination with D/C FDC tablet, would the Division agree with using F/TAF as the reference drug. The division stated that it depends on how F/TAF is approved. The proposed FDC drug should either have its own standalone safety and efficacy data or it needs to be bioequivalent to an approved product containing TAF for which safety and efficacy have been shown.

The Division stated that if data is available to show that D/C/F/TAF is bioequivalent to approved reference products, then 24 week safety and efficacy study could be submitted (b) (4) *The Division reminded Janssen that this information is also stated in Guidance for Industry HIV-1 Infection: Developing Antiretroviral Drugs for Treatment.*

Question 3: The primary objective of the proposed Phase 3 study (TMC114IFD3013) is to demonstrate noninferiority in efficacy of switching to a D/C/F/TAF-containing tablet

relative to continuing the current bPI in combination with FTC/TDF FDC in virologically-suppressed HIV-1 infected subjects, as to the proportion of virologic responders determined by having HIV-1 RNA <50 copies/mL at Week 24 (FDA snapshot analysis), with a maximum allowable difference of 10%. Does the Agency agree that a maximum allowable difference of (b) (4)% is acceptable to demonstrate non-inferiority?

FDA Response to Question 3:
No, the Agency does not agree with a maximum allowable difference of (b) (4)% for this switch study. FDA requests a more conservative assessment of efficacy in switch studies because subjects are already virologically suppressed and have demonstrated adequate adherence to therapy. FDA recommends such studies be powered for a very conservative, clinically–based noninferiority margin such as 8 % for better preservation of treatment effect. This NI margin is consistent with that applied during the FDA review of previous switch studies.

Janssen's Follow-Up Questions and Discussions:

Janssen Clarifications:

Does the Agency consider that D/C/F/TAF could be approvable based on the following elements:
2/ in treatment-naive and treatment-experienced patients w/o DRV RAMs based on:
- a bioavailability study in healthy volunteers (Study GS-US-299-0101);
- a Phase 2b randomized, double-blind, multicenter, active-controlled study in HIV-1 infected, ARV treatment-naïve adult subjects (Study GS-US-299-0102);
- one Phase 3 randomized, clinical trial comparing D/C/F/TAF to an approved regimen in treatment naïve subjects demonstrating at least non-inferiority (in the absence of a switch study):
  - Is a non-inferiority margin of 12% in this population acceptable?
  - Components of the FDC will be approved and efficacy will be well established. Is a submission based on week 24 results acceptable, along with W48 data submission during the review process?

The Division advised that a single phase 3 randomized clinical trial comparing D/C/F/TAF to an approved regiment in treatment-naïve patients can be done but the Division recommends the population be relatively straightforward. If Janssen proposes to conduct a comparative study that includes both treatment naïve and experienced patients, we will need to review the protocol before we can provide additional feedback. In addition, if Janssen proposes to submit treatment-naïve data at the time of the original NDA submission, the full package with 48 week data must be submitted. The Division stated that under PDUFA V, we are no longer able to receive efficacy data after the application is submitted for review without an agreement during the pre-NDA meeting. In general these agreements are reserved for novel products or drugs with breakthrough therapy designation. Since D/C/F/TAF is not a breakthrough therapy, the complete 48 week data must be submitted at the time of original NDA submission.

Non-inferiority margin of 10-12 is acceptable for this population.

2.3 Clinical Pharmacology

Question 4: Based on the available data for the individual components, the Company proposes to administer the study drugs with food in the proposed Phase 3 (TMC114IFD3013) switch study. Does the Agency agree that this proposal is appropriate?

FDA Response to Question 4:
Yes, your proposal is acceptable.

Discussion:
No additional discussion.

Question 5: As summarized in the briefing document, comprehensive drug-drug interaction studies have been conducted or are planned with the individual components. Consequently, the Company does not plan to conduct additional drug-drug interaction studies for the D/C/F/TAF FDC. Does the Agency agree that sufficient drug-drug interaction data exist to support submission of a future NDA for the D/C/F/TAF FDC?

FDA Response to Question 5:

We agree with the approach. However, it is unclear from the meeting package which drug-drug interaction studies are proposed for extrapolation. Please provide a list of the drug-drug interactions studies from other development programs for which you plan to extrapolate data to the current application.

Discussion:
No additional discussion.

2.4 Regulatory

Question 6: Does the Agency agree that a clinical development program consisting of the following studies is adequate to support approval of D/C/F/TAF FDC for once daily use in the intended populations?

- **a bioavailability study in healthy volunteers (Study GS-US-299-0101);**
- **a Phase 2b randomized, double-blind, multicenter, active-controlled study in HIV-1 infected, ARV treatment-naïve adult subjects (Study GS-US-299-0102);**
- **a Phase 3 randomized, active-controlled, open-label study to evaluate switching to a D/C/F/TAF-containing once-daily tablet regimen versus continuing the current regimen consisting of a bPI in combination with FTC/TDF FDC in virologically-suppressed, HIV-1 infected subjects (Study TMC114IFD3013).**

FDA Response to Question 6:

We do not agree with your plan to seek approval of D/C/F/TAF (10mg) based on the single switch study (TMC114IFD3013). The pharmacokinetic data from GS-US-299-0101 indicates the TAF exposure at 10 mg as part of D/C/F/TAF is not bioequivalent to the reference TAF 25 mg exposure (about 40-50% lower for the FDC). Conversely, the tenofovir (TFV) exposures following administration of D/C/F/TAF appear to be about 50% higher than the reference TAF. To achieve approval of D/C/F/TAF, you must either demonstrate bioequivalence of the components of D/C/F/TAF to approved product(s) for which efficacy has been demonstrated or you must submit data from an adequate and well-controlled clinical trial comparing D/C/F/TAF to an approved regimen in treatment-naïve subjects demonstrating at least non-inferiority. The proposed switch study TMC114IFD3013 will not be acceptable as the only well-controlled trial. Study GS-US-299-0102 is not adequate to serve as the confirmatory clinical trial.

Janssen's Follow-Up Questions and Discussions:

Does the Agency consider that D/C/F/TAF would be approvable based on the following elements
3/in virologically suppressed patients, based on :
- a bioavailability study in healthy volunteers (Study GS-US-299-0101);
- a Phase 2b randomized, double-blind, multicenter, active-controlled study in HIV-1 infected, ARV treatment-naïve adult subjects (Study GS-US-299-0102);
- One single Phase 3 randomized, active-controlled, open-label study (in the absence of a study a treatment-naive) to evaluate switching to a D/C/F/TAF-containing once-daily tablet regimen versus continuing the current regimen consisting of a bPI in combination with FTC/TDF FDC in virologically-suppressed, HIV-1 infected subjects (Study TMC114IFD3013)
- with a 8% non-inferiority margin
- Components of the FDC will be approved and long-term efficacy will be well established. Is a submission based on week 24 results acceptable for switch indication, along with 48wk data submitted during review?

The Division stated that Janssen could conduct one phase 3 trial in treatment naïve patients if the study is well powered. The Division inquired if there was an issue with using E/C/F/TAF as a comparator and Janssen responded that as seen in results from Study -0101, the combination with F/TAF and D/C behaves differently than E/C/F/TAF. The mechanism for this difference is unknown so it is more difficult to show bioequivalence to the reference drug. Janssen asked that if at the time the NDA is approved, F/TAF is used in combination with D/C, then they would compare F/TAF to D/C/F/TAF. The Division stated that if we see drug interaction between F/TAF and D/C to be 50%, then we may label not to use these two combinations together. The Division advised Janssen that if there are other clinical data to show that D/C and TAF could be used together, then Janssen could use that study instead of doing a full study but Janssen would need to obtain a right of reference to do this.

Janssen inquired if they are able to show bioequivalence of D/C/F/TAF to approved reference products whether they could do one phase 3 trial and the Division replied that this is possible but it depends on the results of the BE study.

The Division clarified whether Janssen was asking if the drug could be approved only in virologically suppressed patients for the original NDA for D/C/F/TAF and Janssen stated that was the question being asked. The Division stated that this is not our thinking at this time. A drug has never been approved for this specific population or indication in an original application. However, the Division stated if in the future there are new reduced regimens (such as fewer drugs or dosing on a weekly or monthly basis) developed only for maintenance of suppression after an initial induction, such an indication could potentially be done at that time.

Additional Comments:

Clinical Virology:

1. For study TMC114IFD3013, in order to minimize the development of resistance, we recommend that HIV-1 RNA retesting should occur in 2 - 4 weeks rather than 3 - 6 weeks in subjects with HIV-1 RNA ≥50 copies/mL.

   Janssen's Follow-Up Question and Discussions:

   Janssen considers 2 weeks is too short to manage such patients and considers 3-6 weeks more feasible.

   The review team will consider the Sponsor's proposal and provide comments on the specific timeframe once the protocol is submitted for review.

2. For study GS-US-299-0102, please provide line item virology data that include dose, HIV-1 subtype, genotypic/phenotypic resistance, and viral load for all available time points.

3. Please use the following to describe HIV-1 RNA results:

   - HIV-1 RNA <LLOQ, Target Not Detected
   - HIV-1 RNA <LLOQ, Target Detected
   - HIV-1 RNA copies/mL

Clinical Pharmacology:

4. Please discuss the observed reduced TAF exposure and increased TFV exposure in the D/C/F/TAF arm in part 3 of study GS-US-299-0101. It seems logical that reduced TAF following the administration of D/C/F/TAF would have led to reduced TFV exposure.

5. Please submit, if available, TDF pharmacokinetic parameters in part 2 of study GS-US-299-0101.

Janssen's Follow-Up Question and Discussions:

Janssen will acknowledge these above noted FDA requests at the time of the NDA filing.

The Division agreed and stated that if Janssen decides to utilize the bioequivalence study route for approval, then these study(ies) must be done in both fed and fasted conditions. The Division also requested that Janssen submit the protocol for review prior to starting the study.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) 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.

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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

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

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

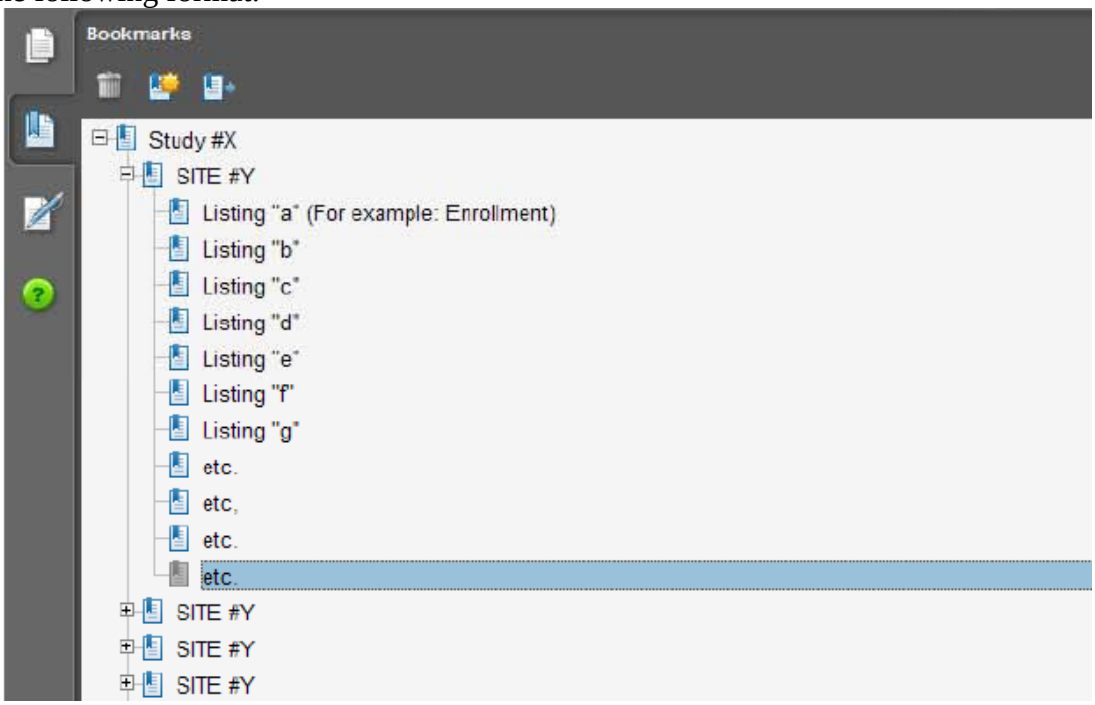
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

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

References:

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting minutes will be provided within 30 days of the teleconference	FDA	November 21, 2014
Will submit the follow-up questions that were emailed on October 22, 2014 in an official submission to the IND.	Sponsor	As soon as possible
Will submit protocols for review prior to initiating the studies.	Sponsor	When the protocol is ready for review.

6.0 ATTACHMENTS AND HANDOUTS

Copy of slides that were emailed by Janssen on October 22, 2014, prior to the teleconference is attached below. Janssen has also submitted an official copy of the slides to the IND.

7 Page(s) has 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/

JEFFREY S MURRAY
10/30/2014