

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212950Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 73916

MEETING PRELIMINARY COMMENTS

ViiV Healthcare Company
Attention: Sherry Watson
Regulatory Affairs Manager, GlaxoSmithKline
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Ms. Watson:

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

We also refer to your December 18, 2017 correspondence, requesting a meeting to discuss the proposed schedule for a rolling New Drug Application and key content/format issues to facilitate submission of the application.

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 (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Nina Mani, PhD, MPH
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:

- Preliminary Meeting Comments
- Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment - Draft Guidance



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 28, 2018; 1:30 pm – 3:00 pm (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 73916
Product Name: fostemsavir

Proposed Indication:



Sponsor Name: ViiV Healthcare Company

FDA ATTENDEES (tentative)

Edward Cox, Director, Office of Antimicrobial Products (OAP)
John Farley, Deputy Director, OAP
Katherine Schumann, Associate Director for Regulatory Affairs, OAP
Debra Birnkrant, Director, Division of Antiviral Product (DAVP)
Jeffrey Murray, Deputy Director, DAVP
Poonam Mishra, Deputy Director for Safety, DAVP
Prabha Viswanathan, Medical Officer, DAVP
Adam Sherwat, Clinical Team Lead, DAVP
Fraser Smith, Biometrics Reviewer
Thamban Valappil, Biometrics Team Lead
K.M. Wu, Non-Clinical Reviewer, DAVP
Hanan Ghantous, Non-Clinical Team Lead, DAVP
Lisa Naeger, Clinical Virology Reviewer, DAVP
Julian O'Rear, Clinical Virology Team Lead, DAVP
Su-Young Choi, Clinical Pharmacology Reviewer
Shirley Seo, Clinical Pharmacology Team Lead
Ruoqing Li, Pharmacometrics Reviewer
Chao Liu, Pharmacometrics Team Lead
Sharon Gershon, OSI Reviewer
Stephen Miller Chemist Lead, Office of New Drug Products (ONDP)

LCDR Luz E Rivera, Quality Assessment Lead (Acting), OPRO
Karen Winestock, Chief Project Management Staff, DAVP
Nina Mani, Senior Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

ViiV Healthcare Company

Amy Pierce	Clinical Development Director
Cyril Llamoso	Medical Development Leader
Karen Grainger	VP, Regulatory Affairs
Margaret Gartland	Clinical Development Manager
Marty St. Clair	Clinical Development Director
Max Lataillade	VP, Head of Clinical Development
Peter Ackerman	Physician Project Leader

GlaxoSmithKline

Bridin McCaughey	Clinical Development Manager
Chris Jones	Medicine and Product Delivery Team Leader
Chet Bowen	Sr. Regulatory Project Manager, Nonclinical
David Chen	Programming Manager
Keith Barker	Safety Development Leader
Lan Nguyen	Manager, Global CMC Regulatory Affairs
Mark Baumgartner	Senior Director & Team Leader, Global Regulatory Affairs
Frank Mannino	Director, Statistics
Mindy Magee	Director, Clinical Pharmacology
Sherry Watson	Regulatory Affairs Manager

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 28, 2018; 1:30 pm – 3:00 pm (Eastern) at the location noted above between ViiV Healthcare Company (ViiV) 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 and/or changing the format of the meeting (e.g., from face to face to teleconference). 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

The purpose of the meeting is to discuss ViiV's plans to submit a New Drug Application (NDA) for fostemsavir tablets in 2019. In particular, the Sponsor seeks agreement on the schedule and elements for a rolling NDA review, and on the content/format of their proposed NDA.

Fostemsavir (GSK3684934; formerly known as BMS-663068) is a methyl phosphate prodrug of BMS-626529 (temsavir) and belongs to the gp120 attachment inhibitor class. Fostemsavir prevents interaction of HIV-1 envelope glycoprotein, gp120 with the host CD4 receptor. It is active against HIV-1 virus regardless of tropism (i.e., CCR5-, CXCR4-, or dual-tropic virus).

In June, 2015, fostemsavir received Breakthrough Therapy Designation for its use in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in highly treatment experienced (HTE) adult patients with continuing HIV-1 replication despite ongoing ARV therapy.

Fostemsavir was developed by Bristol-Myers Squibb (BMS) who transferred sponsorship of the IND to ViiV in September 2016, with GlaxoSmithKline (GSK) providing technical expertise.

Initially, ViiV planned to submit a NDA in the second half of 2017, but the report to the Agency in May 2016

delayed these plans.

At FDA's recommendation, ViiV commissioned an Expert Panel of three allergy-immunology subspecialists with expertise

The Expert Panel concluded that the (b) (4) has very low potential to induce an immune response in an individual who is not already sensitized (b) (4)

To address these chemistry, manufacturing, and controls (CMC) concerns, during 2016 - 2017 and ongoing, ViiV and FDA have been in regular communications (b) (4)

In November, 2017 the Agency agreed with ViiV's proposed approach for a biowaiver which would support the bridging between the Phase 3 supply site (b) (4) and the proposed commercial manufacturing site (Parma) without the need to conduct a bioequivalence (BE)

study. FDA accepted ViiV's proposal pending the acceptance of dissolution results of the three registration batches from the proposed commercial site that must be within the constructed "dissolution safe space" and meet f2 criteria when tested against the reference Phase 3 batch in multiple-buffer pH media.

Two key studies will support the NDA application for fostemsavir. These include an ongoing Phase 3 study (205888) in heavily treatment-experienced patients, and a completed Phase 2b study (205889) in generally treatment-experienced patients.

The expected outcome of the meeting is to arrive at an agreement regarding the content/format plans for the NDA and the timing of the planned delivery of NDA modules.

2.0 DISCUSSION

2.1. Clinical/Statistical

Question 1: Does FDA accept the proposal to not produce a separate Integrated Summary of Efficacy (ISE) for inclusion in m5.3.5.3, but to include supporting tables and figures for m2.7.3 in m5.3.5.3?

FDA Response to Question 1: *DAVP agrees that a separate ISE does not need to be included in m5.3.5.3 since pivotal efficacy data come from a single Phase 3 trial.*

Question 2: The end-of-study report produced by ViiV for the Phase 2b study (205889) will be comprehensive (beginning to end of study) and will reflect outputs of all study parameters relating to the primary and secondary endpoints specified in the study protocol. However, not all data displays included in the Week 96 report produced by BMS will be provided in the ViiV-produced end-of-study report. Since the end-of-study report is intended to supplant the Week 96 report, ViiV proposes to not provide the BMS-produced Week 96 study report in the NDA. Does FDA agree with this approach?

FDA Response to Question 2: *Yes, this approach is acceptable.*

Question 3a: Does FDA agree with the proposed rolling NDA review schedule?

FDA Response to Question 3a: *The Sponsor is proposing that FDA review begin immediately upon submission of Delivery 1 (Week 48) data. However, the Sponsor also proposes that final labeling will be based on submission of data in Delivery 2 (Week 96 data), in which case review of pivotal efficacy and safety data cannot commence until Delivery 2 has been submitted. In order to maximize the efficiency of the review, the Division has the following suggestion for an alternative strategy for your consideration.*

- i. Include efficacy and safety data through Week 48 of the Phase 3 trial (Trial 205888) in labeling. This approach will allow the majority of the review team to begin a full review upon receipt of Delivery 1. Given the short-term primary*

- endpoint for trials in the HTE population, data from Day 7, Week 24 and Week 48 are sufficient to characterize initial treatment response and durability.*
- ii. As a component of Rolling Review Delivery 2, submit a summary of the Week 48 to Week 96 safety data from the Phase 3 trial (Trial 205888) in a format consistent with a Safety Update Report (SUR). This should also include narratives for all deaths, SAEs, AEs leading to discontinuation, and AESIs occurring from Week 48 to Week 96.*
 - iii. Week 96 safety and efficacy data can be formally incorporated into labeling post-approval through submission of an efficacy supplement.*

Please note that if the Sponsor opts not to deviate from the initially proposed Rolling Review strategy and to include information from Week 96 of the Phase 3 trial (Trial 205888) in labeling, then the Sponsor will need to provide complete information supporting this labeling as a component of Module 2. This includes updates to the clinical module 2 summaries, Integrated Summary of Safety (ISS), and the datasets incorporating the Week 96 data.

Question 3b: Does FDA agree with the proposal not to update the clinical module 2 summaries or the Integrated Summary of Safety (ISS) at the time of delivery of the Week 96 Phase 3 CSR?

FDA Response to Question 3b: *If the alternative strategy we have outlined in Question 3a is adopted, then your approach is acceptable. Otherwise, clinical module 2 and the ISS should be updated with the Phase 3 Week 96 data (please see our response to Question 3a for details).*

Question 3c: Does FDA agree with ViiV's plan to deliver the ISS with the clinical data sections of the NDA and not update at the time of delivery of the Week 96 study report and 60-day safety update?

FDA Response to Question 3c: *Please see FDA's response to Questions 3a and 3b.*

Question 3d: Does FDA agree with the proposal to provide draft annotated labeling with delivery of the clinical data sections (1Q2019) and update the proposed annotated labeling with delivery of the Week 96 Phase 3 study (205888) CSR?

FDA Response to Question 3d: *Please see FDA's response to Questions 3a and 3b.*

Question 4: Does FDA agree that the Phase 3 study (205888) Week 24 report will not be submitted in the NDA since the 24-week data will be subsumed within the Week 48 report delivered with the clinical sections (projected 1Q2019)?

FDA Response to Question 4: *Yes, the Week 48 report is sufficient.*

Question 5: Does FDA agree with the approach described herein for delivering datasets in accordance with FDA data standards requirements?

FDA Response to Question 5: Yes, we agree and have the following additional requests. For your phase 2b and 3 studies, please submit statistical programs for primary/secondary analyses of the primary efficacy endpoint, analyses of secondary efficacy endpoints and for any inferential statistical analyses of safety endpoints. In addition, please submit programs used to create analysis datasets for the corresponding analyses. Please also submit the corresponding datasets for these programs if the programs do not use the CDISC-conforming (SDTM and ADaM) datasets.

Please submit the datasets corresponding to those specified in the attached draft guidance entitled “Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment.”

Question 6: Does FDA agree with the overall approach outlined for the organization and delivery of the planned ISS?

FDA Response to Question 6: Although the totality of safety data from studies 206267, 205889, and 205888 will be evaluated during the NDA review, data from Trial 205888 will be the primary focus of labelling for Sections 6 and 14. Therefore, we ask that you incorporate flags in the ISS dataset for each of the studies. Additionally, given the differences in patient populations and treatment regimens used in the clinical trials, we suggest that discrete safety summaries are provided for the Phase 2b and the Phase 3 clinical trials. Please see Additional Comments for further requests regarding structure of the safety datasets.

Question 7: Does FDA agree with the approach planned for case report forms, patient narratives, and brief case summaries for adverse events of special interest (AESIs) within the ISS?

FDA Response to Question 7: The multitude of confounding variables in this population with advanced HIV-related illness complicates adjudication of the relationship between fostemsavir and AEs. Therefore, the Division requests full narratives for all deaths, SAEs, AEs leading to discontinuation, and AESIs.

Question 8: Does FDA agree with the approach planned for reporting information from the Early Access Program (EAP)?

FDA Response to Question 8: This approach is acceptable. Full narratives should be provided for all deaths, SAEs, AEs leading to discontinuation, and AESIs.

Question 9: Does FDA agree with the proposed timing and content of the safety update report

FDA Response to Question 9: The proposed timing of the SUR is acceptable. The requested content of the SUR will be based on the final rolling review strategy adopted by the Sponsor.

2.2. Virology

Question 10: Does FDA agree with the approach outlined for the content/format of virology data to be provided in module 2.7.2.4 of the NDA?

FDA Response to Question 10: *The approach seems reasonable. Please place virology study reports and resistance dataset under Module 5 “Other Studies” in section 5.3.5.4. Please also submit the resistance data in a separate dataset for each study.*

2.3. Clinical Pharmacology

Question 11: Does FDA agree with the population PK and PK/PD strategy for fostemsavir as outlined herein?

FDA Response to Question 11: *The proposed approach seems reasonable. We recommend that all available PK data, including the ones from phase 1 clinical studies, should be incorporated in the population PK analysis. In addition, we suggest including all Phase 2b data for the exposure-response relationship analysis for safety to determine whether there are any exposure-dependent adverse events.*

2.4. Non-Clinical

Question 12: Does FDA agree that no further nonclinical studies are required to support a decision to approve the NDA for fostemsavir?

FDA Response to Question 12: *We agree that no additional nonclinical studies are required to support a decision for the NDA approval. Please include a more in-depth discussion in the Integrated Summary on prodrug conversion site profiles (e.g., GI fluids, GI mucosa border, systemic [organs/tissues], enzymes involved and the estimated proportions), and whether the profiles could be variable, or dose-dependent (e.g., clinical vs. toxicological dose range). This discussion would help reconcile some effects and phenomena reported; for example, that renal signals in the 2-week rat study (original IND) were claimed to be due to formaldehyde/formic acid liberated locally upon conversion of the prodrug into active drug.*

Question 13: Does FDA agree that the data standards for the provided nonclinical datasets as described herein are acceptable?

FDA Response to Question 13: *We agree. We also understand that the datasets you described should have included all nonclinical studies filed under the IND to this date, and that any additional reports to be included in the NDA will be highlighted in the listing.*

2.5. Chemistry, Manufacturing, and Controls

Question 14: Does FDA agree that the proposed stability package is sufficiently complete to support a possible approval decision?

FDA Response to Question 14: The proposed plan for stability data to be included in the 2Q2019 rolling submission is acceptable for completing the NDA submission for this Breakthrough Designation drug. We have the following recommendations to strengthen the product quality aspects of the NDA submission.

(b) (4)

2.6. Regulatory/Administrative

Question 15: Does FDA agree with the plan to request a deferral for submission of pediatric study data at the time of delivery of the NDA in 2019?

FDA Response to Question 15: Yes, a deferral request for pediatric data is acceptable. To facilitate your plan to request a deferral of pediatric studies and change in scope of proposed studies, please submit an amended iPSP with these revisions, including justification of the changes for the Agency’s review. Once you receive an Agreed Amended iPSP, submit that with your NDA application (Section 1.9.4). Please note that an Agreed iPSP is required to be submitted with your marketing application.

Question 16: ViiV understands that FDA will not decide about the need for an Advisory Committee meeting until the NDA is under review. However, given what is known about the benefit/risk profile and expected data package to be included in the NDA, does FDA envision that an Advisory Committee Meeting is likely?

FDA Response to Question 16: The need for an Advisory Committee will be a review issue. However, as noted by the Sponsor, FDA makes every effort to streamline the review for products with Breakthrough Designation in order to facilitate timely regulatory action.

Question 17: Does FDA agree that only the Phase 2b study (205889) and Phase 3 study (205888) should be considered “covered studies” for financial disclosure by clinical investigators, as defined under the provisions of 21 CFR 54.2?

FDA Response to Question 17: Yes, as per 21 CFR 54.2, covered studies for purposes of financial disclosure include those supporting efficacy and/or safety. Study 205888 is a phase 3 efficacy and safety study and study 205889 provides supportive data for safety. Therefore, financial disclosure statements are required for these two studies.

Please submit financial disclosure information consistent with the February 2013 Financial Disclosure Guidance. We request that you specifically provide the following information:

- a. Total number of investigators (primary and sub-investigators) for Studies 205888 and 205889*
- b. For the investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:*
 - i. Significant payments of other sorts*
 - ii. Proprietary interest in the product tested held by investigator*
 - iii. Significant equity interest held by investigator in sponsor of covered study*
 - iv. If applicable, please provide a description of the steps taken to minimize potential bias.*

Question 18: Substantial evidence of efficacy/safety for the intended use will be provided by a single Phase 3 study in heavily treatment-experienced patients (205888), supported by confirmatory efficacy/safety from a Phase 2b study in generally treatment-experienced patients (205889). Will FDA require delivery of information from both the Phase 2b and the Phase 3 study or is it expected that Office of Scientific Investigations (OSI) inspection assignments will be limited to only the Phase 3 study?

FDA Response to Question 18: *Studies 205888 and 205889 both provide pivotal data in support of your application. Therefore, the OSI required documents should be submitted for both studies.*

Additional Comments:

- 1. Please provide your proposed definition of treatment-emergent adverse events (e.g. events occurring on-treatment or within 2 weeks of cessation of investigational product). In addition, please ensure that the ISS and AE datasets will contain a treatment-emergent flag.*
- 2. Please provide mock ISS datasets in order for us to assure that the format will be compatible with our data review tools (e.g., JReview and JMP).*
- 3. The review team requests the following information to assist in selection of clinical inspection sites. Please submit the following for each clinical site used in Studies 205888 and 205889:*
 - a. Number of patients screened*
 - b. Number of patients enrolled*
 - c. Number of protocol violations*
 - d. Brief description of each protocol violation.*
- 4. The Division believes that the expert panel convened for the White Paper could provide valuable advice about whether (and how) the beta-lactam containing impurity should be addressed in labeling.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 26, 2017 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

4.0 PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

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

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

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

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

6.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**,

ANDA, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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>.

7.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

8.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

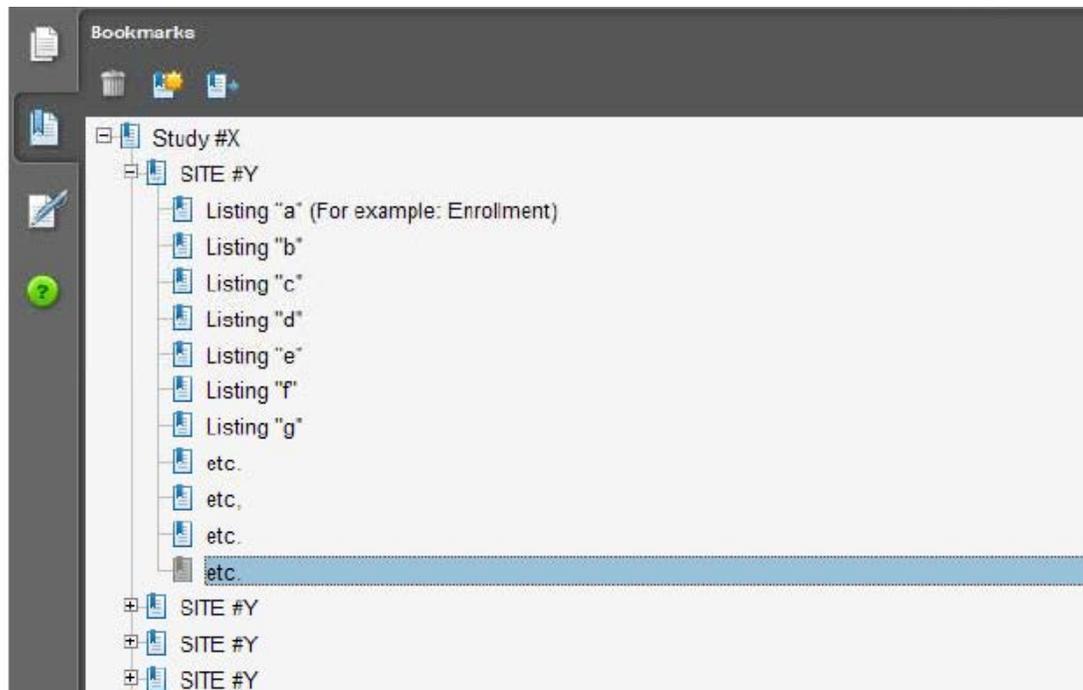
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item¹	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 to

Human Immunodeficiency Virus-1 Infection:
Developing Antiretroviral Drugs for Treatment

Guidance for Submitting Clinical Trial Data Sets

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Jeffrey Murray at 301-796-1500.

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2016
Clinical/Antimicrobial**

Guidance for Submitting Clinical Trial Data Sets

Introduction

This guidance provides detailed information to assist applicants in constructing and submitting clinical trial data sets (FDA analysis data sets) to aid statistical and clinical reviewers in their review of HIV drug applications. These data sets are recommended in addition to the standard *raw* data sets, usually in Study Data Tabulation Model, and the applicant's analysis data sets, which could be Analysis Data Model data sets. The FDA analysis data sets should be *one statistical procedure away* from the statistical results wherever possible. This approach eliminates or greatly reduces the amount of programming required of the statistical reviewers. The following data tabulation data sets are recommended.

I. Efficacy Outcomes Data Sets (See Table 1)

Data sets should have only one record per subject and should include information as outlined in detail in Table 1 for the following:

- Demographic variables
- Baseline characteristics (including, for example, 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

II. Raw Laboratory Data Sets (See Table 2)

The raw HIV-RNA (viral load) and other laboratory data sets should include all HIV-RNA measurements during the course of the trial for all subjects. It should have multiple records per subject and include the derived window variables, which are defined in the protocol or statistical analysis plan for each scheduled visit. Deviations from the plan should be identified and documented. Selected laboratory data should be put in eight data sets as follows:

- (1) HIV-RNA (viral load)
- (2) Immunologic parameters: cluster of differentiation 4 positive cell counts (absolute count and percentage)

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- 47 (3) Lipid laboratory parameters: total cholesterol, low-density lipoprotein, high-density
 48 lipoprotein, triglycerides
 49
- 50 (4) Liver laboratory tests: alanine aminotransferase, aspartate aminotransferase, total
 51 bilirubin, albumin, total protein, preferred term/international normalized ratio, gamma-
 52 glutamyl transferase
 53
- 54 (5) Hematology laboratory tests: white blood cell absolute neutrophils, hemoglobin,
 55 hematocrit, platelets, eosinophils
 56
- 57 (6) Renal laboratories: blood urea nitrogen, creatinine, creatinine clearance, bicarbonate,
 58 phosphate
 59
- 60 (7) Other laboratory tests: sodium, potassium, chloride, bicarbonate, amylase, lipase,
 61 creatine phosphokinase
 62
- 63 (8) Adverse reactions
 64

III. Adverse Events Data Sets (See Table 3)

66 All adverse events records should be included. Table 3 follows the Analysis Data Model Data
 67 Structure for Adverse Event Analysis.
 68

IV. Tables¹

69 The recommended three types of data sets are provided in the following tables. The tables
 70 include recommendations for variable name, variable label, and codes and provide comments.²
 71

Table 1. Efficacy Outcomes and Related Covariates (ADEffOUT)³

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
1. Demog (DM)				
STUDYID	Study identifier	Char		Unique identifier for a study
USUBJID	Unique subject identifier	Char		Unique among all subjects submitted for the drug
SUBJID	Subject identifier for the study	Char		Subject identifier, which should be unique within the study. Often the identifier of the subject as recorded on a CRF.
SITEID	Study site identifier	Char		

continued

¹ The abbreviations and acronyms found in the following tables are defined in the Glossary of Abbreviations and Acronyms at the end of this guidance.

² Years should be entered in four digits, such as 1983, 2003.

³ CDISC — SDTM V1.2 and SDTM IG V3.1.2

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77 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
SITEGRP	Pooled site group	Char		Character description of the grouping of clinical sites for analysis purposes if permissible
INVID	Investigator identifier	Char		
INVNAM	Investigator name	Char		
RANDDT	Randomization date	Num (Date9.)	DDMMYYYY	Date the subject is randomized
RFSTDTC	Reference start date/time	Char		Reference start date/time for the subject in ISO 8601 character format. Usually equivalent to date/time when subject was first exposed to study treatment. Needed for all randomized subjects; should be null for all subjects who did not meet the milestone the date requires, such as screen failures or unassigned subjects.
RFSTDT	Reference start date	Num (Date9.)	DDMMYYYY	Numeric date of reference start date
RFENDTC	Reference end date/time	Char		Reference end date/time for the subject in ISO 8601 character format. Usually equivalent to the date/time when subject was determined to have ended the trial, and often equivalent to date/time of last exposure to study treatment. Needed for all randomized subjects; null for screen failures or unassigned subjects.
RFENDT	Reference end date	Num (Date9.)	DDMMYYYY	Numeric date of reference end date
BRTHDTC	Date/time of birth	Char		Date/time of birth of the subject in ISO 8601 character format
DOB	Date of birth	Num (Date9.)	DDMMYYYY	Numeric date of birth of the subject
AGE	Age	Num		Age expressed in AGEU. Can be derived as (RFSTDTC-BRTHDTC), but BRTHDTC may not be available in all cases (because of subject privacy concerns).
AGEU	Age units	Char	Years	Units associated with age. Should be the same across studies when appropriate.
SEX	Sex	Char	M or F	Sex of the subject
SEXCD	Sex code	Num	1=Male 2=Female	Optional
RACE	Race	Char	White, Black, Asian, Other	
RACECD	Race code	Num	1=White 2=Black 3=Asian 4=Other	Optional

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79 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
ETHNIC	Ethnicity	Char	Hispanic and non-Hispanic	
ARMCD	Planned arm code	Char		ARMCD should be limited to 20 characters and should not have special character restrictions
ARM	Description of planned arm	Char		Name of the arm to which the subject was assigned (randomized)
COUNTRY	Country	Char		
REGION	Region	Char		
2. Baseline Characteristics				
WEIGHT	Weight measure at baseline	Num		Optional
HEIGHT	Height measure at baseline	Num		Optional
HIP	Hip measure at baseline	Num		Optional
WAIST	Waist measure at baseline	Num		Optional
BMI	Body mass index	Num		Optional
VLOADBLC	Baseline HIV viral load category	Char		Optional. Category used to stratify the randomization. For example, < 10 ⁵ at screening visit or ≥ 10 ⁵ at screening visit.
VLOADBLN	Baseline HIV viral load value	Num		Optional. Numeric value of HIV-RNA, viral load, at baseline. Sometimes this is the average of viral load of several visits before dosing.
CD4BLN	Baseline CD4 count	Num		Numeric value of CD4 at baseline. Should use LOCF if missing at randomization.
CD4PBLN	Baseline CD4 percentage	Num		
CD8BLN	Baseline CD8 count	Num		
CD8PBLN	Baseline CD8 percentage	Num		
CD48RBL	Baseline ratio of CD4 cells to CD8 cells	Num		
COINFECT	Baseline co-infection	Text	“HBV HCV TB” or “HBV” or “HCV” or “TB” or “HBV HCV” or “HBV TB” or “HCV TB”	
HIVSTAT	HIV status at baseline	Char		Depending on the CRF design and data collection, the possible values could be, for example, “AIDS,” “Asymptomatic,” “Symptomatic HIV Infections”

80

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81 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
HBVSTAT	Hepatitis B virus surface antigen at baseline	Text	“Negative,” “Positive”	
HCVSTAT	Hepatitis C virus antibody at baseline	Text	“Negative,” “Positive”	
Additional Baseline Variables				Should be created as needed according to the protocol
HAPLOF	CCR5 promoter haplotype at baseline	Char		This is an example. Can be changed accordingly.
Additional Stratification Factors				Should be created as needed according to the protocol
REGION_S	Region for randomization stratification	Char		This is the region used in the stratification, which may not be the same as the geographic region definition
RD_STF1	First randomization stratification factor	Text		Optional. Should be the first stratification factor name used in the trial; for example, “CD4 count at baseline,” “Screening Visit Viral Load.”
RD_STF2	Second randomization stratification factor	Text		Optional
RD_STF3	Third randomization stratification factor	Text		Optional
RD_STF1V	The value of first randomization stratification factor	Text		Optional. The category value of first randomization stratification factor. For example, “Screening HIV VL < 10 ⁵ ” or “Screening VL ≥ 10 ⁵ ” if the first stratification factor is “Screening VL.”
RD_STF2V	The value of second randomization stratification factor	Text		Optional
RD_STF3V	The value of third randomization stratification factor	Text		Optional

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83 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
TRTHIST	Treatment experience at entry of study	Char	Naïve NRTI-Experienced PI-Experienced INSTI-Experienced ...	For example, Naïve, NRTI-Experienced, PI-Experienced
PR_VF	Subject had prior virologic failure?	Char	Yes or No	Optional. Depending on the criteria used in the protocol.
2.1 Baseline genotypic and phenotypic data				
T_PI	Total number of PIs in the baseline background regimen	Num		
T_NRTI	Total number of NRTIs in the baseline background regimen	Num		
T_NNRTI	Total number of NNRTIs in the baseline background regimen	Num		
T_FI	Total number of FIs in the baseline background regimen	Num		
T_II	Total number of integrase inhibitor in the baseline background regimen	Num		
T_CCR5	Total number of CCR5 antagonists in the baseline background regimen	Num		
T_Total	Total number of antiretrovirals	Num		

84

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85 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
P_PI	PSS for PI	Num		PSS for PI including darunavir
P_NRTI	PSS for NRTI	Num		
P_NNRTI	PSS for NNRTI	Num		
P_FI	PSS for FI	Num		PSS for FI including enfuvirtide
P_II	PSS for integrase inhibitor	Num		
P_CCR5	PSS for CCR5 antagonist	Num		
P_TOTAL	Total PSS score	Num		
G_PI	GSS for PI	Num		GSS for PI including darunavir
G_NRTI	GSS for NRTI	Num		
G_NNRTI	GSS for NNRTI	Num		
G_FI	GSS for FI	Num		GSS for FI including enfuvirtide
G_II	GSS for integrase inhibitor	Num		
G_CCR5	GSS for CCR5 inhibitor	Num		
G_TOTAL	Total GSS score	Num		
3. Exposure (EX)				
TRTA	Actual treatment received	Char		Treatment arm name received in the trial
TRTP	Planned treatment	Char		The planned treatment for the subject
TRTSEQP	Planned treatment sequence	Char		
TRTSEQA	Actual treatment sequence	Char		
EXSTDY	Study day of start of treatment	Num		Study day of start of treatment relative to the applicant-defined RFSTDTC
EXENDY	Study day of end of treatment	Num		Study day of end of treatment relative to the applicant-defined RFSTDTC
EXDUR	Duration of treatment	Num		Total duration of the treatment

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87 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
BG_TRT	Background regimen at the entry	Char		1. All the background drugs' generic names should be listed; “,” should be used between the drug 2. The generic name of each drug for the combination drug should be listed (e.g., “tenofovir, emtricitabine”)
F_BG_TRT	Failed regimen used at DAY1 before switching to optimized/constructed background regimen	Char		1. All the background drugs' generic names should be listed; “,” should be used between the drug 2. The generic name of each drug for the combination drug should be listed (e.g., “tenofovir, emtricitabine”)
COMPPCT	Compliance to the study drug	%		Average compliance percentage before discontinuation of study drug
3.1 HIV drug change				
ANYCHGDY	Study days of first change of any drug, either study drug or background drug	Num		Study days from RFSTDT of first change of any drug
ANYCHGDT	Date of first change of any drug either study drug or background drug	Num (Date9.)	DDMMYYYY	
ANYCHGRS	Reason for the change	Char		
ANYCHGAE	Any ongoing AE when discontinued?	Char	N, Y	
ANYCHAEG	Grade level of the ongoing AE	Char	I, II, III, IV	
3.2 Study drug change				
DGCHGDY	Study days of changing the study drug	Num		
DGCHGDT	Date of first change of the study drug	Num (Date9.)	DDMMYYYY	
DGCHGRS	Reason for the change	Char		
DGCHGAE	Any ongoing AE when discontinued?	Char	N, Y	
DGCHAEG	Grade level of the ongoing AE	Char	I, II, III, IV	

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continued

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89 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
3.3 Background drug changes				
STNDT	Subject reference start date/time for adding a new drug	Num (Date9.)	DDMMMYYYY	Some change of background drug or temporary dose modification during the trial may be permitted by the protocol and will not be considered adding a new drug. Removal of a particular drug without replacement is not considered as a drug change.
STADT	Subject reference start date/time for adding a new drug	Num (Date9.)	DDMMMYYYY	Similar to STNDT except protocol-specified changes also should be recorded
BGCHG1DY	Study days adding a new background drug	Num		Some predefined changes should be excluded
BGCHG1DT	Date of first change of the background drug	Num (Date9.)	DDMMMYYYY	This should be equivalent to STADT
BGCHG1RS	Reason for the change	Char		
BGCHG1OD	First drug removed from background drug	Char \$20		The generic name should be used
BGCHG1N	First drug used to replace the removed old drug in background drug, or drug adding in the background therapy	Char \$20		The generic name should be used
BGCHG1AE	Any ongoing AE when discontinued?	Char	N, Y	
BGCH1AEG	Grade level of the ongoing AE	Char	I, II, III, IV	
BGCHG2DY	Study day of second time adding a new background drug	Num		If there are more than two drug changes, variables should be created; for example, BGCHG3DY, BGCH3DT
BGCHG2DT	Date of second change of new background drug	Num (Date9.)	DDMMMYYYY	

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91 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
BGCHG2RS	Reason for the change	Char		
BGCHG2OD	Second drug removed from background drug	Char \$20		The generic name should be used
BGCHG2N	Second drug used to replace the removed old drug in background drug, or drug adding in the background therapy	Char \$20		The generic name should be used
BGCHG2AE	Any ongoing AE when discontinued?	Char	N, Y	
BGCH2AEG	Grade level of the ongoing AE	Char	I, II, III, IV	
4. Population Flag				
ITTFL	ITT population flag	Char	N, Y	ADaM character indicator for the ITT population. It should include all subjects who enrolled. For randomized trials it should include all randomized subjects.
ITTFLN	ITT population flag, Num	Num	0, 1	ADaM numeric indicator for the ITT population
PPROTFL	Per-protocol population flag	Char	N, Y	ADaM indicator for the per-protocol population
PPROTFLN	Per-protocol population flag	Num	0, 1	
FASFL	Full analysis set population flag	Char	N, Y	ADaM indicator for the full analysis set population. This population is for the primary efficacy analysis and the variable name could be different, such as mITT.
FASFLN	Full analysis set population flag, Num	Num	0, 1	
SAFFL	Safety population flag	Char	N, Y	ADaM indicator for the safety population. It should include all treated ITT patients.
SAFFLN	Safety population flag, Num	Num	0, 1	
5. Efficacy Outcomes				
	5.1 Snapshot outcomes (cutoff=50 and 400 copies/mL) at Weeks 24, 48, and 96, and related variables			
V24_S50	Snapshot outcome < 50 copies/mL at Week 24	Char	N, Y	

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continued

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93 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V24_S5C	Category of snapshot outcome < 50 copies/mL at Week 24	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	
V24_S5S	Category of snapshot outcome < 50 copies/mL at Week 24	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 50 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 50 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 50 copies/mL 3c=Missing data during the window but on study	
V24_S400	Snapshot outcome < 400 copies/mL at Week 24	Char	N, Y	
V24_S40C	Category of snapshot outcome < 400 copies/mL at Week 24	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	

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continued

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95 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V24_S40S	Category of snapshot outcome < 400 copies/mL at Week 24	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 400 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 400 copies/mL 3c=Missing data during the window but on study	
V24_VL	HIV-RNA level used to determine the snapshot outcome at Week 24	Num		If viral load observations are not used in the snapshot because of various reasons, these variables should be left blank
V24_VLDY	Study day when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 24	Num		If viral load observations are not used in the snapshot because of various reasons, these variables should be left blank
V24_VLDT	Date when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 24	Num		If viral load observations are not used in the snapshot because of various reasons, these variables should be left blank
V48_S50	Snapshot outcome < 50 copies/mL at Week 48	Char	N, Y	

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continued

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97 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V48_S5C	Category of snapshot outcome < 50 copies/mL at Week 48	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	
V48_S5S	Category of snapshot outcome < 50 copies/mL at Week 48	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 50 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 50 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 50 copies/mL 3c=Missing data during the window but on study	
V48_S400	Snapshot outcome < 400 copies/mL at Week 48	Char	N, Y	
V48_S40C	Category of snapshot outcome < 400 copies/mL at Week 48	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	

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continued

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99 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V48_S40S	Category of snapshot outcome <400 copies/mL at Week 48	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 400 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 400 copies/mL 3c=Missing data during the window but on study	
V48_VL	HIV-RNA level used to determine the snapshot outcome at Week 48	Num		
V48_VLDY	Study day when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 48	Num		
V48_VLDT	Date when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 48	Num		
V96_S50	Snapshot outcome < 50 copies/mL at Week 96	Char	N, Y	

100

continued

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101 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V96_S5C	Category of snapshot outcome < 50 copies/mL at Week 96	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	
V96_S5S	Category of snapshot outcome < 50 copies/mL at Week 96	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 50 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 50 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 50 copies/mL 3c=Missing data during the window but on study	
V96_S400	Snapshot outcome < 400 copies/mL at Week 96	Char	N, Y	
V96_S40C	Category of snapshot outcome < 400 copies/mL at Week 96	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2=Virologic failure 3=No virologic data	

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continued

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103 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V96_S40S	Category of snapshot outcome < 400 copies/mL at Week 96	Char	1=Virologic success (HIV-RNA < 50 copies/mL) 2a=HIV-RNA ≥ 400 copies/mL 2b=Discontinued because of virologic failure 2c=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was ≥ 400 copies/mL 2d=OBT changed 3a=Discontinued because of AE or death 3b=Discontinued because of other reasons and HIV-1 RNA at the time of discontinuation was < 400 copies/mL 3c=Missing data during the window but on study	
V96_VL	HIV-RNA level used to determine the snapshot outcome at Week 96	Num		
V96_VLDY	Study day when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 96	Num		
V96_VLDT	Date when the HIV-RNA level was assessed and used to determine the snapshot outcome at Week 96	Num		

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continued

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105 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V24_T5C	Category of TLOVR outcome < 50 copies/mL at Week 24	Char	0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 24 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	
V24_T40C	Category of TLOVR outcome < 400 copies/mL at Week 24	Char	0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 24 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	

106

continued

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107 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V48_T5C	Category of TLOVR outcome < 50 copies/mL at Week 48	Char	0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 48 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	
V48_T40C	Category of TLOVR outcome < 400 copies/mL at Week 48		0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 48 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	

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continued

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109 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V96_T5C	Category of TLOVR outcome < 50 copies/mL at Week 96	Char	0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 96 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	
V96_T40C	Category of TLOVR outcome < 400 copies/mL at Week 96	Char	0=Never treated 1=Responder 2a=Rebound 2b=Never suppressed by Week 96 2c=Discontinued study drug or added new drug because of protocol-defined virologic failure or insufficient viral load response 3=Discontinued study drug or added new ART before achieving suppression 4=Discontinued study drug or added new ART while suppressed	
5.2 Other efficacy outcomes				
TAD	Time averaged difference	Num		Corresponding to the longest time point in the trial available
V48_TAD	Time averaged difference of viral load at Week 48	Num		LVCF (censored at last available visit)
V48_TADB	Time average distance of viral load at Week 48	Num		BLCF

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continued

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111 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
V48_CB	Week 48 viral load change from baseline	Num		
V24_CB	Week 24 viral load change from baseline	Num		1. If there were multiple measurements within a visit window, the last one should be used 2. If the subject withdrew from the study or discontinued the assigned study before Week 24, then the subject should be considered as no change from baseline (i.e., BOCF) 3. Otherwise, if the measurement at Week 24 is missing but the one at the next visit is available, then the one at the next visit should be used; and if the one at the next visit is missing as well, then the one at the previous visit should be carried forward to Week 24
V96_CB	Week 96 viral load change from baseline	Num		
CD448	CD4 cell counts at Week 48	Num		CD4 (/ul)
CD4CB48	Change in CD4 cell counts from baseline to Week 48	Num		
CD4P48	CD4 cell percentage at Week 48	Num		CD4 (%)
CD4PCB48	Change in CD4 cell percentage from baseline to Week 48	Num		
CD496	CD4 cell counts at Week 96	Num		
CD8CB48	Change in CD8 cell counts from baseline to Week 48	Num		
CD8P48	CD8 cell percentage at Week 48	Num		
CD8PCB48	Change in CD8 cell percentage from baseline to Week 48	Num		

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continued

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113 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
VF400_TS	Time of confirmed response < 400 copies/mL	Num		If never, then the day should be set to 100000
VF400_TF	Time of first rebound	Num		
VF400_T2	Time to confirmed resuppression	Num		Resuppression after confirmed rebound
VF50_TS	Time of confirmed response < 50 copies/mL	Num		
VF50_TF	Time of first rebound	Num		
VF50_T2	Time to confirmed resuppression	Num		
VFNDR_T	Time first reached nadir	Num		
VFNDR_TF	Time of rebound from nadir	Num		1 log above nadir should be used with confirmation
Add Other Variables When Appropriate				
6. Covariates/Subgroup				
DrugCat	HIV drug classes for the investigational drug	Char		For example, NRTI, NNRTI, PI, FI, CCR5. If the investigational drug is more than one and from more than one drug class, MIX can be used.
DrugID	Investigational drug generic name	Char	Lamivudine, tipranavir ...	ADaM can be used by the applicant for ISE, or for reviewers for drug class analysis
APV	Amprenavir (APV) in the randomized background regimen?	Num	0=No 1=Yes	Variables should be created only for the drugs used
ATV	Atazanavir (ATV) in the randomized background regimen?	Num	0=No 1=Yes	Variables should be created only for the drugs used

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continued

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115 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
DRV	Darunavir (DRV) in the randomized background regimen?	Num	0=No 1=Yes	
FAPV	Fosamprenavir (FAPV) in the randomized background regimen?	Num	0=No 1=Yes	
IDV	Indinavir (IDV) in the randomized background regimen?	Num	0=No 1=Yes	
LPV	Lopinavir (LPV) in the randomized background regimen?	Num	0=No 1=Yes	
NFV	Nelfinavir (NFV) in the randomized background regimen?	Num	0=No 1=Yes	
RTV	Ritonavir (RTV) in the randomized background regimen?	Num	0=No 1=Yes	
SQV	Saquinavir (SQV) in the randomized background regimen?	Num	0=No 1=Yes	
TPV	Tipranavir (TPV) in the randomized background regimen?	Num	0=No 1=Yes	
ABC	Abacavir (ABC) in the randomized background regimen?	Num	0=No 1=Yes	

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continued

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117 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
DDI	Didanosine (DDI) in the randomized background regimen?	Num	0=No 1=Yes	
FTC	Emtricitabine (FTC) in the randomized background regimen?	Num	0=No 1=Yes	
3TC	Lamivudine (3TC) in the randomized background regimen?	Num	0=No 1=Yes	
D4T	Stavudine (D4T) in the randomized background regimen?	Num	0=No 1=Yes	
TDF	Tenofovir (TDF) in the randomized background regimen?	Num	0=No 1=Yes	
FTC	Zalcitabine (FTC) in the randomized background regimen?	Num	0=No 1=Yes	
ZDV	Zidovudine (ZDV) in the randomized background regimen?	Num	0=No 1=Yes	
DLV	Delavirdine (DLV) in the randomized background regimen?	Num	0=No 1=Yes	
EFV	Efavirenz (EFV) in the randomized background regimen?	Num	0=No 1=Yes	

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119 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
ETV	Etravirine (ETV) in the randomized background regimen?	Num	0=No 1=Yes	
NVP	Nevirapine (NVP) in the randomized background regimen?	Num	0=No 1=Yes	
T20	Enfuvirtide (T20) in the randomized background regimen?	Num	0=No 1=Yes	
RAL	Raltegravir (RAL) in the randomized background regimen?	Num	0=No 1=Yes	
MVC	Maraviroc (MVC) in the randomized background regimen?	Num	0=No 1=Yes	
EVG	Elvitegravir (EVG) in the randomized background regimen?	Num	0=No 1=Yes	
COBI	Cobicistat (COBI) in the randomized background regimen?	Num	0=No 1=Yes	
DTG	Dolutegravir (DTG) in the randomized background regimen?	Num	0=No 1=Yes	
7. Disposition (DS)				
DSCAT	Category for disposition event	Char		
DSSCAT	Subcategory for disposition event	Char		A further categorization of disposition event
DSDTC	Date/time of collection	Char	ISO 8601	
DSDT	Date of collection	Num (Date)	DDMMYYYY	

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continued

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121 *Table 1, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
DSSTDTC	Start date/time of disposition event	Char	ISO 8601	
DSSTDT	Start date of disposition event	Num (Date)	DDMMYYYY	
DSSTDY	Study day of start of disposition event	Num		
DSCNRSN	Investigator classification			For reasons of discontinuation
DSCNRSN1	Additional reasons			
DSCNRSN2	Additional reasons			
DSCNCMT	Comments for discontinuation			Post-hoc findings of the reasons for discontinuation should be described
DSCNVL	Viral load at study discontinuation	Num		In copies/mL. Last available viral load record on or before study discontinuation date.
DGCNVL	Viral load at study drug discontinuation	Num		In log ₁₀ copies/mL. Last available viral load record on or before study drug discontinuation date.
DSCNCD4	CD4 counts at study discontinuation	Num		Last available CD4 record on or before study discontinuation date
DGCNCD4	CD4 counts at study drug discontinuation	Num		Last available CD4 record on or before study drug discontinuation date
DSCNAE	Any ongoing AE when discontinued?	Char		
DSCNAEG	Grade level of the ongoing AE	Char		Highest grade level
CDCDy	Study day of the first new CDC Class C event	Num		
DeathDy	Study day for death	Num		

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123 **Table 2. Example of Data Set to be Used for Raw Viral Load Data (HIV-RNA) and All**
124 **Other Laboratories Previously Outlined⁴**

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
USUBJID	Unique subject identifier	Char		Unique among all subjects submitted for the drug
SUBJID	Subject identifier for the study	Char		Subject identifier, which should be unique within the study. Often the identifier of the subject as recorded on a CRF.
VISITNUM	Visit number	Num		
VISITDY	Study day	Num		
VISIT	Visit name	Char		
AVISIT	Analysis week	Char	Screening Baseline Week 2 Week 4 ...	
AVISITN	Analysis week	Num	1=Screening 0=Baseline 2=Week 2 4=Week 4 ... 48=Week 48 .. 96=Week 96 ... 999=Unscheduled visit ...	
ADTM	Actual date/time of specimen collection	Text		It should be the same as ADTM in IS8601dt. format
ADT	Sample collection date	Integer		IS8601da.
ATM	Sample collection time	Integer		Time5
ADY	Actual study day of specimen collection	Integer		
PARAM	Lab test name	Text	Need input of test codes	The lab test unit should be included in the standard lab test name in this variable
PARAMCD	Lab test code	Text		
PARAMTYP	Parameter type	Text	Derived or empty for original observation	
AVAL	Lab test result in numeric format	Num		
AVALC	Lab test result in text format	Text		

125 *continued*

⁴ CDISC — ADaM 2.1 and ADaMIG 1.0 Draft

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126 *Table 2, continued*

Variable Name (max=8)	Variable Label	Type	Codes (example)	Comments
ANRLO	Reference range lower limit-standard units	NUM		Lower limit for the normal range of the lab measure
ANRHI	Reference range upper limit-standard units	NUM		Upper limit for the normal range of the lab measure
ANLFL	Analysis week flag to indicate the record to be used for the analysis		(Y, or empty)	This is useful for multiple records within the same analysis week to indicate which record was used for the analysis for that visit week
ANLTYPE	Analysis type	Char		For the case where there are multiple observations and an average or a geometric mean will be used for the observation for the visit window in the analysis instead of a single selected real observation. If this is the case, a new record should be created and the records identified by having some values for these records in ANATYPE variable. The possible value could be "AVERAGE," or "GEOMETRIC," or other meaningful values. This should be explained in the define file or SAP.
LBFAS	Lab flag for fasted sample	CHAR	N, Y	Indicator used to identify fasting status such as N, Y, U (unknown), or null if not relevant
BASE	Baseline value for the lab test	Num		
CHG	Changes from baseline	Num		
PHASE			0=Screening 1=On randomized treatment 2=On randomized treatment with nonprotocol-specified change in the background regimen 99=Follow-up period	Phase=1 as long as the subject is on the original randomized treatment even if that is beyond the planned duration of the study and being called follow-up. Protocol-specified changes of background do not count as changes of original treatment. Phase=99 only if subject has changed the original randomized treatment. Protocols may allow treatment interruptions without any rescue medication being given in place of randomized treatment, Phase=1 during such protocol-specified interruptions.
ATOXGR	Toxicity grade assigned	Text		The lab toxicity grade assigned according to the protocol. This should be only for lab measures, not for the viral load, or CD4 counts.
BTOXGR	Baseline toxicity grade assigned	Text		

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128 **Table 3. Adverse Events Data Sets (ADAEOUT)**

Variable Name	Variable Label	Type	Codes (example)	Comments
STUDYID	Study identifier	Char		
USUBJID	Unique subject identifier	Char		
AETERM	Verbatim AE term	Char		
AEPT	Standardized AE preferred term	Char		
AESOC	Body system of organ class	Char		
MDR_VER	MedDRA coding dictionary version	Char	13.1	
PTCODE	MedDRA preferred term code	Char		
SOCCODE	MedDRA system organ class code	Char		
AELLT	MedDRA lowest level term	Char		
LLTCODE	MedDRA lowest level term code	Char		
AEHLT	MedDRA high level term	Char		
HLTCODE	MedDRA high level term code	Char		
AEHLGT	MedDRA high level group term	Char		
HLGTCODE	MedDRA high level group term code	Char		
TRTEMFL	Treatment-emergent flag	Char	N, Y	New or worsening AE after taking experimental treatment
AESEQ	Sequence number of the AE	Num		
AESTDTC	Starting date of the AE episode (character)	Char	ISO8601.	
AESTDTN	Starting date of the AE episode (numeric)	Num	DATE9.	
AESTDPI	Numeric starting date of AE is imputed because of the partial source date?	Char	N, Y	
AEENDTC	Ending date of the AE episode (character)	Char	ISO8601.	

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continued

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130 *Table 3, continued*

Variable Name	Variable Label	Type	Codes (example)	Comments
AEENDTN	Ending date of the AE episode (numeric)	Num	DATE9.	
AEENDPI	Numeric ending date of AE is imputed because of the partial source date?	Char	N, Y	
AEENDTCI	Imputed character ending day of the AE	Char	0=Not imputed 1=By RFENDTC 2=By DSSTDTC 3=Last available date for the subject 4=By AESTDTC 5=Partially imputed	By AE onset date
AEDUR	Duration of the AE	Num		
AEDURNF	Reason for negative AEDUR	Char	1=Source data error 2=Starting or ending date is imputed	
AEONGOIN	Ongoing AE	Char	Y, Null	
AESEV	Severity	Char	Mild Moderate Severe Life-Threatening Not Applicable	This could be different among the trials because of the different applicants
AESER	SAE	Char	N, Y	
AEREL	Related to the study drug	Char	N, Y	
AERELNST	Relationship to nonstudy treatment	Char		
AEACN	Action caused by AE	Char		
AEOUT	AE outcome	Char		
AETOXGR	Standard toxicity grade	Char		The protocol for the detailed definitions should be followed
CATCAE	CDC Class C AE flag	Char	N, Y	This flag should be used to indicate whether the AE event is the CDC Class C event
CDCDY	Study day of first new CDC Class C event	Num		

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continued

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132 *Table 3, continued*

Variable Name	Variable Label	Type	Codes (example)	Comments
CATC_PT	Preferred term list of the Class C event	Char		This should be the CDC Class C event list specified in the protocol. A preferred term from the list that corresponds to this AE should be the possible value for this variable.
TRT01PN	Planned treatment for Period 01 (N)	Num		
TRT01P	Planned treatment for Period 01	Char		
TRT01AN	Actual treatment for Period 01 (N)	Num		
TRT01A	Actual treatment for Period 01	Char		
SAFFL	Safety population flag	Char	N, Y	
ITTFLL	ITT population flag	Char	N, Y	
PPROTFL	Per-protocol population flag	Char		
RANDFL	Randomized population flag	Char	N, Y	
TRTSTDT	Date of first exposure to treatment	Num	DATE9.	
TRTENDT	Date of last exposure to treatment	Num	DATE9.	
RFSTDT	Subject reference start date	Num	DATE9.	See the comments in ADEFFOUT for details
RFENDT	Subject reference end date	Num	DATE9.	
RFSTDTC	Subject reference start date	Char	ISO8601.	
RFENDTC	Subject reference end date	Char	ISO8602.	
RANDDT	Date of randomization	Num	DATE9.	
AEWI30FL	If the record within the 30 days passed the last dosing date	Num	0=No 1=Yes	
DDCNAE	Any ongoing AE when disc study drug	Char		
DCCNAE	Any ongoing AE when disc study	Char	N, Y	

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135 **GLOSSARY OF ABBREVIATIONS AND ACRONYMS**

136

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

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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/

NINA MANI
02/22/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 073916
Request Receipt Date	April 30, 2015
Product	BMS-663068
Indication	Treatment of HIV-1 infection in heavily treatment experienced (HTE) adult patients when used in combination with other antiretroviral (ARV) agents
Drug Class/Mechanism of Action	HIV Attachment Inhibitor
Sponsor	Bristol-Myers Squibb
ODE/Division	OAP/DAVP
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	June 29, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

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

BMS-663068 in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in highly treatment experienced adults with continuing HIV-1 replication despite ongoing antiretroviral therapy.

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

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

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹? YES NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

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

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

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

N/A

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

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

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

The United States Centers for Disease Control (CDC) reported the first clinical evidence of Acquired Immunodeficiency Syndrome (AIDS) in June 1981. Shortly thereafter the link between HIV-1 infection and AIDS was discovered. Since that time HIV/AIDS has been recognized as a global epidemic with an estimated 65 million people being infected and over 25 million deaths from the disease. In 2012, over 35 million people worldwide were living with HIV infection and 1.6 million people died from

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

HIV/AIDS. The CDC's most recent estimate of the US prevalence for HIV infection in 2011, both diagnosed and undiagnosed, is >1.1 million adults and adolescents (447.8 per 100,000) (CDC 2013).

Infection with HIV-1 results in chronic, progressive depletion of T-lymphocytes (CD4+ or helper T-cells) and also affects macrophages and other cells important for immune surveillance. HIV infection, if left untreated or suboptimally treated, is characterized by immune destruction with subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

The primary objective of HIV treatment is to suppress viral replication to undetectable levels, thereby enabling restoration of immune function. The current approach to therapy is the use of a combination of antiretroviral drugs (ARVs) from two or more of the six available ARV classes: nucleos(t)ide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (INI), fusion inhibitors, and attachment inhibitors. For the majority of patients, combination antiretroviral therapy (ART) has effectively changed HIV infection from a disease associated with reduced life expectancy to a chronic disease requiring life-long treatment.

Despite the availability of a multitude of ARVs, treatment failure still occurs and places patients at risk for disease progression and death. The principle reasons for treatment failure include the development of viral resistance, non-adherence, and intolerance to the available medications. Treatment failure may result in selection of an HIV-1 strain that is resistant to one or more ARV, necessitating transition to a second or third line ART regimen that may be less convenient and less tolerable. Hence, new ARVs are needed to provide treatment options that are potent, durable, well-tolerated, and convenient. This is especially true for Highly Treatment Experienced (HTE) patients who, by definition, have failed multiple ARV classes/regimens and have no more than 2 fully active ARVs available to be combined in a suppressive regimen. This is the population for which BMS-663068 is being developed.

BMS-663068 prevents HIV from infecting the host cells by binding to viral gp120, thereby blocking the initial HIV-1 envelope interaction with cellular CD4 receptors and inhibiting HIV entry. This constitutes a novel mechanism to inhibit viral entry.

To date there are two FDA approved agents that treat HIV infection by inhibiting HIV-1 entry: Fuzeon[®] (enfuvirtide; T 20) and Selzentry[®] (maraviroc). Both of these compounds have been shown to be efficacious in clinical trials with treatment-experienced patients when combined with an optimized background regimen (OBR). However, there are substantial limitations to the use of these agents. Fuzeon[®] requires twice daily subcutaneous administration and is associated with local injection site reactions in the majority of treated patients; Selzentry[®] requires the patient to be infected solely with CCR5-tropic HIV-1, an unusual scenario in HTE patients who are often infected with dual/mixed- or CXCR-4-tropic virus. However, the safety and efficacy data from clinical trials with these agents still support the rationale for studying agents that intervene in the process of HIV-1 pathogenesis at the point of entry into host cells.

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

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary endpoint in Phase 2 studies conducted to date has been short-term (b) (4) reduction in HIV-1 RNA from baseline. HIV-1 RNA at Week 24 was another key efficacy endpoint to assess for the durability of the initial antiviral response. Selection of this virologic endpoint is in accordance with the Division's guidance for HIV-1 drug development in the HTE population. [1] The Division accepts this surrogate endpoint as a clinically significant endpoint for HIV-1 treatment trials in HTE patients because HIV-1 viral suppression has been associated with reduced morbidity and all-cause mortality.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

Decrease in HIV RNA level (viral load) is used as the primary endpoint in HIV-1 treatment studies. This virologic endpoint was utilized in early clinical trials to support both accelerated and traditional approvals of antiretrovirals because this surrogate marker is predictive of meaningful clinical benefit. Early trials assessed efficacy at 24 weeks (accelerated approval) or 48 weeks (traditional approval) where the drug's contribution toward the durability of the effect on HIV RNA levels was assessed. HIV RNA is now considered a validated surrogate for predicting the efficacy of antiretrovirals and the paradigm of accelerated approvals based on HIV RNA levels at 24 weeks followed by traditional approvals based on levels at 48 weeks is no longer necessary.

At present, approval is dependent on the timing of HIV RNA assessments in the population under study. For HTE patients, the Division is now assessing virologic response (proportion of patients with HIV-1 RNA decreases from baseline exceeding 0.5 log₁₀ viral copies/mL) (b) (4) plus virologic follow-up at 24 weeks. Of note, trials evaluating short-term virologic response in the HTE population would support only a limited treatment indication for use in patients who cannot construct a viable regimen without a new antiretroviral drug.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Change in CD4 cell count is also an important surrogate marker that is followed in all HIV-1 treatment trials. Restoration of a normal CD4 cell count is associated with decreased risk of morbidity and mortality associated with opportunistic infections.

- 8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

Treatment of HTE HIV patients is challenging. The goal is to construct an optimized regimen containing at least 2 fully active antiretroviral drugs, which are identified by genotypic and phenotypic resistance profiles. Unlike first-line ARV regimens which typically consist of a dual NRTI "backbone" plus one "anchor drug" – usually a PI, NNRTI, or INI – regimens for HTE patients often consist of two or more "anchor" drugs. In order to effectively reduce viral load to undetectable levels, these anchor drugs must have potent and durable antiviral activity with a high barrier to resistance and minimal cross-resistance within and between ARV class.

Table 1 summarizes ARV drugs that are currently approved for treatment-experienced subjects. Of note, only dolutegravir has been approved since implementation of the current development paradigm for HTE patients, in which the primary endpoint is short-term reduction of HIV-1 RNA. This list includes maraviroc and enfuvirtide, two drugs with a similar mechanism of action to BMS-663068 (attachment/entry inhibitors) but with different pharmacologic targets.

Please note that this list is not all-inclusive, as any ARV can theoretically be used in HTE patients based on the individual’s resistance profile. For the same reason, not all drugs on this list may be active for HTE patients, who are a subset of the “treatment experienced” subjects enrolled in the clinical trials and who often carry more extensive resistance-conferring substitutions than the overall “treatment experienced” population.

Table 1: FDA-approved ARVs for Treatment-Experienced Subjects, by ARV Class

ARV Class/Drug Name	Clinical Trial Name	Number of Subjects (study drug/comparator)	Key Inclusion Criteria	Comparator Drug*	% of Subjects meeting the Primary Endpoint
NNRTI					
Etravirine	DUET 1 and 2	1203 (599/604)	HIV-1 RNA > 5000 copies/mL despite >8 weeks of ART AND 1 or more protocol-specified NNRTI/PI resistance substitutions	Placebo + OBR (all had DRV/r [#] + 2 ARVs)	60% vs. 38% HIV-1 RNA < 50 copies/ml at Week 48 (investigational drug vs. comparator), FDA Snapshot algorithm
PI					
Atazanavir/r [#]	AI424-045	237 (119/118)	Failing ART regimen containing PI + NNRTI + NRTI	Lopinavir/r + OBR (tenofovir + one additional NRTI)	38% vs. 45% HIV-1 RNA < 50 copies/ml at Week 48, FDA Snapshot algorithm
Darunavir/r [#]	POWER 1 and 2	255 (131/124)	HIV-1 RNA > 1000 copies/mL despite >8 weeks of PI-based ART AND 1 or more protocol-specified PI resistance substitutions	Placebo + OBR (must contain a PI)	57% vs. 10% ≥ 1 log ₁₀ decrease in HIV-1 RNA below baseline (Week 96)
Tipranavir/r [#]	RESIST 1 and 2	1483 (746/737)	HIV-1 RNA > 1000 copies/mL on a PI-based ART regimen AND 1 or more	Placebo + OBR (containing PI)	34% vs. 15% ≥ 1 log ₁₀ decrease in HIV-1 RNA below baseline

			protocol-specified PI resistance substitutions		
INI					
Dolutegravir	VIKING-3	183	Failing an INI-based ART regimen with resistance to raltegravir or elvitegravir	N/A: single-arm trial	1.4 log ₁₀ (95% CI 1.3 log ₁₀ , 1.5 log ₁₀) Mean decrease in HIV-1 RNA at Day 8
Elvitegravir	145	702 (351/351)	Treatment experienced	Raltegravir + OBR (containing 1 fully active PI/r + another ARV)	52% vs. 53% HIV-1 RNA < 50 copies/ml at Week 48, FDA Snapshot algorithm
Raltegravir	BENCHMARK 1 and 2	699 (462/237)	Documented resistance to at least 1 drug in the NNRTI, NRTI, and PI class	Placebo + OBR	55% vs. 27% HIV-1 RNA < 50 copies/ml at Week 48, FDA Snapshot algorithm
Entry Inhibitor					
Enfuvirtide	TORO 1 and 2	997 (663/334)	Either 1. Viremia despite 3 to 6 months ART with NRTI, NNRTI, + PI OR 2. Resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes	Placebo + OBR	46% vs. 18% ≥ 1 log ₁₀ decrease in HIV-1 RNA below baseline
CCR5 Antagonist (Attachment Inhibitor)					
Maraviroc	MOTIVATE 1 and 2	635 (426/209)	CCR5-Tropic, Baseline HIV-1 RNA > 5000 copies/mL despite >6 months of ART OR documented resistance to at least one agent in each	Placebo + OBR	46% vs. 17% HIV-1 RNA < 50 copies/ml at Week 48, FDA Snapshot algorithm

			ARV class		
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Source: Table constructed using US Prescribing Information for each product

* OBR = Optimized Background Regimen

/r = combined with ritonavir as a pharmacokinetic boosting agent

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Breakthrough designation has been granted to **ibalizumab**, a humanized monoclonal antibody that inhibits HIV entry by inhibiting binding to the conformational epitope on domain 2 of CD4 cells. Because ibalizumab binds to domain 2, it inhibits infection by a wide variety of clinical isolates spanning all HIV subtypes. Unlike maraviroc, ibalizumab is active against both CCR5 and CXCR4 tropic viruses.

Other notable advantages conferred by ibalizumab include:

- Lack of cross-resistance with other antiretroviral agents
- Infrequent dosing (every 2 or 4 weeks) which may lead to improved adherence
- Parenteral dosing leads to few GI side effects.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results. Data from two Phase 2 studies provide preliminary clinical evidence that BMS-663068 provides a valuable treatment benefit for the hard-to-treat HTE population. Key design elements and efficacy outcomes are summarized in Table 2.

Table 2: Preliminary Clinical Evidence of Substantial Improvement in Treatment Benefit

Study ID	Phase	Design	Study Population	Endpoints	Treatment Groups	Number of Subjects	Results by Group Mean (SE)
AI438006	2a	Randomized proof-of-concept study in HIV-1 infected subjects treated for 7 days with BMS-663068 (068*) +/- ritonavir (RTV).	-HIV-1 subtype B infection - Plasma HIV RNA level $\geq 5,000$ copies/mL -ARV naïve or experienced - CD4+ T-	Mean decrease in \log_{10} HIV-1 RNA from baseline Subjects were stratified by prior treatment	1: 068 600mg Q12H + RTV 100mg Q12H 2: 068 1,200mg QHS + RTV 100mg	50 overall, 10 in each treatment group	Reduction in \log_{10} HIV-1 RNA at Day 9 1: -1.34 (0.08) 2: -1.25 (0.11) 3: -1.24 (0.11)

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

			<p>cell count ≥ 200 cells/μL</p> <p>- Off all ART for ≥ 8 weeks</p> <p>-Had not previously received an HIV-1 attachment inhibitor</p>	<p>experience</p>	<p>QHS</p> <p>3: 068 1,200mg Q12H + RTV 100mg Q12H</p> <p>4: 068 1,200mg Q12H + RTV 100mg QAM</p> <p>5: 068 1,200mg Q12H</p>		<p>4: -1.19 (0.13)</p> <p>5: -0.89 (0.27)</p>
AI438011	2b	<p>Randomized, dose-blinded, active-controlled dose-finding study in HIV-1-infected treatment-experienced subjects. Subjects received 068+OBR (RAL+TDF) for 48 weeks.</p> <p>An elective monotherapy substudy was conducted in subjects who were not on ART. Subjects were randomized to 068+ placebo instead of 068+RAL+TDF.</p>	<p>- HIV-1 RNA ≥ 1000 copies/mL</p> <p>- ART-experienced</p> <p>- INI treatment naïve</p> <p>-resistance genotype and phenotype indicating susceptibility to ATV/r , RAL, and TDF</p> <p>-Screening phenotype indicating BMS-626529 IC50 $< 0.1 \mu$M (active compound)</p> <p>- CD4+ T-cell count > 50 cells/mm^3</p>	<p>Primary: Proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 24</p> <p>Monotherapy sub-study: Mean decrease in HIV-1 RNA after 7 days of monotherapy</p>	<p>1: 068 400 mg BID +OBR</p> <p>2: 068 800 mg BID +OBR</p> <p>3: 068 600 mg QD +OBR</p> <p>4: 068 1200 mg QD +OBR</p> <p>5: ATV/r + OBR</p>	<p>Primary Study: 251 subjects in total from the 5 treatment arms</p> <p>Monotherapy sub-study: 32 subjects total in the 4 068-containing treatment arms</p>	<p>Primary Endpoint in Primary Study: See Table 3</p> <p>Primary Endpoint of sub-study: Reduction in log10 HIV-1 RNA at Day 8</p> <p>1: -0.69 (0.22)</p> <p>2: -1.37 (0.16)</p> <p>3: -1.22 (0.13)</p> <p>4: -1.47 (0.22)</p>

*BMS-663068 is abbreviated as 068, ritonavir is abbreviated at RTV

Table 3: Study AI438011 Response Rates and Mean Change from Baseline Weeks 24 and 48

HIV-1 RNA	No. of Subjects/Total No. of Subjects (%)									
	Week 24					Week 48				
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
	400 mg BID	800 mg BID	600 mg QD	1,200 mg QD		400 mg BID	800 mg BID	600 mg QD	1,200 mg QD	
	mITT					mITT				
<50 c/mL	40/50 (80)	34/49 (69)	39/51 (77)	36/50 (72)	38/51 (75)	41/50 (82.0)	30/49 (61.2)	35/51 (68.6)	34/50 (68.0)	36/51 (70.6)
<400 c/mL	46/50 (92)	39/49 (80)	46/51 (90)	40/50 (80)	42/51 (82)	43/50 (86.0)	37/49 (75.5)	42/51 (84.3)	40/50 (80.0)	38/51 (74.5)
	Observed Case (Subjects with Data Within the Week 24 Window)					Observed Case (Subjects with Data Within the Week 48 Window)				
<50 c/mL	40/46 (87)	34/42 (81)	39/50 (78)	36/43 (84)	38/44 (86)	41/43 (95.3)	30/39 (76.9)	35/45 (77.8)	34/42 (81.0)	36/41 (87.8)
<400 c/mL	46/46 (100)	39/42 (93)	46/50 (92)	40/43 (93)	42/44 (96)	43/43 (100)	37/39 (94.9)	43/45 (95.6)	40/42 (95.2)	38/41 (92.7)
Mean change from baseline (log ₁₀ c/mL)	-2.944	-2.891	-3.042	-2.739	-2.830	-3.110	-2.905	-3.036	-2.791	-2.911

Source: Sponsor's Breakthrough Request Materials

- b. Include any additional relevant information. Consider the following in your response:

Efficacy Summary:

The data from the two Phase 2 trials summarized above provide preliminary clinical evidence of a substantial improvement over available therapies, as evidence by the demonstration of ≥ 1 log₁₀ reduction in HIV-1 RNA in all but one 068 dose cohort (400 mg BID) after short-term monotherapy. The Week 24 and Week 48 virologic data from Study AI438011 demonstrate the durability of this initial response over time.

Safety Results:

Study AI438006: No deaths, SAEs, or AEs leading to treatment discontinuation occurred. Most AEs were Grade 1 in severity. No Grade 3 or 4 AEs were reported. The most frequently reported AEs were headache (36%), rash (16%), micturition urgency (14%), and nasopharyngitis (12%), with no relevant differences in incidence between the different BMS-663068 dose groups. There were no consistent, clinically relevant changes over time in vital signs, ECG parameters, or physical examination. There were no relevant differences in incidence of laboratory abnormalities between BMS-663068 treatment groups.

Study AI438011: No deaths have occurred during the study. Eight subjects have discontinued due to AEs, of which 5 were in 068 treatment arms: 1 subject in the 400mg BID arm discontinued due to cocaine use; 1 subject in the 800 mg BID arm discontinued due to bone tuberculosis and a second subject discontinued due to acute renal failure (Grade 3, treatment related); 1 subject in the 1200 mg QD

arm discontinued due to lymph node tuberculosis and a second subject discontinued due to disseminated tuberculosis. In the ATV/r group, 3 subjects discontinued due to treatment-related GI AEs.

SAEs were reported in 20/251 subjects, of which 2 were treatment-related: 1 subject in the 800 mg BID 068 arm had myalgia and renal failure (deemed due to TDF, no action taken with study drug) and one subject in the ATV/r arm had diarrhea and flu-like illness resulting in study drug interruption.

Of the 251 treated subjects, 196 experienced at least one treatment emergent AE. Most treatment-related AEs were low-grade and there were no trends for dose-relationship. Grade 2-4 related AEs reported in 068 groups occurred in 1 subject each.

Safety Summary: The results from the 2 Phase 2 studies suggest that 068 is well-tolerated. No dose-related toxicities have been identified.

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

GRANT :

Provide brief summary of rationale for granting:

The Division endorses granting Breakthrough Designation for the following reasons:

- 1: The drug targets a serious condition. There is a need for new ARVs that confer potent, durable antiviral activity against viral strains that are resistant to multiple existing ARV options. This need is most acute for HTE subjects who have limited remaining treatment options. Lack of virologic control leads to further immune destruction and an increased risk of mortality caused by opportunistic infections.
- 2: BMS-663068 has a novel pharmacologic target. No available ARVs, including other attachment/entry inhibitors, bind to viral gp120. Hence, BMS-663068 retains activity against HIV-1 strains that are resistant to multiple other ARV classes. In turn, resistance that may develop to BMS-663068 does not confer resistance to other ARV classes.
- 3: Available Phase 2 data demonstrates potent and durable anti-viral activity at a variety of doses. Efficacy has been demonstrated both in the short-term (less than 2 weeks) and long-term, in combination with an OBR.
- 4: BMS-663068 appears to be safe and well tolerated. No safety signals have been detected from Phase 1 and 2 trials conducted to date.

DENY:

Provide brief summary of rationale for denial: N/A

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

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division reviewed the Sponsor's End-of-Phase 2 meeting package in April 2014 and provided comments and feedback regarding Phase 3 trials in HTE patients. The protocol for study AI438047 was subsequently submitted and reviewed by the Division and the study was initiated in February 2015. In brief, Study AI438047 is a Phase 3 study in HTE patients, defined as subjects who are failing their current ARV regimen (HIV-1 RNA \geq 400 copies/ml) and have \leq 2 classes of ARVs with a least 1 but no more than 2 fully active ARVs remaining to construct a viable regimen. As outlined in the Guidance Document for ARV Development, the primary endpoint will be reduction in HIV-1 RNA during short term monotherapy and a second assessment at 24 weeks will be made to assess durability of antiviral activity and safety. This study will use a 068 dose of 600 mg BID, which is supported by demonstration of both safety and antiviral activity at doses that are both lower and higher than this total daily dose.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

1. Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Draft Guidance, Issued June 2013. Available at:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf>

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

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

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

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

4-6-15/M. Raggio

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

/s/

PRABHA VISWANATHAN
06/11/2015

ADAM I SHERWAT
06/11/2015

DEBRA B BIRNKRANT
06/12/2015



IND 73916

MEETING MINUTES

Bristol Myers Squibb
Attention: Susan Behling
Group Director, Global Regulator Science
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Behling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-663068.

We also refer to the teleconference between representatives of your firm and the FDA on May 6, 2014. The purpose of the meeting was to discuss the proposed development plans that are intended to support the registration of BMS-663068 in heavily treatment experienced (HTE) patients with HIV-1 infection.

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 Suzanne Strayhorn, Regulatory Project Manager at (301) 796-1500 or (240) 402-4247.

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
BMS Slides
BMS Revised Slide (Post EOP2 Meeting Update)



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: May 6, 2014: 1:00 pm – 2:30 pm
Meeting Location: Teleconference

Application Number: IND 73916
Product Name: BMS-663068
Indication: Treatment of HIV-1 Infection
Sponsor/Applicant Name: Bristol Myers Squibb

Meeting Chair: Linda Lewis, MD, Medical Team Leader
Meeting Recorder: Suzanne Strayhorn, MSc, Regulatory Project Manager

FDA ATTENDEES

Edward Cox	Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant	Director, Division of Antiviral Products (DAVP)
Jeffrey Murray	Deputy Director, DAVP
Linda Lewis	Medical Officer Team Lead, DAVP
Tafadzwa Vargas-Kasambira	Medical Officer, DAVP
William Tauber	Medical Officer, DAVP
Prabha Viswanathan	Medical Officer, DAVP
Hanan Ghantous	Non Clinical Team Lead, DAVP
Kuei Meng Wu	Non Clinical Reviewer, DAVP
Julian O'Rear	Clinical Virology Team Lead, DAVP
Sung Rhee	Clinical Virology Reviewer, DAVP
Takashi Komatsu	Clinical Virology Reviewer, DAVP
Elizabeth Thompson	Chief Project Management, DAVP
Suzanne Strayhorn	Regulatory Project Manager, DAVP
Shirley Seo	Clinical Pharmacology, Team Lead, Office of Clinical Pharmacology (OCP)
Su-Young Choi	Clinical Pharmacology Reviewer, OCP
Greg Soon	Biostatistics Team Lead, Office of Biostatistics (OB)
Fraser Smith	Biostatistics Reviewer, OB

SPONSOR ATTENDEES

Doug Manion	Sr. Vice President, Development Neuroscience, Virology and Japan
George Hanna	Vice President, Development Lead
Max Lataillade	Executive Director, Virology Global Clinical Research
Samit Joshi	Director, Virology Global Clinical Research
Thomas Kelleher	Group Director, Global Biometric Sciences Virology
David Stock	Director, Global Biometric Sciences Virology
David Boulton	Group Director, Exploratory Clinical & Translational Research (ECTR)

SPONSOR ATTENDEES, continued

Ishani Savant Landry	Associate Director, Clinical Pharmacology and Pharmacometrics ECTR
Mark Krystal	Director, Discovery Virology
Marc Davies	Group Director, Drug Safety Evaluation (DSE)
Mike Peden	Director, DSE -Pathology
Margo Heath-Chiozzi	Vice President, Global Regulatory Strategy, Virology
Joseph Lamendola	Vice President, U.S. Regulatory Sciences and Regulatory Policy
Susan Behling	Group Director, Global Regulatory Strategy, Virology
Alan Mart	Director, Global Regulatory Strategy, Virology
Hyekyung Yang	Associate Director, Global Regulatory Sciences - US Liaison
Nicole Barnor	Manager, Global Regulatory Strategy Management

1.0 BACKGROUND

On November 8, 2005, Bristol-Myers Squibb (BMS) submitted IND 73916 for BMS-663068 which remains under development as a therapeutic agent for treatment of patients with human immunodeficiency virus type 1 (HIV-1) infection. BMS-663068 is a methyl phosphate prodrug, which when administered orally, in both animals and humans, is hydrolyzed to an active moiety BMS-626529 as well as phosphate and formaldehyde. The active moiety, BMS-626529 blocks attachment by binding to the viral gp120, inhibiting HIV-1 envelope interaction with cellular CD4 receptors. The mechanism of action by BMS-663068 in preventing HIV-1 attachment is novel and may offer an alternative antiretroviral treatment strategy to patients infected with HIV-1, particularly those with heavy prior treatment experience, who have developed resistance to existing antiviral drugs. In February 2011, the Division of Antiviral Products (DAVP) approved BMS' request for Fast Track Designation for this IND.

On February 19, 2014, BMS submitted a request for an End of Phase 2 (EOP2) meeting with DAVP to discuss and gain DAVP consensus for their proposed development plans to support registration of BMS-663068. A briefing document in preparation for this meeting was submitted by BMS on April 4, 2014. DAVP sent preliminary comments to BMS on May 1, 2014. On May 2, 2014, following review of DAVP preliminary comments, BMS requested a teleconference in lieu of a face to face meeting. BMS also requested to focus the meeting on the following questions:

- Q2: Clarification of our current data and further plans for understanding whether BMS-663068 is an UGT1A inhibitor.
- Q5: We are considering the Division's suggestion to use a higher viral load cutoff for inclusion and would like to further discuss.
- Q8: We are considering changing the primary endpoint and would like to discuss how we then handle the endpoint of proportion with 0.5 log drop in the protocol.
- Q11: We would like to understand the Division's concerns about potential testicular toxicity. BMS does not agree that this has been seen in 2 toxicology species. We previously (prior to the Phase 2 study start) submitted our position on this and we thought this had been resolved.
- Q13, 14, 16, 17: We would like to discuss the responses to these questions as a whole to ensure alignment that the program we conduct will ultimately serve the needs for registration and the patients' best interests, including those who may not qualify per se for the proposed HTE study.

On May 15, 2014 BMS provided DAVP with updates to the OATPB1/B3 slide which was provided to the division for discussion at the time of the EOP2 meeting. The updated slide included new and revised OATP-mediated drug interaction data. The update has direct relevance to the discussions which occurred at the meeting and the revised information is therefore incorporated with these minutes as a post meeting addendum in Section 2.3.

2.0 DISCUSSION

Questions submitted by the Sponsor are in **bold** font, the Agency's preliminary responses are in *italics* and discussions that occurred during the meeting are in regular font.

Note: Slides (appended to minutes), were provided by BMS in advance of the teleconference with the intent to facilitate discussions related to the above comments raised by DAVP. It should be noted that information provided within the slides contained new data which the Division had not yet seen.

2.1 CHEMISTRY, MANUFACTURING AND CONTROLS

BMS does not have CMC questions or topics planned for the EOP-2 Meeting. BMS plans to submit a future Type C meeting request to review CMC topics.

2.2 NONCLINICAL

Question 1:

**Does FDA agree that the nonclinical toxicology plan should be sufficient to:
(a) Initiate the Phase 3 study AI438P12 and (b) support registration?**

FDA Response to Question 1:

The nonclinical toxicology plan is adequate to initiate the Phase 3 study and may support registration.

Meeting Discussion:

No further discussion occurred.

2.3 CLINICAL PHARMACOLOGY

Question 2:

Does FDA agree that, based on the available data for BMS-663068, the completed, ongoing and planned clinical pharmacology studies are sufficient to: (a) Initiate Phase 3 and (b) Support registration?

FDA Response to Question 2:

- 1. We disagree with your rationale not to conduct DDI studies with protease inhibitors. Some protease inhibitors are OATP1B1/3 inhibitors (e.g., lopinavir/ritonavir) thus may substantially increase the exposure of BMS-626529 if it is a substrate of OATP1B1/3. Therefore, if you plan to include such protease inhibitors in your choices of allowable background regimens, we strongly recommend completing an in vitro evaluation of drug interaction potential via major transporters and determine the necessity of in vivo drug interaction trials prior to Phase 3. We also recommend that you determine whether BMS-626529 is an inhibitor of OATP1B1/3 if you plan to include statins as allowable concomitant medications in your phase 3 trials, since many commonly used statins are substrates of OATP1B1/3.*

2. *Although efavirenz is not commonly used in the heavily treatment-experienced population, it is a moderate CYP3A4 inducer which will likely decrease the exposure of BMS-626529. Please clarify your plan with respect to the use of efavirenz in your phase 3 trials.*
3. *Please clarify whether BMS-663068 or BMS-626529 are substrates or inhibitors of UGT enzymes.*

Meeting Discussion:

BMS provided the following clarifications:

Drug interaction potential via OATP1B1/3

BMS presented new data from *in vitro* OATP1B1 inhibition studies. Preliminary assessments suggest that BMS-663068 (pro-drug) does not inhibit OAT1B1/B3 substrates and BMS-626529 (active moiety) has low interaction potential with OAT1B1/B3 substrates. Based on these results, BMS has concluded that drug interactions with statins are unlikely and concomitant use in the Phase 3 study will be acceptable. DAVP agreed that IC₅₀ values are relatively high and it is likely a weak inhibitor or the effect is not clinically relevant pending a detailed review of the *in vitro* studies. BMS also does not expect BMS663068 and BMS626529 to be sensitive substrates of OATP1B1/3 based on *in vitro* and *in vivo* results. Specifically, ATV/rtv increased the exposure of BMS626569 less than 2-fold. BMS believes this suggests either a weak or no drug interaction potential via OATP1B1/3. DAVP agreed the overall assessments appear to be reasonable but has not had the opportunity to review all relevant data. However, DAVP requested all available *in vitro* study reports for further assessment prior to the initiation of Phase 3.

Drug interaction potential via UGT

BMS clarified that they intend to conduct *in vitro* assessments to determine whether BMS-663068 and BMS-626529 are inhibitors of UGT1A prior to Phase 3. BMS also stated that BMS-663068 and BMS-626529 are unlikely to be clinically relevant UGT1A inhibitors based on their Phase 2 trial. Analysis of PK samples obtained from subjects who were co-administered raltegravir (RTV) in the Phase 2b study, (ref: A1438011) suggest that BMS-663068 and BMS-626529 do not have a clinically important inhibitory effect on UGT1A1. BMS believes that the *in vitro* results and the raltegravir PK results from the Phase 2 study will be sufficient to determine whether BMS-663068 and BMS-626529 are clinically relevant UGT1A inhibitors. DAVP preliminarily agrees with BMS' approaches and plans to compare the submitted raltegravir PK data to historical raltegravir PK data. DAVP has also requested submission of *in vitro* study results once they become available.

Based on the clinical ADME study AI438005, BMS believes that the clearance of BMS-663068/BMS-626529 via the UGT mediated metabolic pathway is minor. Based on the findings of this study and *in vivo* DDI study results, BMS does not plan to conduct additional studies. DAVP agreed that no additional work is needed to evaluate BMS-663068 and BMS-626529 as substrates of UGT1A, pending a review of the ADME study in conjunction with results from the *in vitro* assessments.

Post Meeting Addendum:

ADME Study Report

DAVP has confirmed receipt of ADME Study Report number AI438005, received on September 8, 2011 and identified as submission sequence 113.

Revised in Vitro OATP1B1/3 Drug Interaction Results (new data, corrected calculations)

On May 15, 2014, DAVP received a post-EOP2 meeting update from BMS. This update was in the form of a revised slide detailing corrected calculations and newly obtained results, relative to the OATP1B1/3 in vitro drug interaction studies with BMS-663068/626529 (slide appended to these minutes).

- 1. Based on analysis of the new data, BMS will conduct a statin drug interaction study prior to initiation of Phase 3.*
- 2. As BMS has decided to conduct DDI trials with statins prior to Phase 3, DAVP requests review of the DDI clinical trial results in lieu of the in vitro study reports requested at the time of the EOP2 meeting. The action items have been amended to reflect BMS' post meeting decision to investigate drug interaction with statins. Ideally, a full clinical study report (CSR) should be made available for division review; however, if this poses significant restraints on time to initiate the Phase 3 program, DAVP will accept a summary of results with supporting conclusions and clinical recommendations.*

2.4 CLINICAL

2.4.1 PROPOSED PHASE 3 TRIAL IN THE HIV-1 INFECTION

Question 3:

Does FDA agree with the general design, treatment arms and number of subjects, (as described above and in the Synopsis shown in Appendix 1) for the Phase 3 HTE study?

FDA Response to Question 3:

In general, we agree with the superiority design of your trial. Your plan to enrich your trial population with the 3:1 randomization ratio for BMS-663068 versus placebo, respectively, is acceptable, as are the two treatment arms.

We understand that as part of the Phase 2b study (AI438011), a 7-day monotherapy substudy was conducted in 32 subjects, and that three of the BMS-663068 treatment groups in that study produced better than a 1 log decrease in HIV-1 RNA count. The Phase 2b study population was not as heavily treatment experienced as that proposed for the Phase 3 study but provides sufficient proof of concept. We also note that there was minimal evidence of selection for BMS-626529 high-level resistance over the 8 days of monotherapy with BMS-663068 (Ray N et al, J Acquir Immune Defic Syndr 2013; 64(1):7-15) making study of a short period of functional monotherapy acceptable in the Phase 3 population.

Meeting Discussion:

No further discussion occurred.

2.4.1.1 Dose Selection for Proposed Phase 3 Study

Question 4:

Does FDA agree with the proposed Phase 3 dose of 600 mg BID BMS-663068?

FDA Response to Question 4:

Although the proposed dose of BMS-663068 600 mg BID was not actually studied in the Phase 2b trial, it appears that a BMS-663068 dose of 600 mg BID may produce a similar AUC, a lower C_{max}, and a higher C_{min}, compared with the 1200 mg QD dose (assuming dose-proportionality).

While it is preferable to use a dose in Phase 3 trials that has been previously studied in subjects, we find your proposed dose of BMS-663068 600 mg BID acceptable, given the information above and the nature of the trial population and limited treatment options available for these HTE patients.

Meeting Discussion:

No further discussion occurred.

2.4.1.2 Study Population

Question 5:

Does FDA agree that the proposed patient population and inclusion and exclusion criteria meet the FDA's definition of a HTE population to support an indication in this setting?

FDA Response to Question 5:

In general, we agree with your inclusion and exclusion criteria.

We have two additional comments regarding study entry criteria. We suggest that you consider expanding the HIV-1 RNA viral load enrollment criterion to ≥ 1000 copies/mL. There is precedent for this approach in studies in similar HTE populations, and this change may allow more robust determination of antiviral effect during the functional monotherapy period. In addition, we suggest that you exclude use of concomitant drugs that possess the potential for increasing the QTc interval.

Meeting Discussion:

BMS would like to continue with the proposed Phase 3 HIV-1 RNA viral load study entry criteria of ≥ 400 copies/mL. BMS foresees that increasing the study inclusion viral load requirements to ≥ 1000 copies/mL, per the Division's suggestion, will impact the recruitment rate in an already difficult to recruit patient population. BMS also stated that maintaining the planned viral load cutoff would allow for an assessment of a ≥ 1 log₁₀ drop, and would allow for an evaluation of resistance at baseline. The Division agreed that this would be acceptable but cautioned that viral load decreases may be difficult to differentiate, especially for subjects

enrolling at or just above the 400 copies/mL cut-off. The Division suggested that BMS consider to report viral load results as “<LLOQ, target detected” or “<LLOQ, target not detected”.

2.4.1.3 Primary Endpoint

Question 6:

Does FDA agree with the proposed primary efficacy endpoint and statistical analysis?

FDA Response to Question 6:

We agree with your proposed primary efficacy endpoint for treatment-experienced patients with few or no available treatment options, namely that of comparison of BMS-663068 to placebo, when given on the background of a failing antiretroviral regimen, on the proportion of subjects with a decrease from baseline in HIV-1 RNA that exceeds 0.5 log₁₀ copies/mL at Day 8 (early time point).

Meeting Discussion:

Refer to discussion under Question 8

2.4.1.4 Secondary Endpoint

Question 7:

Does FDA agree that the proposed secondary endpoints and statistical plan are appropriate and would support inclusion of these results in the labeling?

FDA Response to Question 7:

The proposed secondary endpoints are appropriate. The issue of whether these results would be appropriate for inclusion in labeling will be an NDA review issue. The Statistical Plan does not contain sufficient detail for us to evaluate at this time; please provide more complete information in the study protocol.

Meeting Discussion:

No further discussion occurred.

2.4.1.5 Alternate Primary Efficacy Endpoint

Question 8:

Does the FDA agree that the mean decline in log₁₀HIV-1 RNA levels from baseline to Day 8 could serve as the primary endpoint instead of the proportion of subjects with a decrease in HIV-1 RNA of > 0.5 log₁₀c/mL at Day 8 in the proposed BMS-663068 Phase 3 study (AI438P12)?

FDA Response to Question 8:

The primary endpoint that you propose is one that the Division recommends as a secondary endpoint in trials such as your Phase 3 study. We acknowledge your concerns with the primary endpoint recommended in the FDA draft guidance (June 2013), and your proposal to use instead the mean decline in log₁₀ HIV-1 RNA from baseline to Day 8. There is precedent for using the

primary endpoint that you have suggested (see approved label for TIVICAY (dolutegravir)). We are therefore willing to consider the mean decline in \log_{10} HIV-1 RNA levels from baseline to Day 8 as a primary endpoint for your Phase 3 trial.

Alternatively, if the proportion of responders is too high in a blinded pooled analysis, you could consider using the proportion of subjects with a decrease in HIV-1 RNA $> 1 \log_{10}$ c/mL at Day 8 as the primary efficacy endpoint. The details for such an approach would need to be pre-specified.

Meeting Discussion:

The Division agreed it is acceptable for BMS to use the mean decline in \log_{10} HIV-1 RNA levels from baseline to Day 8 as the primary endpoint in the proposed Phase 3 Study. The proportion of subjects with a decrease from baseline in HIV-1 RNA that exceeds $0.5 \log_{10}$ copies/mL at Day 8 will become the secondary endpoint. DAVP acknowledged BMS' concern that subjects assigned to the placebo arm of the study could potentially achieve a $> 0.5 \log_{10}$ decline in HIV-1 RNA levels due to a renewed focus on taking their background medication as prescribed, simply because of clinical trial participation. DAVP indicated that this type of placebo response would have an impact on both endpoints. The Division suggested that BMS consider building in a longer baseline/screening assessment period into the Phase 3 study, to address concerns related to the potential impact on endpoints due to prior poor adherence to the ARV treatment regimen. BMS stated that baseline adherence counseling will be operationally difficult to implement and will increase the screening window, however, BMS will take the Division's suggestion under advisement.

The Division also suggested that the primary endpoint could be defined as either 1) a decrease in HIV-1 RNA $> 0.5 \log_{10}$ c/mL at Day 8, or, 2) a decrease in HIV-1 RNA $> 1 \log_{10}$ c/mL at Day 8 and the final primary analysis endpoint could be established after reviewing the overall response rate (both arms pooled) prior to unblinding the data. The protocol and Statistical Analysis Plan, (SAP) could define a predetermined analysis algorithm and data-cut time points. BMS declined and said they would use mean decline in \log_{10} HIV-1 RNA levels from baseline to Day 8 as the primary endpoint.

2.4.1.6 BMS-626529 Phenotypic Assay

Question 9:

Does FDA agree with the planned use of the BMS-626529 phenotypic susceptibility assay in the proposed Phase 3 study?

FDA Response to Question 9:

The sponsor's proposal not to use the BMS-626529 susceptibility of screening virus samples to determine the subject's eligibility for the study appears to be reasonable, given the population to be targeted.

Meeting Discussion:

No further discussion occurred.

Question 10:

Given that the phenotypic assay is not planned for selection of subjects inclusion in the proposed Phase 3 study, does FDA agree that a companion diagnostic will not be needed?

FDA Response to Question 10:

We agree. However, approval of BMS-626529 for use in other populations may require FDA review of the susceptibility assay(s).

Meeting Discussion:

No further discussion occurred.

2.4.1.7 Proposed Safety Monitoring Plan

Question 11:

Is the safety monitoring plan acceptable?

FDA Response to Question 11:

Given the safety events noted with previous clinical use of BMS-663068 in Phase 2 studies, as well as the results of the thorough QT study (QTc interval prolongation at supratherapeutic doses of 2400 mg BID), we find your safety monitoring plan for the proposed Phase 3 study to be acceptable.

We do, however, recommend that you include in this plan monitoring for testicular toxicity, given the findings noted in the animal studies.

Meeting Discussion:

The Division has reviewed the animal studies again and does not have further concerns about testicular toxicity. We do believe there are sufficient margins of safety and there is no need to monitor testicular toxicity at this time. The Division asked that BMS resubmit their position paper on the topic that was submitted prior to Phase 2 study start.

2.4.1.8 Resistance Testing Plan

Question 12:

Is the resistance testing plan appropriate?

FDA Response to Question 12:

In general, the proposed resistance testing plan for Study AI438P12 is acceptable. Please confirm that genotypic resistance to BMS-663068 will be determined for all subjects who develop protocol-defined virologic failure or meet protocol-defined criteria for viral resistance testing, regardless of phenotypic results of their on-study isolates (reduced susceptibility to BMS-626529 or decrease in maximum percent inhibition compared to Baseline or not). Please include in the protocol submission performance characteristics and a detailed description of the methodology of your genotypic and phenotypic resistance assays.

Meeting Discussion:

BMS intends to use geno/phenotyping in the Phase 3 study and will include information on the assays in the protocol submission as requested.

2.4.1.9 Adequacy of Phase 3 Study Design

Question 13:

Does the FDA agree that the design of Study AI438P12 should support approval for use of BMS-663068 in combination with other antiretroviral agents for the treatment of HIV-1 infection in heavily treatment-experienced adults with HIV-1 replication despite ongoing antiretroviral therapy?

FDA Response to Question 13:

The design of your Phase 3 trial is appropriate for consideration for an NDA application. We have some concern, however, that you plan to seek approval for BMS-663068 based upon a single Phase 3 study that will only have a maximum of 200 subjects enrolled (assuming no attrition, which is highly unlikely). We do note, however, that your Phase 2b study may be considered supportive of the pivotal Phase 3 trial.

Meeting Discussion:

BMS asked the Division to review any specific concerns as related to their proposed Phase 3 plans. The Division reiterated that the overall Phase 3 study proposal is appropriate. The Division's main concern is that the planned Phase 3 enrollment of a *maximum* of 200 subjects may be insufficient to fully characterize the safety of the investigational product, particularly if significant attrition becomes an issue. The safety database can be augmented to include the subjects (approximately 80 subjects) enrolled in the Phase 2 trial's 800 mg BID and 1200mg QD arms. The inclusion of Phase 2 data from subjects who switched to the 1200mg dose from a lower starting dose may confound the overall data analyses. BMS reiterated that they anticipate enrollment into the study will be difficult, and that recruitment of 200 subjects is estimated to take up to 24 months. BMS stated that they are receiving multiple requests for allowing access to BMS-663068 for patients who have no fully active antiviral options remaining. BMS inquired if the Division would consider allowing the inclusion of these patients in the Phase 3 study as a separate "Observational Cohort." These subjects would receive the attachment inhibitor with an optimized background regimen, but would not go through a period of monotherapy. Those enrolled in this cohort would be followed over 24 weeks with similar safety and efficacy data collection requirements as the principal cohort. The Division agreed that this would be a reasonable approach to increase the size of the safety database in a more controlled setting. BMS clarified that the proposed "Observational Cohort" would be different from the group of patients that they plan to enroll in their Expanded Access Program (EAP). The expanded access (compassionate use) program is intended for patients who are not eligible for the Phase 3 study (including the "Observational Cohort) or who do not live near a study site.

2.4.1.10 Proposed Handling of Subjects with No Remaining Fully Active Antiretrovirals

Question 14:

Does FDA agree that it is appropriate to plan for an open-label expanded access protocol in parallel with Study AI438P12 to provide BMS-663068 access to HTE subjects who have no remaining fully-active antiretroviral therapies available and to use the safety data from this expanded access study as part of the registration database?

FDA Response to Question 14:

We consider your plan to initiate an open-label expanded access protocol (EAP) for HIV-1 infected patients who are heavily treatment-experienced and have no further treatment options reasonable and appropriate. You should be cognizant, however, of the issues associated with this undertaking should patients decide to enroll in more than one EAP or treatment IND simultaneously, including the need for additional data to characterize the potential for PK-based drug interactions and potential for overlapping toxicity (other issues are included in the Guidance). Ideally, enrollment in the EAP should occur once enrollment in the Phase 3 trial is complete. We are hesitant to allow subjects enrolled in an open-label treatment IND or EAP, to form a significant portion of the overall safety database for your NDA unless the safety data collection in this population is comparable to that collected in the Phase 3 trial.

Meeting Discussion:

Refer to discussion under Question 13

2.4.2 PROPOSED REGISTRATION PLAN FOR BMS-663068

Question 15:

Does FDA agree that efficacy from the proposed Phase 3 study in HTE subjects, together with the data from the Phase 2 studies, can support full approval for an HTE only indication?

FDA Response to Question 15:

The decision on whether the efficacy from the Phase 2 and 3 trials are sufficient to support full approval for an HTE-only indication, will be a review issue once the NDA is submitted. Your study plan is, however, consistent with our Guidance document.

Meeting Discussion:

No further discussion occurred.

2.4.2.1 Safety Database for Registration

Question 16:

Does FDA agree with the size and composition of the proposed safety database for registration?

FDA Response to Question 16:

Ideally, we expect that the safety database will comprise subjects who received the investigational drug at the proposed dose for an informative duration. You anticipate you will have at least 160 subjects from your Phase 3 trial who have received the proposed to-be-marketed dose. The remainder of your safety database is comprised of subjects who have received initial doses of BMS-663068 of 1200 mg QD and 800 mg BID. Safety data from subjects who received lower initial doses of BMS-663068 in the Phase 2b study may be difficult to interpret as they were escalated to the 1200 mg QD dose after 48 weeks. Safety data from subjects enrolled in the EAP/treatment IND may provide supportive data for the safety database if data collection is similar to that in the clinical trials. The size and composition of your safety database appears relatively limited but it may be acceptable to characterize safety in the intended population.

Meeting Discussion:

Refer to discussion under Question 13

Question 17:

Does FDA agree with the plan to monitor the discontinuation rate in the AI438P12 study and potentially increase the randomized sample to ensure adequate numbers are achieved for the safety database?

FDA Response to Question 17:

We prefer that an appropriate number of subjects be enrolled initially to account for drop-outs.

Meeting Discussion:

Refer to discussion under Question 13

2.4.2.2 Potential Request for Breakthrough Therapy Designation

Question 18:

Does FDA agree that it may be appropriate to consider early submission of data from the randomized phase of Study AI438P12 in a request for Breakthrough Therapy status?

FDA Response to Question 18:

Breakthrough Therapy designation is intended for products for serious/life-threatening diseases and must be based on clinical evidence of substantial improvement over existing therapies. If BMS-663068 shows good activity in the 7-day randomized phase of the trial, it may meet the criteria necessary to consider an application for Breakthrough Therapy status. If you wish to submit a request based on early data, an interim review of the data generated in this phase should be pre-specified in the protocol statistical analysis plan. The decision on whether to grant Breakthrough Therapy status to your study drug will be made after review of your application for this status.

Meeting Discussion:

No further discussion occurred.

3.0 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. 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 Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Items from EOP2 Meeting

Action Item/Description	Owner	Due Date
Submit clinical trial results for statin DDI study with conclusion/clinical recommendation (This action item is revised based on post meeting update from BMS regarding Q2)	BMS	Prior to initiation of Phase 3 clinical trial(s)
Submit in vitro UGT inhibition results	BMS	Prior to initiation of Phase 3 clinical trial(s)
Resubmit Testicular Toxicity position paper	BMS	Prior to initiation of Phase 3 clinical trial(s)
Submit Phase 3 Protocol (to include addition of 50 patients in "Observational Cohort" as proposed during meeting)	BMS	Prior to initiation of Phase 3 clinical trial(s)

6.0 ATTACHMENTS AND HANDOUTS

BMS Slides provided on May 6, 2014 in reference to Question # 2.

BMS Revised Slide provided on May 15, 2014 in reference to Question #2.

8 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

DEBRA B BIRNKRANT
06/03/2014