CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213983Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 075382
NDA 204790

MEETING MINUTES

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

Dear Mr. Troughton:

Please refer to your investigational new drug application (IND) and new drug application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TIVICAY® (dolutegravir) tablet.

We also refer to the teleconference between representatives of your firm and the FDA on September 11, 2019. The purpose of the meeting was to discuss and reach agreement on the content and format of the planned applications and in principle the adequacy of the data that will be submitted to support the proposed dosing regimens for pediatric patients using the tablet and/or dispersible tablet formulation.

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

If you have any questions, e-mail me at Philip.Villasurda@fda.hhs.gov or call at (301) 796-2586 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA and Pre-sNDA
Meeting Date and Time:	September 11, 2019 from 11:30 a.m. to 12:30 p.m. EDT
Meeting Location:	Teleconference
Application Number:	IND 075382 and NDA 204790
Product Name:	TIVICAY® (dolutegravir)
Indication:	Treatment of HIV-1 infection
Sponsor/Applicant Name:	ViiV Healthcare Company
Meeting Chair:	Debra Birnkrant
Meeting Recorder:	Philip Villasurda

FDA ATTENDEES

Debra Birnkrant, MD, Director
Kimberly Struble, PharmD, Clinical Lead
Yodit Belew, MD, Clinical Reviewer
Julian O'Rear, PhD, Virology Lead
Sung Rhee, PhD, Virology Reviewer
John Dubinion, PhD, Pharm/Tox Reviewer
Su-Young Choi, PhD, Clinical Pharmacology Lead
Erika Englund, PhD, Acting Product Quality Lead
Valerie Wilson, PharmD, Safety Evaluator
Linda Onaga, MPH, Senior Regulatory Project Manager
Philip Villasurda, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

ViiV Healthcare
Mark Baker, PhD, MSc (Med) – Director, Clinical Pharmacology
Cindy Brothers, MSPH – Director, Clinical Development
Annie Buchanan, MD, MPH – Physician Project Lead
Justin Green, MD, PhD – Medicines Development Leader
Karen Grainger – Head of ViiV Regulatory Affairs
Christine Lampkin, PharmD – Director Global Regulatory Affairs
Cindy Vavro, PhD – Clinical Development Manager.

GlaxoSmithKline
Martha Anne Auld, RPh – Senior Director, Global Regulatory Affairs
Mark Davies, MSc – Director, CMC, Medicine & Process Delivery
Judy Hopking, MSc – Principal Statistician

Michael McKenna, MB, ChB – Medical Director
Rajendra Singh, PhD – Director, Clinical Pharmacology Modeling and Simulation
Katya Sullivan, Pharm D – Director, Global Regulatory Affairs
Jeffrey Troughton, MS, RAC – Director, Global Regulatory Affairs

1.0 BACKGROUND

Tivicay (dolutegravir) tablets is approved for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patient weighing at least 30 kg. ViiV submitted a [redacted] (b) (4)

A Post-Action meeting was held between the Division and ViiV to seek agreement on the additional data needed to support pediatric dosing for patients weighing less than 30 kg. An agreement was reached to submit data from ongoing pediatric studies P1093 and ODYSSEY in new application(s). ViiV intends to submit, in December 2019, prior approval supplements and an original NDA that will support dosing recommendations for HIV-1 treatment-naïve or treatment-experienced INSTI-naïve pediatric patientsaged 4 weeks and older and weighing at least 3 kg.

On February 25, 2019, ViiV submitted a Type B WRO meeting request to discuss with the Division the content and format of the planned submissions to support pediatric dosing. Upon further discussions with the Division, ViiV requested that this meeting be converted to a Type C Guidance meeting. It was recommended, when the top line results from the studies are available, ViiV will submit a Type B pre-sNDA meeting.

On July 12, 2019, ViiV requested a pre-sNDA meeting for NDA 204790 and a pre-NDA meeting under IND 075382 on July 25, 2019, to discuss the content and formatting of their planned pediatric submissions.

FDA sent Preliminary Comments to the Sponsor on September 6, 2019. The Sponsor provided their responses to the Agency's Preliminary Comments, with a request to focus on Question 3 for the teleconference.

2. DISCUSSION

Sponsor questions are in italicized font. The Division's responses are in standard font.

2.1. Multidisciplinary

Question 3
In addition to the extrapolation of efficacy from PK exposures that approximate those seen in adults, the Sponsor will provide an aggregate summary of efficacy from the P1093 study

(HIV-1 RNA <50 c/mL through Week 24 and 48) to reflect efficacy across the proposed dosing ranges.

Does the Agency agree this would serve as an appropriate summary of efficacy for Section 14 (Clinical Studies) in the US Prescribing Information?

FDA Response:
Your proposal to submit the Week 24 and 48 efficacy outcomes across the proposed dosing ranges is acceptable.

The efficacy assessment for P1093 should include the following additional analyses according to:

- weight-bands for the proposed dosing regimen
- age, given the initial enrollment for P1093 was based on age
- formulations, if subjects within a cohort received a different formulation based on ability to swallow tablet (e.g. x% of subjects in the 20-30kg weight band received film coated tablets while y% received dispersible tablets).
- ARV treatment history, if the population enrolled varies significantly (e.g. naïve and treatment-experienced).

Please include variable flags in your efficacy datasets to allow efficacy analyses as outlined above.

If you plan to include efficacy outcome from ODYSSEY trial as supportive evidence, please present both pooled and individual trial results for ODYSSEY and P1093. The various analyses for ODYSSEY should be similar to the P1093 analyses plan.

For additional technical advice on the format of the datasets, please refer to FDA technical specifications document titled, 'Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection, Guidance for Industry'
https://www.fda.gov/media/112667/download

Sponsor Responses to FDA Preliminary Comments
Thank you for your responses. We agree that the efficacy assessment should include the components you outline above. Within P1093, we can provide efficacy by the starting formulations for this population (film-coated tablets or dispersible tablets). Our investigation of proposed dose population will not include a blending of DTG formulations within a weight-band or cohort. Efficacy datasets will be flagged as outlined for the planned submissions.

We would like to provide further clarity on the intent to include "ARV treatment history" as part of the efficacy analysis during the teleconference. We can provide the requested analyses by patient groups as defined by the P1093 protocol:

- **ARV-treatment experienced participants include those currently receiving a failing regimen of ARVs (all ages) or recently started an empiric regimen outside of the study (<2 years old only);**
- **ARV-treatment naïve participants include those ARV-treatment naïve (no exposure to ARVs for treatment; could have received ARVs for prophylaxis or prevention of perinatal transmission) and those starting an empiric regimen during study 30-day Screening period.**

Regarding efficacy outcomes from ODYSSEY, as noted in the Meeting Package we do not plan to include efficacy data from ODYSSEY at this time as the data are not yet available. However, a final study report will be submitted to IND 075382 when available per the Type C Written Responses of 30 April 2019 (FDA Ref ID: 4426454).

Meeting Discussion

The Sponsor recapped their response to FDA's preliminary comment related to the efficacy analysis by formulation within a weight-band (or age) cohort. The FDA clarified that the intent of the request was to evaluate if there are differences in treatment response based on formulation administered within a given cohort. The requested efficacy analysis will not be necessary because the Sponsor clarified that multiple formulations were not used within a cohort. The Agency agreed with the Sponsor's plan and had no further comments and questions.

No other discussion points were made regarding the other questions contained in the Agency's Meeting Preliminary Comments letter.

3.0 PREA REQUIREMENTS

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

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

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

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

4.0 PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

format items in regulations and guidances.

5.0 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)				

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide*

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[3]

7.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues require further discussion.

8.0 ACTION ITEMS

No action items were agreed on.

9.0 ATTACHMENTS AND HANDOUTS

- Sponsor Responses to FDA's preliminary comments.

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

[3] https://www.fda.gov/media/85061/download

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

/s/

PHILIP R VILLASURDA
09/24/2019 11:37:29 AM