

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212950Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 5, 2020

To: Nina Mani, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for RUKOBIA (fostemsavir) extended-release tablets, for oral use

NDA: 212950

In response to DAVP consult request dated December 9, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for RUKOBIA (fostemsavir) extended-release tablets, for oral use (Rukobia).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Nina Mani) on May 22, 2020, and two comments on the PI in Section 14 are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on June 4, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 6, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

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/s/

WENDY R LUBARSKY
06/05/2020 03:26:00 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 4, 2020

To: Nina Mani
Senior Regulatory Project Manager
Division of Antivirals (DAV)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): RUBOKIA (fostemsavir)

Dosage Form and Route: extended-release tablets, for oral use

Application Type/Number: NDA 212950

Applicant: ViiV Healthcare Company

1 INTRODUCTION

On December 4, 2019, Viiv Healthcare Company submitted for the Agency's review an original New Drug Application (NDA) 212950 for RUBOKIA (fostemsavir) extended-release tablets, for oral use. The Applicant proposes that fostemsavir (FTR) was developed to address the unmet medical need of HIV-1-infected heavily treatment-experienced (HTE) patients who are otherwise unable to form a viable ARV regimen out of the remaining fully active agents due to multi-drug resistance, intolerance, contraindication, or other safety considerations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on December 9, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RUBOKIA (fostemsavir) extended-release tablets, for oral use.

2 MATERIAL REVIEWED

- Draft RUBOKIA (fostemsavir) extended-release tablets PPI received on December 4, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on May 22, 2020.
- Draft RUBOKIA (fostemsavir) extended-release tablets Prescribing Information (PI) received on December 4, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on May 22, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
06/04/2020 10:52:23 AM

WENDY R LUBARSKY
06/04/2020 01:53:50 PM

SHARON R MILLS
06/04/2020 03:00:42 PM

LASHAWN M GRIFFITHS
06/04/2020 03:31:15 PM

Clinical Inspection Summary

Date	04/15/2020
From	Karen, Bleich, MD Yang-min (Max) Ning, MD, PhD Kassa Ayalew, MD, MPH GCPAB/OSI/CDER/FDA
To	Anitra Johnson, DAV Prabha Viswanathan, MD, DAV Sarita Boyd, PharmD, DAV Adam Sherwat, MD, DAV
NDA #	212950
Applicant	GlaxoSmithKline, LLC
Drug	Fostemsavir (RUKOBIA)
NME (Yes/No)	Yes
Therapeutic Classification	Human immunodeficiency virus type 1 (HIV-1) attachment inhibitor
ClinicalTrials.gov Registration	NCT 02362503
Proposed Indication	Treatment of HIV Infection
Consultation Request Date	12/12/2019
Summary Goal Date	5/15/2020
Action Goal Date	7/7/2020
PDUFA Date	8/4/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a two-cohort Phase 3 clinical trial (Study 205888) were submitted to the Agency in support of an original new drug application (NDA 212950) for RUKOBIA (fostemsavir) for the treatment of HIV-1 infection in heavily treatment-experienced patients with multidrug-resistant HIV-1 who are failing their current antiretroviral regimen. Three clinical investigators, including Drs. Beatriz Grinsztejn (Site 0118), Judith Aberg (Site 0174), and Shannon Schrader (Site 0163), and the study sponsor (ViiV Healthcare) were selected for clinical inspections.

Based on the results of these inspections, Study 205888 appears to have been conducted adequately, and the study data appear reliable in support of the NDA.

II. BACKGROUND

The applicant GlaxoSmithKline LLC submitted clinical data from the Week 96 results of Study 205888, “A multi-arm, phase 3, randomized, placebo-controlled, double-blind clinical trial to investigate the efficacy and safety of fostemsavir in heavily treatment-experienced subjects infected with multi-drug-resistant HIV-1,” in support of an original new drug application (NDA 212950) for RUKOBIA (fostemsavir). Fostemsavir is an anti-retroviral (ARV) drug with a novel mechanism of action, known as an attachment inhibitor. It is intended for the treatment of heavily treatment-experienced patients infected with HIV-1 who are otherwise not able to form a viable combination antiretroviral regimen due to multi-drug resistance, intolerance, or other contraindications to currently available drugs.

Study 205888 was initiated by Bristol-Myers Squibb (BMS) in February of 2015. ViiV Healthcare, the current study sponsor, acquired fostemsavir from BMS on February 22, 2016. The study is currently on-going. The Week 96 results were submitted in support of NDA 212950. The data cut-off date for the week 96 analysis was 8/14/2018.

The study was conducted in heavily treatment-experienced HIV-1-infected subjects with multi-drug class resistance. All subjects were required to have a viral load of ≥ 400 copies/mL and ≤ 2 classes of antiretroviral drugs remaining available due to resistance, intolerability, contraindication, or safety concern. Subjects with 1 or 2 fully active and available antiretroviral drugs available (which could be combined as part of an efficacious background regimen) were to be enrolled into a randomized, placebo-controlled study cohort. Subjects with no fully active ARV drugs available at screening were to be enrolled into a nonrandomized study cohort.

Subjects in the randomized study cohort were allocated (3:1) to receive either blinded fostemsavir 600 mg twice daily or placebo (matching for study treatment) for Day 1 through Day 8 of the study. From Day 9 onwards, all study subjects received open-label fostemsavir 600 mg twice daily plus investigator-selected optimized background therapy (OBT). Subjects in the nonrandomized cohort received open-label fostemsavir 600 mg twice daily plus their current failing ARV regimen from Day 1 onward for the duration of the study.

The primary endpoint was the adjusted mean change in plasma HIV-1 RNA \log_{10} (copies/mL) from Day 1 to Day 8 in the randomized cohort. The safety data included subjects in both cohorts.

From 02/23/2015 through 08/14/2018 (data cutoff date for the submitted Week 96 analysis), the study enrolled 272 subjects into the randomized cohort, with 203 assigned to the fostemsavir group and 69 to the placebo group. For the nonrandomized cohort, 99 subjects were enrolled.

The study was conducted at 108 sites in 22 countries across Africa, Asia-Pacific, Europe, North America, and South America. Forty percent of subjects in the randomized cohort were from the United States.

In consultation with the statistical and medical review teams from the Division of Antivirals, three clinical investigator sites and the study sponsor were chosen for inspections. The review division identified subjects' eligibility criteria as critical data for verification. Specifically, the review division wanted to verify that the subjects in the study were highly treatment-experienced, with multi-drug resistance to multiple classes of ARV drugs, according to the eligibility criteria. The eligibility criteria required that subjects were unable to use any anti-retroviral drugs across at least 4 of 6 currently available ARV classes (due to resistance, intolerance, or other contraindications). Additionally, the review division specified verification of the primary efficacy endpoint HIV-1 RNA in Day 1 and Day 8 (in the randomized cohort), and verification of HIV-1 RNA levels at Weeks 24, 48, and 96, when available.

III. RESULTS

1. Dr. Beatriz Grinsztejn

Hospital Evandro Chagas
Avenue Brasil, 4365
Manguinhos, Fiocruz
Rio de Janeiro, Brazil 21040-900

Inspection Dates	3/2/20 – 3/6/20
Prior Inspection Classification	NAI (3/4/2005)
Study/Protocol Number	Study 205888
Site Number	118
Number of Subjects Screened	36
Number of Subjects Enrolled	19

Dr. Grinsztejn's site was selected because of high enrollment (highest enrollment in the study) and the absence of recent inspections. Currently, the Established Inspection Report is unavailable for this site. The following inspection information is based on the preliminary feedback from the inspector.

The inspection included a review of documents and procedures related to the conduct of Study 205888, including the clinical site training, study authority and administration (including Form FDA 1572), study protocol and amendments, informed consent, IRB approvals, financial disclosures, electronic records and electronic data collection methods, study drug accountability, and study monitoring.

Data verification was performed by comparison of data from source documents at the clinical investigator's site to the data contained in the data listings submitted with the application. Data verification included the primary endpoint data, eligibility criteria, and adverse events.

The inspection found that 36 subjects were screened and 19 subjects were enrolled at Site 118. 12 of the enrolled subjects were enrolled into the randomized cohort (10 into the fostemsavir arm and two into the placebo arm), and 7 were enrolled

into the non-randomized cohort. At the time of the inspection, 15 subjects remained on study in follow-up. Subject (b) (6) (non-randomized cohort) was withdrawn on 4/2/2018 (Study Day 628) for prolonged QT_cF. Three subjects had died: Subject (b) (6) (non-randomized cohort) died on (b) (6) (Study Day 392) from pulmonary/cutaneous sepsis as of the data cutoff; Subjects (b) (6) (randomized cohort on the fostemsavir arm) and (b) (6) (non-randomized cohort) died after the data cutoff date.

Informed consent documents were reviewed for all subjects and found to be adequate. The primary endpoint data (HIV-1 RNA levels at Day 1 and Day 8) and the HIV-1 RNA levels at weeks 24, 48, and 96 (when available) were verified for all enrolled subjects. For six enrolled subjects, eligibility criteria, adverse events, and concomitant medications were verified.

The inspection revealed no significant deficiencies, and no Form FDA 483 was issued to the investigator at the conclusion of this inspection.

2. Dr. Judith Aberg

Icahn School of Medicine at Mount Sinai
1 Gustave Levy Place
New York, NY 10029

Inspection Dates	1/27/20 – 1/29/20
Prior Inspection Classification	No prior inspection
Study/Protocol Number	Study 205888
Site Number	174
Number of Subjects Screened	14
Number of Subjects Enrolled	10

Dr. Aberg's site was selected because of high U.S. enrollment and the lack of prior inspections.

The inspection included a review of documents and procedures related to the conduct of Study 205888 including the clinical site training, study authority and administration (including Form FDA 1572), study staff delegation, study protocol and amendments, informed consent, IRB approvals, financial disclosures, electronic records and electronic data collection methods, study drug accountability, and study monitoring.

Data verification was performed by comparison of data from source documents at the clinical investigator's site to the data contained in the data listings submitted with the application. Data verification included the primary endpoint data, eligibility criteria, and adverse events.

Ten subjects were enrolled at the site. Seven of the enrolled subjects were enrolled into the randomized cohort (6 into the fostemsavir arm and one into the placebo

arm), and 3 were enrolled into the non-randomized cohort. At the time of the inspection, 6 subjects remained on study in follow-up. Four subjects had died as follows: Subject (b) (6) (fostemsavir arm of randomized cohort) died from anal squamous cell carcinoma on Study Day 765, Subject (b) (6) (non-randomized cohort) died from cerebrovascular accident on Study Day 879, Subject (b) (6) (fostemsavir arm of randomized cohort) died from metastatic rectal cancer, after the subject had been withdrawn from the study upon entering hospice, and Subject (b) (6) (non-randomized cohort) died from advanced AIDS with failure to thrive secondary to CMV colitis, after subject was withdrawn from the study for adverse event of severe CMV colitis.

Eligibility criteria were reviewed for all enrolled subjects. For two study subjects (Subject (b) (6) and (b) (6)), the inspection included verification of the data provided by the review division in Table 1 (Subject (b) (6)) and Table 2 (Subject (b) (6)). The source data at the site was copied and provided to the review team for their review.

Table 1: Subject (b) (6) Eligibility Criteria Verification

Subject #/ Site #/ TRT	Resistance Reports (e.g. PhenoSense) Showing Resistance to	Genotype showing these substitutions	Historical resistance reports or Dr. notes indicating resistance to	Doctor's report indicating
(b) (6) / 0174/ Randomized Cohort on FOSTEMSAVIR 600mg BID	NNRTI: Nevirapine PIs: Fosamprenavir Lopinavir Nelfinavir Ritonavir Darunavir	RT: D67N K70R T215 K219E IN: T97A Y143C E157Q	PIs: Atazanavir Darunavir Fosamprenavir NNRTIs: Efavirenz Etravirine Ralpivirine NRTIs: Lamivudine Emtricitabine Tenofovir	Efavirenz and Ralpivirine ineligibility

Abbreviations

Classes of Antiretroviral Medications: **NNRTI** – non-nucleoside reverse transcriptase inhibitor; **PI** – protease inhibitor; **NRTI** – nucleoside reverse transcriptase inhibitor

Amino acid substitutions: **RT** – reverse transcriptase; **IN** – integrase

Subject (b) (6) was randomized on (b) (6). The eligibility criteria in Table 1 was verified with the data contained in the following source documents:

(b) (6)

Table 2: Subject (b) (6) Eligibility Criteria Verification

Subject #/ Site/ TRT	Resistance Reports (e.g. PhenoSense) Showing Resistance to	Historical resistance reports or Dr. notes indicating resistance to	Tropism Report showing	Doctor's report indicating
(b) (6) / 0174/ Randomized Cohort on FOSTEMSAVIR 600mg BID	NRTIs: Abacavir Emtricitabine Lamivudine NNRTIs: Etravirine Nevirapine Ralpivirine	NRTIs: Emtricitabine Lamivudine NNRTIs: Ralpivirine Etravirine	Dual Mixed	PI intolerance: rash, hypersensitivity; Efavirenz (EFV) ineligibility

Subject (b) (6) was randomized on (b) (6). The eligibility criteria in Table 2 was verified with the data contained in the following source documents: HIV-1

(b) (6)

The primary endpoint data (HIV-1 RNA levels at Day 1 and Day 8) and the HIV-1 RNA levels at weeks 24, 48, and 96 (when available) were verified for all enrolled subjects. There was no under reporting of adverse events or protocol deviations for any of the subjects at the site.

3. Dr. Shannon Schrader

Research Access Network
4101 Greenbriar, Suite 200
Houston, TX 77098

Inspection Dates	2/25/2020 – 3/3/2020
Prior Inspection Classification	VAI (7/10/2017), NAI (5/3/2007)
Study/Protocol Number	Study 205888
Site Number	0163
Number of Subjects Screened	7
Number of Subjects Enrolled	5

Dr. Schrader's site was selected because of moderate U.S. enrollment, financial disclosure greater than \$25,000 (for a sub-investigator), and a prior inspection history of VAI for failure to adhere to protocol and inadequate records.

The inspection included a review of documents and procedures related to the

conduct of Study 205888 including the clinical site training, study authority and administration (including Form FDA 1572), study protocol and amendments, informed consent, IRB approvals, financial disclosures, electronic records and electronic data collection methods, study drug accountability, and study monitoring.

Data verification was performed by comparison of data from source documents at the clinical investigator's site to the data contained in the data listings submitted with the application. Data verification included the primary endpoint data, eligibility criteria, and adverse events.

Five subjects were enrolled at the site, all into the fostemsavir arm of the randomized cohort. One subject died from viral meningoencephalitis (Subject (b) (6)) on (b) (6) Study Day 101. The primary endpoint data (HIV-1 RNA levels at Day 1 and Day 8) and the HIV-1 RNA levels at weeks 24, 48, and 96 (when available) were verified for all enrolled subjects. There was no under-reporting of adverse events.

Table 3: Subject (b) (6) Eligibility Criteria Verification

Subject #/ Site/ TRT	Resistance Reports (e.g. PhenoSense) Showing Resistance to	Genotype showing these substitutions	Historical resistance reports or Dr. notes indicating resistance to	Tropism Report showing	Doctor's report indicating
(b) (6) / 0163/ Randomized Cohort on FOSTEMSAVI R 600 mg BID	NNRTIs: Delavirdine Efavirenz Etravirine Nevirapine Ralpivirine PIs: Atazanavir Fosamprenavir Darunavir Saquinavir Tipranavir	RT: M41L D67N T69D K70R L74I L210W T215N	PIs: Atazanavir Darunavir Fosamprenavir Tipranavir Lopinavir NNRTIs: Efavirenz Etravirine Ralpivirine NRTIs: Lamivudine Emtricitabine	Dual Mixed	Efavirenz ineligibility

Subject (b) (6) was randomized on (b) (6). The eligibility criteria in Table 3 was verified with the data contained in the following source documents:

(b) (6)

The inspection identified regulatory deficiencies in the investigator's conduct of this study and a Form FDA 483 was issued to Dr. Schrader at the conclusion of the inspection based on failure to conduct the study according to the investigational plan and failure to appropriately re-consent subjects when necessary. The deficiencies in the issued 483 included the following:

Physical examinations not performed

Per the protocol, physical exams were to be performed at screening, on Day 1, Day 8, and at every clinical visit thereafter. Physical exams were missed according to the source documents for Subject (b) (6) at Day 1 and for Subject (b) (6) at Day 1 and Week 16.

Reviewer comment: According to the study records, for both Subjects (b) (6) and (b) (6) there were 38 days between the screening visit and the Day 1 visit. It is plausible that physical evidence of an exclusion criteria could have developed between screening and Day 1 and have been missed because of the absence of a physical examination. Both subjects, however, reported at the Day 1 visit that they had had no changes in their health since the screening visit. For Subject (b) (6), the physical exam at the Week 16 study visit was also not performed. The failure to conduct these physical examinations is unlikely to have been an issue for subject safety or for data integrity, and there is no evidence that these subjects subsequently developed significant new physical exam findings. All the missed physical exams were already reported as protocol deviations by the sponsor in the submitted BIMO listings.

Missed study visits and out of window visits

The inspection found many instances of missed study visits and out of window visits involving Subjects (b) (6)

Reviewer comment: The missed study visits and out of window visits identified during the inspection are all included in the BIMO data listings submitted with the application. In addition, the out of window Day 1 visit (more than 42 days between screening visit and Day 1 visit) for Subject (b) (6) was approved by the study sponsor at the time of the Day 1 visit, and the IRB was appropriately notified. According to Table 1.5 Summary of Protocol Deviations (p.1010 of Report Body), out of window visits and missed assessments/procedures occurred for 69% and 10%, respectively, of subjects in the randomized cohort. Thus, while out of window study visits were common study-wide, missed study visits were significantly less common. The missed study visits identified for 3 of the 5 subjects at Dr. Schrader's site suggest a lack of adequate effort at the site to bring subjects into compliance with study visits.

Study treatment non-compliance by subjects

There were multiple instances of poor subject compliance with IP doses, and

failure of subjects to return IP diaries and bottles involving Subjects (b) (6). For example, Subject (b) (6) reported that he had lost his IP diary at the visits of Week 36, Week 48, Week 84, and Week 96. At the Week 48 visit, that subject's protocol compliance was 61.8% according to the adherence assessment based on returned IP and at the Week 96 visit the subject did not return IP bottles because they were lost.

Reviewer comment: The instances of poor subject compliance with IP doses identified at the inspection were already reported in the BIMO protocol deviations listings submitted with the application. According to the Study Report (Table 1.5: Summary of Important Protocol Deviation), study treatment non-compliance by subject occurred in 41% of subjects in the randomized cohort.

IP dispensing errors

On (b) (6), the research coordinator dispensed 12 weeks of IP to Subject (b) (6) at the Week 84 study visit when he should have only dispensed 4 weeks of IP per protocol. For the same subject, drug dispensing records show that no IP was dispensed on week 76 and week 80.

Reviewer comment: An administrative protocol amendment (announced on 8/9/2016, effective as of 1/16/2017) changed the IP dispensation schedule as follows: instead of dispensing 12 weeks of IP at a time, the protocol now required that only 4 weeks of IP was to be dispensed at study visits. The change was made by then study sponsor BMS because of a limited supply of the study drug and was not based on any safety issues. In the case of Subject (b) (6), the study coordinator dispensed a 12-week supply of IP at the Week 84 study visit. In order to access a 12-week supply of IP, the study coordinator entered prior dates (Week 76 and Week 80). This created the appearance that Week 76 and Week 80 visits were missed when the IP had been dispensed correctly previously. While the protocol for dispensing IP was not adhered to, there is no evidence of a safety or data integrity concern related to this error.

Subjects had not signed most recent versions of ICF

The inspection identified that four of the subjects at the site (Subjects (b) (6)) did not sign the updated consent form (IRB approved on 12/8/16) until 8 or 9 visits after the new ICF was approved by the IRB.

Reviewer comment: The ICF approved on 12/8/16 included information regarding the change in the study sponsor from BMS to ViiV and HIPPA information. The 4 subjects above were seen in clinic multiple times after the new consent form received IRB approval and there was ample opportunity for the subjects to have been appropriately consented. While the subjects should have had the opportunity to review and consent to the new study information, the changes in the updated consent did not directly affect

subject safety, and all subjects subsequently were appropriately consented with updated consent forms.

Dr. Schrader provided a written response to the 483, dated March 19, 2020. In the response, Dr. Schrader acknowledged the deficiencies listed by the inspector on the Form FDA 483, and stated that he takes full responsibility for the conduct of the study.

Reviewer comment: The specific findings in the 483 were carefully reviewed for each subject and do not appear to have affected either patient safety or the integrity of study data, as discussed above after each finding. Additionally, none of the subjects at Site 0163 were excluded from the per-protocol population for protocol deviations. The corrective and preventive actions taken are adequate.

4. ViiV Healthcare Company

Five Moore Drive
Research Triangle Park, NC 27709

Inspection Dates	2/3/2020 – 2/7/2020
Prior Inspection Classification	No prior inspections
Study/Protocol Number	Study 205888

Inspection of the sponsor was requested because the study sponsor (ViiV Healthcare) has not been previously inspected and because the application is an original NDA.

ViiV Healthcare is a pharmaceutical company specializing in the development of therapies for HIV infection. ViiV was created as a joint venture by Pfizer and GSK in 2009. In 2012 Shionogi, a Japanese company, joined the partnership. ViiV is currently 76.5% owned by GSK, 13.5% by Pfizer, and 10% by Shionogi. The applicant for NDA 212950 is GSK.

Study 205888 was initiated by Bristol-Myers Squibb (BMS) on 2/23/2015. ViiV Healthcare acquired fostemsavir from BMS and took over the sponsorship of the study in February of 2016. Since transfer of the study to ViiV, the study has been conducted with oversight and team members from GlaxoSmithKline (GSK), ViiVHealthcare, and (b) (4) was responsible for investigators, monitors, and record retention; GSK and ViiV were responsible for safety reporting and event escalation and investigation.

The inspection included a review of documents and procedures related to the conduct of Study 205888, including organization and personnel, clinical trial registration, selection of clinical investigators, selection of monitors, monitoring procedures/activities, quality assurance, safety/adverse event reporting, data collection and handling, record retention, financial disclosure, electronic records

and signatures, and test article accountability.

The inspection additionally reviewed records related to the monitoring activities for 8 clinical investigator sites (the three above sites chosen for inspection and an additional 5 sites selected by the inspector). The review of the site records included CI selection and qualification, Form FDA 1572s, financial disclosures, training, and monitoring reports and communications.

The review of monitoring activities at Site 0058 (Dr. Lalezari) demonstrated that the site had been placed on an sPIP in 2017 for concerns regarding GCP compliance. The source document from ViiV Healthcare, “205888 – Site Summary for Dr. Lalezari (0058)”, was collected at the inspection. According to the document, the initial concerns that led to the sPIP included concerns about PI oversight including lack of lab report review and handling of source documentation. Corrective actions included increased monitoring, a site audit, and re-training. Per the sponsor, on-site monitoring performed in January of 2020 demonstrated improvement in source documentation and PI oversight.

Reviewer comment: Site 0058 is not cited for GCP concerns in the CSR. The corrective actions taken in response to the identified GCP compliance issues appear adequate. The site summary document obtained during the inspection suggests that sponsor oversight was adequate.

The review of monitoring activities at Site 0176 (Dr. Ballesteros) identified documentation of persistent non-compliance, including backdating and subjects improperly consented. An issue investigation was conducted by ViiV, GSK, and (b)(4) at the site. Identified site issues included inadequate source documentation (including supporting documentation for subject eligibility and informed consent), predated PI reviews of laboratory reports, and lack of knowledge of GCP principles. The decision was made that the site could be brought back into compliance and that there had been no evidence that patient safety had been compromised. From a patient safety perspective, it was determined to be in the best interest of the subjects at the Site 0176 to remain in the study because they had limited other options for care. The site was placed on a site improvement plan on 8/16/17. Enhanced monitoring was implemented to include monitoring every 6-8 weeks. Additionally, the decision was made to exclude Dr. Ballesteros from participation in future GSK studies.

Site 0176 had enrolled 5 subjects, all into the randomized cohort (4 in the fostemsavir arm and 1 in the placebo arm). According to Listing 10 (Listing of Protocol Deviations Leading to Exclusion from the Per-Protocol Population), two of the subjects from Site 0176 were excluded from the per-protocol population: Subject (b)(6) and Subject (b)(6). Both subjects had been enrolled in the fostemsavir arm of study and both subjects were excluded from the per-protocol population because of missed endpoint assessments.

Reviewer comment: The non-compliance issues identified at the sponsor investigation of Site 0176 is included in the Study Report submitted by the applicant. No significant additional information regarding this site was identified through inspection. The source documentation collected demonstrates adequate sponsor oversight of Site 0176. As described in the Study Report, the decision by the sponsor that sensitivity analyses of the site were not indicated given the site's low contribution to the overall study population seems reasonable.

The review of monitoring activities at Site 0189 (Dr. Bartczak) identified documentation of persistent, serious GCP non-compliance including inadequate management of IP (subject may not have received adequate supply) and subject safety assessments not performed in compliance with protocol (missed clinical visits for follow-up assessment). There was no evidence of any unreported adverse events. The sponsor's "Issue Investigation Report" dated 12/12/2017 stated that there had been "serious and irresolvable GCP non-compliance and it was in the best interest of the study subject to proceed with closure of Dr. Bartczak's site and transfer of subjects to alternative sites." A total of four subjects had been enrolled at the site: one into the randomized cohort, and three into the non-randomized cohort. Three of the enrolled subjects were transferred to an alternative site; one of the enrolled subjects was terminated on (b) (6) for virologic failure (Subject (b) (6) non-randomized cohort). Given the small number of enrolled subjects, the sponsor determined that no sensitivity analyses were indicated.

Reviewer comment: The non-compliance issues and the closure of Site 0189 are included in the Study Report submitted by the applicant. The closure of Site 0189 was reported to the FDA by GSK on 7/27/2018. The source documentation obtained at the sponsor inspection demonstrates adequate sponsor oversight of Site 0189.

A for-cause FDA inspection of Dr. Bartczak's site was conducted on 11/6/2019 in response to the notification of IRB termination of approval (Complaint #7887), and to notification that the sponsor had terminated the site (Complaint #8256), as assigned by GCPCOB. A Form FDA-483 was issued to Dr. Bartczak for investigation not conducted in accordance with the investigational plan, inadequate drug dispensation records, and inadequate case histories. The inspection noted that all subjects at the site had been properly consented, and there was no evidence of under-reporting of adverse events at the site. A final review of the for-cause inspection of Site 0189 is pending at this time.

Complete monitoring reports provided for Site 0163 (Dr. Schrader) corroborate the issues related to non-compliance for the site as described above for the inspection of Dr. Schrader.

Reviewer comment: Sponsor oversight of Site 0163 appears adequate based on the review of the monitoring reports collected at the inspection.

In general, the sponsor's conduct, oversight, and management of Study 205888 since acquisition of the study (one year after the start of the study) appeared adequate and no significant deficiencies were identified in the sponsor inspection.

{ See appended electronic signature page }

Karen Bleich, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

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cc:

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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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YANGMIN NING
04/15/2020 09:37:10 AM

KASSA AYALEW
04/15/2020 09:40:19 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 6, 2020
Requesting Office or Division: Division of Antivirals (DAV)
Application Type and Number: NDA 212950
Product Name and Strength: Rukobia (fostemsavir) extended-release tablets, 600 mg
Applicant/Sponsor Name: ViiV Health Care Company (ViiV)
OSE RCM #: 2019-2485
DMEPA Safety Evaluator: Valerie S. Vaughan, PharmD
DMEPA Team Leader: Sevan Kolejian, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 6, 2020 for Rukobia. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Rukobia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Vaughan, V. Label and Labeling Review for Rukobia (NDA 212950). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 23. RCM No.: 2019-2485.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 6, 2020

Container labels



(b) (4)

Carton labeling

(b) (4)



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/s/

VALERIE S VAUGHAN
04/06/2020 11:46:05 AM

SEVAN H KOLEJIAN
04/06/2020 11:47:55 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 23, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 212950
Product Name, Dosage Form, and Strength:	Rukobia (fostemsavir) extended-release tablets, 600 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Health Care Company (ViiV)
FDA Received Date:	September 24, 2019 and December 4, 2019
OSE RCM #:	2019-2485
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the approval process for Rukobia (fostemsavir) extended-release tablets, 600 mg, the Division of Antivirals (DAV) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We reviewed the proposed prescribing information, patient package insert, container label, and carton labeling. Table 2 below includes the identified medication error issues with the submitted container label and carton labeling, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for ViiV Health Care Company (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The principal display panel does not include an alert informing end-users to find out about medicines that should not be taken with Rukobia, which could lead to drug-drug interaction monitoring errors.	The prescribing information describes  (b) (4)	Include an alert on the principal display panel of the container label and carton labeling that states, for example: “Note to pharmacist: Do not cover ALERT box with pharmacy label. ALERT: Find out about medicines that should NOT be taken with RUKOBIA.”
2.	The container label and carton labeling does not include instruction on how to properly administer Rukobia.	The prescribing information indicates to “Swallow tablets whole. Do not chew, crush, or split tablets.” Lack of these administration instructions on the container label and carton labeling could lead to wrong administration technique errors.	To align with the PI and mitigate wrong administration technique errors, include administration instructions on the side panel of the container label, for example: “Swallow tablets whole. Do not chew, crush, or split tablets.”

4 CONCLUSION

Our evaluation of the proposed container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Rukobia received on December 4, 2019 from ViiV Health Care Company.

Table 3. Relevant Product Information for Rukobia	
Initial Approval Date	N/A
Active Ingredient	fostemsavir
Indication	in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations
Route of Administration	Oral
Dosage Form	extended-release tablets
Strength	600 mg
Dose and Frequency	One 600 mg tablet twice daily
How Supplied	Carton containing one bottle of 60 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 734 86°F) [See USP Controlled Room Temperature].
Container Closure	150 cc HDPE bottles with 38 mm (b) (4) child-resistant cap with (b) (4) foil induction heat-seal liner

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Rukobia labels and labeling submitted by ViiV Health Care Company.

- Container label received on September 24, 2019
- Carton labeling received on September 24, 2019
- Prescribing Information (Image not shown) received on December 4, 2019, available from <\\cdsesub1\evsprod\nda212950\0005\m1\us\114-labeling\1141-draft\draft-annotated.pdf>

G.2 Label and Labeling Images

- Container Label



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton Labeling

(b) (4)



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/s/

VALERIE S VAUGHAN
03/23/2020 09:16:58 AM

SEVAN H KOLEJIAN
03/23/2020 09:18:36 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 6, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products / CDER

To: Anitra Johnson, RPM
ORO/DRIOD

Subject: QT Consult to NDA # 212950 (SDN # 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/13/2020 regarding the sponsor's proposed label. We reviewed the following materials:

- Previous IRT review for IND # 073916 dated 05/01/2014 in DARRTS ([link](#)); and
- Sponsor's proposed product label (SN0001; [link](#))

1 Internal Comments to the Division

The IRT has reviewed the thorough QT study results for fostemsavir (IND-073916, Dt: 05/01/2014 in DARRTS). The highest evaluated dose of fostemsavir (2400 mg twice daily for 7 days) resulted in an exposure ~5-fold of therapeutic concentration and ~2-fold the worst-case therapeutic concentration with a mean QTc prolongation of 10 msec. If there is reasonable assurance that the 2400 mg twice daily dose represents temsavir exposures that are unlikely to be seen in the patient population, then the sponsor's thorough QT study provides reassurance of safety because patients are unlikely to experience a clinically significant QTc effect (see ICH E14 Q&A R3 #7.1). Under this scenario, we do not recommend labeling the product with 'Warnings and Precautions' for QTc prolongation.

We propose the following edits to the label submitted by the Sponsor (SN0001; [link](#)). Our changes are highlighted (**addition**, **deletion**) below. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At therapeutic doses, <TRADENAME> does not prolong the QT interval to any clinically relevant extent. At 4-times the recommended dose, the mean (upper 90% confidence interval) QTcF increase was (b) (4) msec ((b) (4) msec). The observed increase in QTcF was temsavir concentration-dependent.



We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.



Reviewer’s comments: Per ICH E14 Q&A 7.1, if there is reasonable assurance that the 2400 mg twice daily dose represents temsavir exposures that are unlikely to be seen in the patient population, then the sponsor’s thorough QT study provides reassurance of safety because patients are unlikely to experience a clinically significant QTc effect. Under this scenario, we do not recommend labeling the product with ‘Warnings and Precautions’ for QTc prolongation.

2 BACKGROUND

ViiV Healthcare is developing fostemsavir (Rukobia) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral agents.

Fostemsavir tromethamine (BMS-663068; MW: 704.6 g/mol; 583.5 g/mol free acid) is a methyl phosphate prodrug of temsavir (BMS-626529), a human immunodeficiency virus type 1 (HIV-1) attachment inhibitor. The sponsor claims that fostemsavir is rapidly hydrolyzed to temsavir (active moiety) following oral administration without detectable levels of fostemsavir in plasma. The proposed dose is 600 mg twice daily (with or without food) and the peak concentrations of 1770 ng/mL (Half-life: ~11 hours) temsavir are expected at steady-state (POP-PK). The product is formulated as an extended-release film-coated tablets containing 725 mg fostemsavir tromethamine (equivalent to 600 mg free acid).

The sponsor claims that the no clinically relevant differences in total and unbound temsavir concentrations were observed in patients with renal impairment (mild to severe groups) and hepatic impairment (mild to severe groups). Based on the submitted information by the sponsor, the concomitant administration of fostemsavir with combination of cobicistat and darunavir is expected to result in ~2-fold increase in the peak concentrations of temsavir. However, the sponsor is not proposing any dose adjustment for fostemsavir during the concomitant administration.

The sponsor conducted a thorough QT study to evaluate the QT effects of fostemsavir in healthy subjects (Protocol # AI438016; 02/06/2012 to 05/27/2012). The study protocol was reviewed by the IRT (IND-073916) prior to conducting the study. The primary objective of the study was to assess the effect of multiple oral doses of fostemsavir on the QTc interval in healthy subjects (Study # 206275). The study was comprised of two-parts – part-1) the sentinel cohort was designed to evaluate the safety, tolerability, and PK of 2400 mg fostemsavir twice daily and; part-2) the main study was designed to evaluate the effect of fostemsavir on the QTc interval in healthy subjects. In this randomized, partially-blinded, placebo-controlled, positive-controlled, (4-period, 4-sequence) crossover (Part-2; using the Williams square design) study, 60 subjects received 1200 mg once daily (for 7 days), 2400 mg twice daily (for 7 days), placebo and moxifloxacin 400 mg. In Part 2, serial triplicate ECGs and serial plasma PK samples for temsavir analysis were collected at the same time points up to 22.5 hours after the morning dose on Day 7 of each period.

The data from thorough QT study was analyzed using central tendency as the prespecified primary analysis, which did not suggest that the therapeutic dose (600 mg twice daily) is associated with significant QTc prolonging effect (refer to original review under IND-073916) – see Table 1 for overall results. The extent of QT prolongation at 1200 mg once daily (Cmax: 3584 ng/mL; n=57) was below 10 msec. However, the mean increase in the QTc interval at the suprathreshold dose (2400 mg twice daily; Cmax: 8900 ng/mL; n=53) was around 10 msec (upper 90% CI: 12.9 msec) which is higher than the threshold for regulatory concern as described in ICH E14 guidelines.

Table 1: The Point Estimates and the 90% CIs (The FDA Analysis; By-time Analysis)

ECG parameter	Treatment (Fostemsavir ER Tablets)	Time (h)	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
QTc	1200 mg Once daily	5	3.9	(1.0 to 6.8)
QTc	2400 mg Twice Daily	5	10.0	(7.0 to 12.9)

For further details on the FDA analysis please see the IRTs review under IND-073916.

The peak concentrations with 1200 mg once daily dosing achieved in this study (Cmax: 3584 ng/mL) are approximately 2-fold of therapeutic exposures (Cmax: ~1770 ng/mL). Similar, the peak concentrations with suprathreshold dose (2400 mg twice daily; Cmax: 8900 ng/mL)

achieved in this study are approximately 5-fold of therapeutic exposures. PK of temsavir appeared to be slightly greater than dose proportional at higher dose studied.

The results of exposure-response analysis agreed with by-time analysis (Table 17 of the study review). A concentration-dependent QTc prolongation over a dose range of 40 to 240 mg was detected in this QT assessment. The predicted $\Delta\Delta\text{QTcF}$ interval at the mean peak temsavir concentration following 1200 mg once daily or 2400 mg twice daily were 3.9 msec (90% CI: 2.0 to 5.6 msec) and 10.8 msec (90% CI: 8.3 to 13.2 msec).

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov.

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/s/

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