CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208255Orig1s000

CLINICAL REVIEW(S)

Summary Review for Regulatory Action
Division Director (DD) and Cross Discipline Team Leader (CDTL) Memorandum

Date	March 7, 2017
From	Jeffrey S. Murray MD, MPH, Deputy Director
Subject	Division Director Summary Review
NDA #	**208255**
Applicant Name	Mylan Pharmaceuticals Inc., USA (Mylan)
Date of Submission	Sept. 13, 2016
PDUFA Goal Date	March 13, 2017
Proprietary Name / Established (USAN) Name	No Proprietary Name Efavirenz 400 mg/Lamivudine 300 mg/Tenofovir disoproxil fumarate 300 mg Fixed Dose Combination (EFV 400 mg/LMV 300 mg/TDF 300 mg FDC)
Dosage Forms / Strength	Tablets
Proposed Indication(s)	As a complete regimen for the treatment of HIV in adults and adolescents at least 12 years old and weight at least 35 kg
Recommended Action:	Tentative Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical/Statistical Review	Kirk Chan-Tack, M.D./Wen Zeng, Ph.D.
Office of Product Quality Review	Application Team Lead: Stephen Miller, Ph.D.
Microbiology Review	Lalji Mishra, Ph.D.
Clinical Pharmacology Review	Islam Younis, Ph.D.

OND=Office of New Drugs

1. Introduction

Scale-up of antiretroviral drugs to meet the global treatment demands of millions of HIV-infected patients in resource-poor nations requires availability of low-cost, well tolerated and convenient treatment regimens, ideally in the form of a once daily oral formulation. The President's Plan for Emergency AIDS Relief (PEPFAR), the Global Fund and others are procuring multiple FDC antiretroviral regimens produced by several "generic" drug manufacturers for use in developing nations with a high prevalence of HIV infection. These procured FDCs are versions of innovator FDCs or are new FDCs composed of previously approved single innovator products. For example, the brand drug ATRIPLA® [EFV 600 mg, emtricitabine (FTC) 200 mg, TDF 300 mg] was the first once daily triple drug FDC treatment for HIV in the U.S. and was the preferred initial treatment regimen in the U.S. until subsequent approval of newer FDCs containing integrase inhibitors. Globally generic versions of ATRIPLA® and a similar FDC containing EFV, LMV (instead of emtricitabine)[1] and TDF are

considered preferred regimens for initiating HIV treatment. The new FDC in this NDA contains the latter regimen, EFV, LMV and TDF with a reduced dose of EFV, 400 mg instead of 600 mg.

Organizations and governments procuring FDCs for developing nations have called for formulations with a reduced dose of EFV (400 mg) because it could offer a cost advantage and could be associated with a fewer adverse reactions. In addition the lower dose was expected to have similar efficacy as the approved dose based on early dose finding studies of EFV and exposure response analyses. To support the clinical efficacy of a reduced dose of EFV, a clinical efficacy trial was needed to demonstrate noninferiority of the 400 mg dose of EFV to the 600 mg dose, when co-administered with TDF and LMV.

2. Background

Because there are no reference listed drugs for this FDC and because the applicant is relying on FDA's previous findings for multiple aspects of the safety and efficacy of the individual agents, this NDA was submitted as a 505(b)(2) application. Mylan received tentative approval of the FDC EFV 600mg, LMV 300mg, and TDF 300 mg under NDA 22142 on Sept. 9, 2009 and has received tentative approvals for each of the individual drugs, at the doses in the previously approved FDC, under separate ANDAs. Sufficient safety and efficacy data existed for this combination (for the doses approved in the previous FDC), such that additional clinical trials were not needed. However, tentative approval of an FDC with a reduced dose, 400 mg, of EFV required an additional clinical trial to demonstrate the comparability of this dose compared to the previously approved dose. The Kirby Institute conducted ENCORE1, owns the study data, and submitted the data as a pre-IND so that Mylan and other commercial sponsors can reference it. Mylan obtained a right-of-reference for this trial data.

1) CMC (Chemistry, Manufacturing, Controls)

For details on CMC, refer to the Quality Assessment review prepared by multiple reviewers in collaboration with the Application Technical Lead, Stephen Miller. The review team recommends a Tentative Approval of NDA 208255 for EFV 400mg/LMV 300mg/TDF 300 mg.

In brief, the drug product is a film-coated (b) (4) tablet that is closely related to Mylan's EFV 600mg/LMV 300 mg/TDF 300 mg tablet that was tentatively approved under NDA 22142. Information on the three drug substances included in this FDC were cross-referenced in Drug Master Files (DMF) submitted by Mylan. The Product Quality team members reviewed all of the DMFs and found them to be acceptable. The drug product specification tests and methods are the same as that approved under NDA 22142 and the acceptance criteria are equivalent.

FDA determined all manufacturing facilities determined to be acceptable and an Overall Manufacturing Facility Recommendation of Approve was entered in Panorama on Feb 14, 2017.

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[1] Lamivudine (LMV) and emtricitabine (FTC) are similar nucleoside analogues and are considered to be clinically interchangeable in HIV treatment regimens.

A 24-month expiration dating period is granted for this product when stored below 30 degrees C and packaged in white or blue HDPE bottles of 30 with desiccant and induction seals. (b) (4)

2) Nonclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology data for review. This 505(b)(2) NDA relies on the FDA's previous determinations of the toxicology profiles of EFV, LMV and TDF.

3) Clinical Pharmacology/Biopharmaceutics

For a complete discussion of the clinical pharmacology issues, please refer to the Clinical Pharmacology Review prepared by Islam Younis, Ph.D. Dr. Younis concurs with tentative approval of this NDA.

As summarized in the Clinical Pharmacology review, the applicant conducted a relative bioavailability study to compare the exposures of EFV, LMV, and TDF following the administration of the FDC tablet (EFV 400 mg/LMV 300 mg and TDF 300 mg) and the individual EFV (Efamat 200mg), LMV (Epivir® 300 mg), and TDF (Viread® 300 mg) agents administered in combination. This study bridges efficacy and safety information from ENCORE1 to the FDC tablet because Efamat was the EFV formulation used in ENCORE1. The exposures of EFV, LMV, and TDF were similar (met bioequivalence criteria) following the administration of the FDC relative to the individual agents.

Although ENCORE1 enrolled adult patients, the indication can be extended to pediatric patients at least 12 years of age and weighing at least 35 kg. The review team made this determination because the current recommended dose of EFV in this age group is 600 mg, the pharmacokinetics of EFV is linear in the dose range of 200 mg to 600 mg, and a dose proportional change to 400 mg in this patient group should lead to similar exposures to that observed in adults in the ENCORE1 trial.

4) Clinical Microbiology

I concur with the Clinical Microbiology Review prepared by Lalji Mishra, Ph.D. who concurs with tentative approval of this NDA. In the ENCORE trial, described below, rates of virologic failure were comparable between the EFV 400 mg and EFV 600 mg treatment groups. Novel amino acid substitutions were not detected in isolates; therefore the 400 mg dose of EFV was not associated with new resistance patterns or an increase in the frequency of resistant isolates.

5) Clinical/Statistical-Efficacy

For more detailed descriptions of the ENCORE trial designs, please refer to the Clinical/Statistical review prepared by Kirk Chan-Tack, M.D. (medical officer) and Wen Zeng, Ph.D. (statistical reviewer). The review recommends Tentative Approval.

Safety and efficacy of EFV 400 mg compared to EFV 600 mg was supported by one clinical trial called ENCORE1, a randomized, double-blind, placebo-controlled, clinical trial to compare the safety and efficacy of reduced dose EFV with standard dose EFV plus nucleos(t)ide analogues in antiretroviral-naïve HIV-infected individuals. The trial was conducted in 38 sites outside of the US between August 2011 and August of 2014. Randomization was stratified by clinical site and screening HIV RNA level (either <100,000 c/mL or ≥100,000 c/mL). The trial used a 10% NI margin, which is commonly used in HIV treatment trials and is also specified in FDA's guidance for HIV-1 treatment for trials of treatment naïve patients. The trial had two arms:

- Active comparator: TDF 300mg QD + FTC 200mg QD + EFV 600mg QD
- Experimental comparator: TDF 300mg QD) + FTC 200mg QD + EFV 400mg QD

Although the protocol specified the proportion of patients with HIV-RNA levels <200 copies/mL as the primary efficacy endpoint, the reviewers treated the proportion with HIV-RNA levels <50 copies/mL as the primary efficacy endpoint because the latter is most commonly used in trials supporting drug approval and is the primary endpoint recommended in the FDA HIV treatment guidance.

Demographics and Baseline Characteristics

Patients had a mean age of 36 years (range 18 to 69), 68% were male, 37% were of African heritage, and 33% were of Asian ethnicity. Mean baseline CD4+ cell count was 273 cells/mm^3 (range 38-679) and median baseline viral load was 56,469 (4.75 log_{10}) copies/mL; 34% had a baseline viral load of ≥ 100,000 copies/mL.

Efficacy Results

The clinical and statistical reviewers were able to duplicate the applicant's efficacy analyses with a few noted discrepancies that did not affect overall results. In brief, the regimen with the lower dose of EFV (400 mg) was noninferior to the regimen with standard dose EFV. The lower bound of the confidence interval for the treatment difference (approximately -4%) was well within the specified margin (-10%). The slight numerical advantage for the lower dose was due to more discontinuations on the standard dose arm. Results that will be displayed in product labeling are shown in the Table below.

Primary Efficacy Endpoint Results at Week 48

	EFV 400 mg (n=321)	**EFV 600 mg (n=309)**	**Rate Difference Mantel Haenszel Adjusted[1]**
<50 c/mL at Week 48	86% (b) (4)	84% (b) (4)	(b) (4)
Virologic Failure	11%	11%	
Death	1%	1%	
Discontinued for other reasons	2%	4%	

HIV-RNA at baseline was used as the stratification factor

Results for the protocol specified endpoint of HIV-RNA < 200 c/mL showed a similar treatment difference of 1.5% with 94.4 of patients in the EFV 400 mg arm and 92.9% of patients in the EFV 600 mg arm having an HIV-RNA < 200 c/mL at 48 weeks. Comparing the two endpoints (< 200 vs. < 50), approximately 8% of individuals had low level viremia (between 50 and 200 copies/mL) and would not necessarily be considered to be "virologic failures" in clinical practice.

Importantly the ENCORE1 results were robust to the important stratification factor of baseline viral load. Antiviral effect in patients with baseline HIV-RNA levels >100,000 c/mL has been a reliable "stress test" for efficacy conclusions. Among patients with baseline HIV-RNA levels >100,000 c/mL the proportion of patients with HIV-RNA < 50 c/mL at 48 weeks for the EFV 400mg and 600 mg treatment arms was 74.4% and 72.8%, respectively. The treatment difference was approximately 1% with a lower bound of -8.9%, also within the specified noninferiority margin for the entire study population.

Mean CD4 cell increases from baseline were comparable between treatment arms with a slightly highly numerical increase for EFV 400 mg. The difference is not clinically relevant.

6) Safety

As might be expected the reduced dose of EFV demonstrated improvements in tolerability compared to the 600 mg dose. Through 48 weeks a slightly lower proportion of patients in the EFV 400mg group compared to standard dose discontinued study drug, 8% vs. 11%. Rash and dizziness, known adverse reactions of EFV, occurred less frequently with EFV 400 mg. Psychiatric adverse events including depression were comparable for the two doses.

7) Advisory Committee Meeting

There was no advisory committee meeting for this NDA.

8) Pediatrics

Dosing for pediatric patients at least 12 years of age and weighing at least 35 kg is included in patient labeling for this tentative approval because the approved dose of EFV in adults and this age group has been the same, the pharmacokinetics of EFV is linear, and noninferiority of EFV 400 mg to EFV 600 mg was considered robust across multiple demographic and baseline covariates in adults.

Because this application can only receive a tentative approval and not a full marketing approval at this time, PREA is not triggered at this point. However, if the applicant seeks marketing approval in the U.S., PREA requirements will be specified in an approval letter.

9) Other Relevant Regulatory Issues

There are no unresolved regulatory issues for a tentative approval action. Inspections of selected clinical sites by the Office of Scientific Investigations found the clinical data to be acceptable. Please see the clinical inspection summary prepared by Dr. Antoine El-Hage.

10) Labeling

Labeling was reviewed by all disciplines and has been completed. [redacted] (b) (4) EFV/LMV/TDF tablets are for use as a complete regimen [redacted] (b) (4) For PEPFAR countries the intended use of this product will be as a complete regimen for initial treatment.

[redacted] (b) (4)

11) Decision/Action/Risk Benefit Assessment

- Regulatory Action

I fully confer with a Tentative Approval action for EFV 400mg, LMV 300 mg, TDF 300 mg tablets as a complete regimen for the treatment of HIV in adults and children at least 12 years of age and weighing at least 35 kg.

- Risk Benefit Assessment

The applicant has demonstrated that a reduced dose of EFV (400 mg) when administered with two nucleo(t)side analogues is as efficacious as the standard approved dose of EFV when administered under the same conditions. The confidence intervals around the treatment difference between trial arms were tight and robust across important subgroups. Importantly, EFV 400 mg appears to be better tolerated specifically with respect to the frequency of rash and dizziness. Therefore, the risk/benefit profile of EFV 400 mg is overall improved compared to EFV 600mg. EFV 400mg is co-formulated with LMV and TDF in the form of a once daily tablet that serves as a complete regimen for treating HIV infection. The lower mg strength of EFV may also have cost advantages in the setting of global HIV treatment programs.

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/s/

JEFFREY S MURRAY
03/07/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208255
Priority or Standard	Priority
Submit Date(s)	September 13, 2016
Received Date(s)	September 13, 2016
PDUFA Goal Date	March 13, 2017
Division / Office	Division of Antiviral Products / Office of Antimicrobial Products
Reviewer Name(s)	Kirk M. Chan-Tack, MD Wen Zeng, PhD
Review Completion Date	February 9, 2017
Established Name	Efavirenz 400 mg/Lamivudine 300 mg/Tenofovir disoproxil fumarate 300 mg Fixed Dose Combination
(Proposed) Trade Name	
Therapeutic Class	Non-nucleoside reverse transcriptase inhibitor/Nucleoside analogue reverse transcriptase inhibitor/Nucleotide analog HIV-1 reverse transcriptase inhibitor
Applicant	Mylan

Formulation(s)	Tablet
Dosing Regimen	Once daily
Indication(s)	Treatment of HIV-1
Intended Population(s)	Adults and pediatric patients at least 12 years old and weighing at least 35 kg

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

These reviewers recommend approval of Efavirenz 400 mg/Lamivudine 300 mg/Tenofovir disoproxil fumarate 300 mg once daily (EFV 400/3TC 300/TDF 300) fixed-dose combination (FDC) for use in treatment naïve adults and pediatric patients at least 12 years old and weighing at least 35 kg. This recommendation is based on data contained in this NDA submission 208255 as well as data from the innovator labels.

The application includes one trial in treatment-naïve adults to support long-term efficacy and safety data in this patient population. The 48-week efficacy and safety results from the ENCORE1 study are presented in support of an alternative dosing regimen, EFV 400 mg once daily (QD), for treatment-naïve adults. Extrapolation of ENCORE1 efficacy data for pediatric patients at least 12 years old and weighing at least 35 kg is reasonable based on the linear pharmacokinetics of EFV and the similarity in the disease course of HIV-1 infection in children compared to adults.

In the ENCORE1 study, EFV 400 mg was non-inferior to EFV 600 mg in treatment-naïve HIV-infected adults. Review of the safety data submitted in this application did not identify any new or unexpected toxicities for EFV 400 mg compared to EFV 600 mg. A higher incidence of rash and dizziness was observed for EFV 600 mg; the incidence and distribution of psychiatric disorders was overall comparable between both doses. The safety profile of EFV 400 mg in adults with creatinine clearance equal to or greater than 50 mL/min was acceptable with no deficiencies to preclude approval. Extrapolation of safety data for the EFV 400 mg dose in pediatric patients at least 12 years old and weighing at least 35 kg is reasonable based on the pediatric safety data in the approved Sustiva® USPI.

1.2 Risk Benefit Assessment

Benefits
Single tablet, once daily regimens offer patient convenience, the potential for increased compliance and fewer patient related dosing errors. Fixed dose combination (FDC) tablets are available using the EFV 600 mg dose. This NDA supports the first FDC tablet with a lower dose (400 mg) of EFV than the currently approved 600 mg dose. The antiviral efficacy of EFV 400 mg has been demonstrated to be non-inferior to that of EFV 600 mg for treatment-naïve adults. The safety profile of EFV 400 mg appears slightly more favorable than EFV 600 mg for EFV toxicities such as rash and dizziness.

Risks

In the approved Sustiva® USPI, the recommended EFV dose for pediatric patients at least 12 years old and weighing at least 40 kg is 600 mg QD. No pediatric patients were enrolled in ENCORE1.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable for this PEPFAR NDA submission.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable for this PEPFAR NDA submission.

2 Introduction and Regulatory Background

2.1 Product Information

Generic (trade) name:	EFV 400/3TC 300/TDF 300
Pharmacological class:	Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI); lamivudine (3TC), a nucleoside analogue reverse transcriptase inhibitor (NRTI); tenofovir disoproxil fumarate (TDF), a nucleotide analog HIV-1 reverse transcriptase inhibitor (NtRTI)
Proposed indication:	Treatment of HIV-1 infection in adults and pediatric patients at least 12 years old and weighing at least 40 kg
Dosing regimens:	Efavirenz 400 mg, Lamivudine 300 mg, Tenofovir disoproxil fumarate 300 mg once daily
Dosage form:	Fixed Dose Combination (FDC) tablet

EFV 400/3TC 300/TDF 300 is a three drug FDC tablet which is intended to provide a complete HIV-1 treatment regimen for patients with susceptible virus. Lamivudine (3TC) and tenofovir (TDF) are approved at the doses in this FDC. This NDA is submitted to support a lower dose (400 mg) of EFV than the approved 600 mg dose.

2.2 Tables of Currently Available Treatments for Proposed Indications

Although many antiretroviral drug (ARV) product versions of previously approved ARVs cannot be currently marketed in the US because of patent and exclusivity restrictions,

FDA is able to review these products for quality, safety, and efficacy and potentially grant a tentative approval. The President's Emergency Plan for AIDS Relief (PEPFAR) will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. Such products may be distributed outside the US, depending on regulatory requirements in other countries.

2.3 Availability of Proposed Active Ingredient in the United States

Efavirenz (EFV) was first approved for treatment of HIV-1 in the US on 17 September 1999 and is currently available for use.

Lamivudine (3TC) was first approved for treatment of HIV-1 in the US on 17 November 1995 and is currently available for use.

Tenofovir (TDF) was first approved for treatment of HIV-1 in the US on 26 October 2001 and is currently available for use.

2.4 Important Safety Issues With Consideration to Related Drugs

EFV 400/3TC 300/TDF 300 is a three drug FDC. It differs from the approved products in the use of a lower dose of EFV. Important safety issues for the approved individual products include the following:

In the licensing trials for EFV 600 mg, the most common adverse reactions are impaired concentration, abnormal dreams, rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting. Laboratory abnormalities include ALT, AST and cholesterol elevations; these laboratory parameters should be assessed before initiating treatment with EFV and periodically during treatment.

In the licensing trials for 3TC 300 mg, the most common adverse reactions are headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough.

In the licensing trials for TDF 300 mg, the most common adverse reactions are rash, diarrhea, headache, pain, depression, asthenia, and nausea. There have been postmarketing reports of renal laboratory abnormalities (renal failure, Fanconi's syndrome, and increased blood creatinine) leading to TDF discontinuation. In patients at risk for renal dysfunction, estimated creatinine clearance, serum phosphorus, urine glucose and urine protein should be assessed before initiating treatment with TDF and periodically during treatment.

The prescribing information for nucleoside analogues includes a boxed warning for lactic acidosis and severe hepatomegaly with steatosis. Sudden discontinuation of

NRTIs that are active against hepatitis B Virus (HBV), including 3TC and TDF, may lead to HBV exacerbations in HIV/HBV co-infected patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the Clinton Health Access Initiative's (CHAI) Supplier Buyer Summit held in Jaipur, India in November 2014, FDA agreed it would be sufficient to submit a single Phase 3 study (ENCORE1) for review in a NDA.

In March 2015, FDA agreed with the Applicant's 505(b)(2) NDA proposal consisting of the following sections:

- CMC: A reference and letters of access to the relevant DMFs for the APIs in TLE400 will be included. A full CMC drug product section containing all relevant TLE400 data will be submitted.
- Nonclinical: A reference to the innovator nonclinical data.
- Clinical: A reference to ENCORE1 data as obtained and granted from the data owners will be included. It is anticipated that the ENCORE1 study data owners will file the data in an IND and provide a letter of access to the Applicant for right of reference to the data. The results from the following pharmacokinetic (PK) bioequivalence study will also be included:
    - Open label, randomized, two treatment, two sequence, two period, crossover, single-dose comparative oral bioequivalence study under fasted conditions of TLE400 versus comparators.
    - (a) Efavirenz bioequivalence: TLE400 versus 2 tablets of Efamat 200™ (ENCORE1 study supply)
    - (b) Lamivudine bioequivalence: TLE400 versus Epivir®, 300 mg (Orange Book RLD)
    - (c) TDF bioequivalence: TLE400 versus Viread®, 300 mg (Orange Book RLD)

FDA also recommended that the Applicant conduct a PK study to evaluate the effect of food on the proposed FDC. The results of this study can potentially support a more flexible labeling language where the FDC can be administered without regard to food if the effect of food on the FDC produces EFV exposures comparable to EFV exposures following the administration of 600 mg dose, which is deemed to be safe and effective.

2.6 Other Relevant Background Information

Fast Track Designation for EFV 400/3TC 300/TDF 300 was granted on 25 April 2016.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A routine consult was submitted to the Office of Study Integrity and Surveillance (OSIS) on September 14, 2016 in response to this NDA submission. Please refer to the OSIS review by Dr. Antoine El-Hage for further details. In ENCORE1, the following sites were inspected (Table 1).

Table 1: ENCORE1, Sites inspected

Site #	Number of Subjects
Site #1201 Thai Red Cross - AIDS Research Centre, Prof Praphan Phanuphak HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration) Thai Red Cross AIDS Research Center 104 Ratchadamri Road Pathumwan, Bangkok 10330, Thailand	68
Site #2003 Desmond Tutu HIV Foundation Dr Catherine Orrell University of Cape Town, Faculty of Health Sciences, Anzio Rd, Observatory, Cape Town, South Africa	64
Site #1301 Tan Tock Seng Hospital, Singapore Dr Barnaby Young Tan Tock Seng Hospital Infectious Disease Research Centre (IDRC) Blk 804, Communicable Disease Centre (CDC 1) Moulmein Road, Singapore 308433	40

The data from these sites were deemed acceptable in support of this submission.

3.2 Compliance with Good Clinical Practices

ENCORE1 was conducted in accordance with the principles of Good Clinical Practices. ENCORE1 was written to conform to accepted ethical standards and were reviewed by Institutional Review Boards overseeing each investigative site. Inspections of selected clinical sites by OSIS found the data provided by the sites to be acceptable. A detailed discussion of the OSIS audit will be available in the Clinical Inspection Summary by Dr. Antoine El-Hage.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. No investigators had any conflicts of interest. There are no financial issues that affect the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Sloan's CMC review for details.

4.2 Clinical Microbiology

Please refer to Dr. Mishra's Microbiology review for details. Rates of virologic failure were comparable between treatment groups. Novel amino acid substitutions were not detected in isolates. Key findings from ENCORE1 are summarized below:

Genotypic resistance data for baseline isolates were available from 286 subjects enrolled in the EFV 400 mg group and 282 subjects in the EFV 600 mg group. Genotypic analysis of on-therapy isolates was performed from a limited number of subjects. Phenotypic analyses of baseline and on-therapy isolates were not performed.

Amino acid substitutions A98G, L100I, K101E/Q/R, K103N/S, V106A/M, V108I, V179D/E, Y181C, Y188L, G190A/S/T, P225H, F227L and M230I/L confer resistance to EFV (Stanford database).

EFV 400 mg group
Baseline isolates from 19/286 (6.7%) subjects in the EFV 400 mg group harbored NNRTI resistance-associated substitutions V90I, A98S, L100V, K101E, K103N, V106I/M, V179D/E, Y181C/F and G190A. The K103N substitution was present in baseline isolates from 8/286 (2.8%) subjects. Of these, isolates from 2 subjects (# (b) (6)) also contained Y181C/F substitutions in addition to the substitution K103N and isolates from another subject (# (b) (6)) contained K103N plus V106M substitutions.

Three of the 19 subjects whose baseline isolates harbored either K103N plus Y181F, or K103N plus Y181F, or K101E plus G190A substitutions were virologic failures at Week 48.

The amino acid substitution V179D/E alone was present in baseline isolates from 6/286 (2.1%) subjects. None of these 6 subjects with baseline isolates containing V179D/E were virologic failures at Week 48.

Subjects whose baseline isolates harbored V90I, A98S, L100V, V06I alone achieved HIV-1 RNA levels <200 copies/mL at Week 48 and were defined as virologic success.

NNRTI resistance-associated substitutions K103N and E138A developed during Week 36 in on-therapy isolates from 1 subject (# (b) (6)).

It should be noted that baseline isolates from subject # (b) (6) and # (b) (6) harbored K103N substitution in combination with Y181C/F and the K103N substitution persisted during treatment at Week 60. Baseline isolates from subject # (b) (6) harbored NNRTI-resistance-associated substitutions K101E and G190A and the substitution G190A persisted during treatment at Weeks 36 and 72. Subjects # (b) (6) and (b) (6) were virologic failures at Week 48. The K103N substitution present in baseline isolates from subject # (b) (6) persisted during treatment at Week 60 and subject # (b) (6) was a virologic success at Week 48.

Baseline isolates from 4 subjects (# (b) (6)) harbored NRTI resistance-associated substitutions M41L, A62V, D67G, T69N, K70R, M184V, T215II/C and K219Q. The substitution M184V is associated with a high level resistance to emtricitabine.

Baseline isolates from subject # (b) (6) harbored NRTI-resistance substitutions T69N, K70R, M184V, T215I and K219E and these substitutions persisted during treatment; as mentioned before, subject # (b) (6) was a virologic failure at Week 48.

Nine subjects in the EFV 400 mg group were virologic failures at Week 48 (i.e. did not achieve the protocol defined primary efficacy endpoint of viral load <200 copies/mL at Week48, Table 2). Of these, on-therapy isolates from 1 subject (# (b) (6)) developed NNRTI-resistance associated substitutions during treatment at Week 36.

EFV 600 mg group

Baseline isolates from 15/282 (5.3%) subjects in the EFV 600 mg group harbored NNRTI resistance-associated substitutions V90I, K103N, V106I/M, V108I, E138A, V179D/E, P225H, and P236L. The K103N substitution alone or in combination with V90I, V106I/M, P225H and P236L was present in baseline isolates from 7/282 (2.5%) subjects. Of these 7 subjects, baseline isolates from 4 subjects (b) (6)) harbored substitutions, V90I plus P236L, V106I, P225H and V106M, respectively. Baseline isolates from 2 subjects (# (b) (6); 0.7%) harbored V106I/M substitutions alone. Additionally, baseline isolates from 6/282 (2.1%) subjects harbored amino acid substitutions V179D/E. Baseline isolates from two of these 6 subjects (b) (6)) also harbored additional substitution V108I or E138A.

One of the 15 subjects (# (b) (6) with baseline isolates harboring NNRTI-resistance-associated substitutions was a virologic failure at Week 48.

On-therapy isolates from 3 subjects (# (b) (6)) developed NNRTI resistance-associated substitutions (K103N/R, V106M, V179D, P225H and F227L)

during treatment, ranging from Week 12 to Week 48. The amino acid substitution K103N present in baseline isolates from subject # (b) (6) persisted in on-therapy isolates and additional substitution P225H developed in on-therapy isolates at Week 48.

Baseline isolates from 1 subject (# (b) (6) harbored NRTI resistance-associated substitution T69N. On-therapy isolates from 3 subjects developed NRTI resistance-associated substitutions M41L, K65R, and M184 during treatment at Weeks 36 to 48. One subject (# (b) (6) developed M41L, K65R, and M184 substitutions at Week 36 and isolates from 2 additional subjects (# (b) (6)) developed M184V substitution at Week 48.

Although on therapy isolates from 4 subjects (b) (6)) developed treatment-emergent NNRTI and NRTI resistance-associated substitutions during Weeks 12 to 48, HIV-1 levels for 1 subject ((b) (6)) were below 200 copies/mL at Week 48 and this subject was considered a virologic success. HIV-1 RNA levels for subject # (b) (6) at Week 48 were not available. HIV-1 RNA levels for subject (b) (6) and # (b) (6) were 30749 and 227983 copies/ml, respectively at Week 48 and these two subjects were virologic failures at Week 48.

Eight subjects in the EFV 600 mg group were virologic failures at Week 48 (Table 2). Baseline and on-therapy isolates from subject only 1 subject # (b) (6) contained NNRTI resistance associated substitutions K103N plus P225H. Additionally, on-therapy isolates from virologic failure subject # (b) (6) developed NRTI resistance-associated substitution M184V at Week 48.

Table 2: Summary of Week 48 Virologic Failures

EFV 400 mg		EFV 600 mg	
Subject ID	**Viral Load at Week 48 (copies/mL)**	**Subject ID**	**Viral Load at Week 48 (copies/mL)**
(b) (6)	5556	(b) (6)	577
	232		3295
	524		8225
	42283		209196
	967		1860
	3365		30749
	602266		227893
	3452		430
	8029		

This product is approvable from a virology perspective.

4.3 Preclinical Pharmacology/Toxicology

This 505(b)(2) NDA relies on the FDA's previous determinations of the preclinical profiles of efavirenz, lamivudine, and tenofovir disoproxil fumarate.

4.4 Clinical Pharmacology

Please refer to Dr. Younis' Clinical Pharmacology review for details. Of note, under tentative approval NDA #022461, (b) (4)

4.4.1 Mechanism of Action

Efavirenz (EFV) is an NNRTI of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase. HIV-2 reverse transcriptase and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.

Lamivudine (3TC) is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir disoproxil fumarate (TDF) is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

4.4.2 Pharmacodynamics

No pharmacodynamics data were provided or considered necessary for this submission.

4.4.3 Pharmacokinetics

In ENCORE1, sparse pharmacokinetic (PK) sampling was obtained from 311 subjects receiving EFV 400 mg and from 295 subjects receiving EFV 600 mg. Additionally, a separate sub-study used intensive sampling to derive PK models for both doses of EFV; the intensive PK sub-study was conducted on 28 subjects receiving EFV 400 mg and 18

subjects receiving EFV 600 mg. Comparing EFV 400 mg to EFV 600 mg, the AUC_{0-24}, C_{max}, C_{24} and C_{12} were significantly lower for EFV 400 mg (geometric mean ratio [GMR] 90% CI: 0.73 [0.68-0.78]) compared to EFV 600 mg. These lower exposures were not associated with a lesser virologic response between treatment groups.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This review is based on data from the ENCORE1 study that was conducted by the Kirby Institute. The datasets are located in the folders:

\\CDSESUB1\evsprod\IND128512\0006

Some files which explain the information related to the datasets submitted in the SN0006 were submitted in SN0007 under IND 128,512 in the folders below:

\\CDSESUB1\evsprod\IND128512\0007

The subgroup analysis results required in the filing letter were submitted in SN0008 under the IND 128,512.

The Kirby Institute's responses for the statistical reviewer's query regarding the primary efficacy endpoints were submitted in SN0014 under the IND 128,512.

Reviewer comment:
The quality of the submitted clinical datasets was low. The "define" files did not clearly explain the meaning of variables even in the third submission. The reviewers had to read the submitted SAS programs to determine the meaning of some variables.

5.2 Review Strategy

Efficacy and safety data were reviewed for ENCORE1. Safety data review included dataset analyses as well as review of case report narratives and case report forms when applicable. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. This MO reviewed study design, patient demographics, and performed safety analyses. FDA clinical and statistical reviewers collaborated extensively throughout the review process, and the efficacy analyses in this review were performed by the FDA statistical reviewer. Additionally, there was significant interaction with the FDA CMC, clinical pharmacology, and microbiology reviewers. Their assessments are summarized in this document, but complete details of their findings are available in the respective discipline reviews.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical section of the NDA focuses on efficacy and safety data from ENCORE1 (summarized below):

ENCORE1 (randomized, double-blind, placebo-controlled, clinical trial to compare the safety and efficacy of reduced dose EFV with standard dose EFV plus 2N(t)RTI in antiretroviral-naïve HIV-infected individuals over 96 weeks)

- **Sponsor:** Kirby Institute, Australia
- **Design:** 96-week double-blind, placebo-controlled, non-inferiority (NI) trial. The study randomization was stratified by the clinical sites and the screening visit plasma HIV RNA level, either <100,000 c/mL or ≥100,000 c/mL. A 10% NI margin was used in the study design. This 10% NI margin is a clinical margin cited from a paper without any justification provided in the protocol. Of note, this 10% NI margin is commonly used in HIV treatment trials and is also specified in FDA's guidance for HIV-1 treatment naïve trials (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf).
- **Study locations:** 38 sites in Argentina, Australia, Chile, Germany, Hong Kong, Israel, Malaysia, Mexico, Nigeria, Singapore, South Africa, Thailand, United Kingdom
- **Start date:** August 2011
- **End date:** August 2014
- **Sample size:** 630
- **Key inclusion criteria:**
  - HIV-1 positive by licensed diagnostic test
  - Aged >16 years of age (or minimum age as determined by local regulations or as legal requirements dictate)
  - 50 < CD4 <500 cells/μL
  - No prior AIDS-defining illness, using the CDC 1993 case definition (except pulmonary tuberculosis)
  - HIV-1 RNA ≥1000 copies/mL
  - No prior exposure to ART (including short course ARVs for preventing MTCT)
  - Calculated creatinine clearance (CLCr) ≥50 mL/min (Cockcroft-Gault formula)
  - Written informed consent
- **Key exclusion criteria:**
  - Pregnant women or nursing mothers
  - Active opportuntistic or malignant disease not under adequate control
  - The following laboratory parameters:
    - absolute neutrophil count (ANC) <500 cells/μL
    - hemoglobin <7.0 g/dL
    - platelet count <50,000 cells/μL
    - AST and/or ALT >5 x ULN
  - Use of immunomodulators within 30 days prior to screening
  - Use of any prohibited medications
  - Current alcohol or illicit substance use that might adversely affect study participation
- **Primary efficacy endpoint:** Proportion of subjects with HIV-1 RNA <200 copies/mL at Week 48
- **Secondary endpoints:**

- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL
- Time to achieve HIV-1 RNA <200 copies/mL
- Time to virological failure (HIV-1 RNA ≥200 copies/ml)
- Time to loss of virological response (TLOVR)
- Mean change from baseline in $\log_{10}$ plasma HIV-1 RNA copies/mL
- Mean change from baseline in CD4+ cell count/μL

- **Study arms:**
  - Active comparator: tenofovir (TDF) (300mg QD)/emtricitabine (FTC) (200mg QD) + EFV (600mg QD; 3 x 200mg QD)
  - Experimental comparator: TDF (300mg QD)/FTC (200mg QD) + EFV (400mg QD; 2 x 200mg + 1 x 200mg placebo QD)

- **Interim analyses:**

  Two interim analyses were conducted before the Week 48 analysis.
  - At the first interim: a recommendation to stop the study at this first analysis would only be made in the event that the experimental arm was considered inferior (i.e. if the control arm (600mg) was found to have provided a ≥ 0.5 $\log_{10}$ difference in virological suppression from baseline, using a one-sided significance level of 0.01).
  - At the second interim: the proportions of participants in each study arm at weeks 36 and 48 were also to be compared. The trial could have stopped if one arm was statistically significantly inferior on the endpoint of percentage of participants with plasma HIV RNA < 200 copies/mL plasma at week 24 using a two-sided significance level of 0.001. A recommendation to stop could only be made if the finding for the week 24 data was consistent with the observations made on available week 36 and 48 data (in a directional sense).
  - These two blinded interim analyses were conducted and no adjustment was made. Also no adjustments were made for multiple comparisons (reference: ENCORE1 clinical study report, CSR).

Reviewer Comment

A 10% NI margin is a clinical margin and is acceptable to the reviewers. Typically the proportion of subjects with plasma HIV-1 RNA <50 copies/mL is the primary efficacy endpoint and <200 copies/mL is the secondary efficacy endpoint. Even though the proportion of <200 copies/mL was the primary efficacy endpoint in the protocol, the reviewers will treat the proportion of <50 copies/mL as the primary efficacy endpoint and the proportion of <200 copies/mL will be one of secondary efficacy endpoints. The label will present the proportion of <50 copies/mL.

6 Review of Efficacy

Efficacy Summary

The efficacy analyses were conducted on the modified intended-to treat population (mITT). The mITT population included subjects who were randomized, received at least one dose of study medication, and had at least one follow-up visit.

6.1 Indication

The indication proposed by the Applicant is the following:

(b) (4)

6.1.1 Methods

The ENCORE1 efficacy data were reviewed in support of the proposed indication. FDA statistical reviewer's analyses are presented throughout Section 6. If the applicant's results were presented in this section, they are cited.

6.1.2 Demographics

Baseline demographics were evenly matched between both treatment groups (Table 3).

Table 3: Subject baseline characteristics (mITT)

Subgroup	EFV400	EFV600	Total
Treated (ITT)			
N	321	309	630
Gender			
Female	100(31.2%)	103(33.3%)	203(32.2%)
Male	221(68.8%)	206(66.7%)	427(67.8%)
Ethnicity			
African heritage	118(36.8%)	116(37.5%)	234(37.1%)
Asian	106(33.0%)	103(33.3%)	209(33.2%)
Caucasian	46(14.3%)	36(11.7%)	82(13.0%)
Hispanic or Latino	51(15.9%)	53(17.2%)	104(16.5%)
Australian Aboriginal or Torres Strait or South Sea Islander	0	1(0.3%)	1(0.2%)
Age (Year)			
Mean (SE)	36.08 (0.559)	35.82 (0.567)	35.95 (0.398)
Median	34.38	34.89	34.54
Range	(18.89, 69.30)	(18.33, 66.59)	(18.33, 69.30)

STD	10.02	9.967	9.987
Age Category 1 (35yrs)			
<=35	169(52.6%)	157(50.8%)	326(51.7%)
>35	152(47.4%)	152(49.2%)	304(48.3%)
Age Category 2 (65yrs)			
<65	320(99.7%)	307(99.4%)	627(99.5%)
>=65	1(0.3%)	2(0.6%)	3(0.5%)
Baseline HIV RNA log10 (IU/mL)			
Mean (SE)	36.08 (0.559)	35.82 (0.567)	35.95 (0.398)
Median	34.38	34.89	34.54
Range	(18.89, 69.30)	(18.33, 66.59)	(18.33, 69.30)
STD	10.02	9.967	9.987
Screening HIV RNA Category (copies/mL)			
=<100,000	197(61.4%)	197(63.8%)	394(62.5%)
>100,000	124(38.6%)	112(36.2%)	236(37.5%)
Baseline HIV RNA (copies/mL)			
Mean (SE)	164000 (21278)	164000 (34398)	164000 (20038)
Median	57814	53295	56469
Range	(331, 3990000)	(162, 10000000)	(162, 10000000)
STD	381000	605000	503000
Baseline HIV RNA log10 (copies/mL)			
Mean (SE)	4.71 (0.039)	4.68 (0.041)	4.69 (0.028)
Median	4.76	4.73	4.75
Range	(2.52, 6.60)	(2.21, 7.00)	(2.21, 7.00)
STD	0.697	0.712	0.704
Baseline HIV RNA Category 1 (copies/mL)			
<1000	3(0.9%)	4(1.3%)	7(1.1%)
≥1000, <10K	55(17.1%)	49(15.9%)	104(16.5%)
≥10K, <100K	156(48.6%)	149(48.2%)	305(48.4%)
≥100K	107(33.3%)	107(34.6%)	214(34.0%)
Baseline BMI (kg/m^2)			
Mean (SE)	24.05 (0.261)	24.31 (0.294)	24.18 (0.196)
Median	23.23	23.39	23.34
Range	(15.84, 48.26)	(15.28, 50.09)	(15.28, 50.09)
STD	4.666	5.174	4.920
Baseline BMI Category 1 (kg/m^2)			
<=25	215(67.0%)	204(66.0%)	419(66.5%)
25<=, <30	75(23.4%)	72(23.3%)	147(23.3%)
>=30	30(9.3%)	33(10.7%)	63(10.0%)
missing	1(0.3%)	0(0%)	1(0.2%)
Baseline BMI Category 2 (kg/m^2)			

<=18.5	21(6.5%)	23(7.4%)	44(7.0%)
18.5<=,<25	194(60.4%)	181(58.6%)	375(59.5%)
25<=, <30	75(23.4%)	72(23.3%)	147(23.3%)
30<=, <35	24(7.5%)	21(6.8%)	45(7.1%)
>=35	6(1.9%)	12(3.9%)	18(2.9%)
missing	1(0.3%)	0(0%)	1(0.2%)
CDC AIDS Category			
Category A	264(82.2%)	265(85.8%)	529(84.0%)
Category B	46(14.3%)	33(10.7%)	79(12.5%)
Category C	11(3.4%)	11(3.6%)	22(3.5%)
Mode of Acquisition HIV			
Blood/blood product	1(0.3%)	3(1.0%)	4(0.6%)
Heterosexual contact	156(48.6%)	155(50.2%)	311(49.4%)
Homosexual/bisexual	138(43.0%)	134(43.4%)	272(43.2%)
Injecting drug use	2(0.6%)	0(0%)	2(0.3%)
Other	24(7.5%)	17(5.5%)	41(6.5%)
HBV Surface Antigen			
Negative	203(93.1%)	194(94.2%)	397(93.6%)
Positive	15(6.9%)	12(5.8%)	27(6.4%)
HCV Antibody			
Negative	208(97.7%)	194(98.5%)	402(98.0%)
Positive	5(2.3%)	3(1.5%)	8(2.0%)
Country			
ARGENTINA	36(11.7%)	37(12.6%)	73(12.2%)
AUSTRALIA	22(7.2%)	19(6.5%)	41(6.8%)
CHILE	13(4.2%)	11(3.8%)	24(4.0%)
GERMANY	8(2.6%)	6(2.0%)	14(2.3%)
HONG KONG	3(1.0%)	3(1.0%)	6(1.0%)
ISRAEL	12(3.9%)	11(3.8%)	23(3.8%)
MALAYSIA	15(4.9%)	11(3.8%)	26(4.3%)
MEXICO	11(3.6%)	11(3.8%)	22(3.7%)
NIGERIA	31(10.1%)	28(9.6%)	59(9.8%)
SINGAPORE	20(6.5%)	20(6.8%)	40(6.7%)
SOUTH AFRICA	75(24.4%)	77(26.3%)	152(25.3%)
THAILAND	45(14.7%)	47(16.0%)	92(15.3%)
UNITED KINGDOM	16(5.2%)	12(4.1%)	28(4.7%)

Reviewer Comment
No pediatric patients were enrolled in ENCORE1. The ENCORE1 study provides good representation of women (203/630, 32%) as well as subjects of African (234/630, 37%) and Asian (210/630, 33%) ethnicity. The other baseline demographics, clinical, immunologic, and virologic characteristics are similar to other recent treatment-naïve studies.

6.1.3 Subject Disposition

Overall, 630 subjects (321 in EFV 400mg group; 309 in EFV 600 mg group) received at least one dose of study drug. Subject disposition at Week 48 is summarized in Table 4.

Table 4: Subject disposition at Week 48

	EFV 400 mg	EFV 600 mg	Total
Subjects treated, n	321	309	630
Completed Week 48, n (%)	311 (96.9)	295 (95.5)	606 (96.2)
Discontinued before Week 48, n (%)	10 (3.1)	14 (4.5)	24 (3.8)
Death	2 (0.6)	3 (1.0)	5 (0.8)
Withdrew consent	7 (2.2)	4 (1.3)	11 (1.7)
Lost to follow-up	0	2 (0.6)	2 (0.3)
Missing Week 48 assessment	1 (0.3)	5 (1.6)	6 (1.0)

Reviewer Comment
Overall, there was a high rate of subject retention in the ENCORE1 study, with 606 subjects (311 in the EFV 400mg group; 295 in the EFV 600 mg group) completing study through the first 48 weeks (primary endpoint).

Of note, FDA reviewer results in Table 4 are slightly different from the results in the CSR. Please see the appendix (Section 9.5) for a detailed explanation.

6.1.4 Analysis of Primary Endpoint(s)

The Division's recommendation of the primary analysis is the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 and FDA's efficacy analyses are summarized in Table 5.

Table 5: Primary Efficacy Endpoint (<50 c/mL) Results at Week 48

Treated Subjects *Parameters analyzed*	EFV400 (N=321)	EFV600 (N=309)	Rate Diff	Mantel-Haenszel Rate Diff adjusted by the HIV RNA viral load at Baseline[3]
<50 c/mL at Week 48	**276/321 (86.0%)**	**261/309 (84.4%)**	**1.5%**	**1.6%**
95% CI	(81.7%, 89.8%)[1]	(79.9%, 88.3%)[1]	(-4.0%, 7.1%)[2]	(-3.9%, 7.2%)

[1]: Exact CI was used; [2]: Asymptotic CI was used;
[3]: HIV RNA viral load: <100k or ≥100k c/mL was used as the stratification factor

The lower bound of 95% confidence interval (CI) for rate difference between EFV 400 mg and EFV 600 mg was -4.0% and was -3.9% with adjustment of baseline HIV-1 RNA viral load, which are both greater than -10% NI margin. This demonstrated that EFV400 mg is non-inferior to EFV 600 mg with a NI margin of 10%. The proportions of subjects with plasma HIV-1 RNA <50 copies/mL in both arms were very similar, 86.0% for the EFV 400mg group and 84.4% for the EFV 600mg group.

The subjects not categorized as responders were classified into different categories (Table 6). These results will be presented in the label in the following format.

Table 6: Primary Efficacy Endpoint (<50 c/mL) Results at Week 48 for Labeling

	At Week 48	
Outcomes (<50 copies/mL)	EFV400 (N=321)	EFV600 (N=309)
Responder[a]	**86%**	**84%**
Virologic failure[b]	11%	11%
Rebound	9%	8%
Never suppressed	2%	3%
Death	1%	1%
Discontinued for other reasons[c]	2%	4%

[a]: Subjects achieved confirmed HIV-1 RNA <50 copies/mL at Week 48.
[b]: Includes confirmed viral rebound and failure to achieve confirmed <50 copies/mL through Week 48
[c]: Includes discontinued due to Adverse Event, lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

6.1.5 Analysis of Secondary Endpoints(s)

The Division views the proportion of subjects with plasma HIV-1 RNA <200 copies/mL at Week 48 as the secondary efficacy endpoint even though it was stated as the primary efficacy endpoint in the protocol. Secondary efficacy analyses of HIV-1 RNA <200 copies/mL are summarized in Table 7.

Table 7: Secondary Efficacy Endpoint (<200 c/mL) Results at Week 48

Treated Subjects *Parameters analyzed*	EFV400 (N=321)	EFV600 (N=309)	Rate Diff	Mantel-Haenszel Rate Diff adjusted by the HIV RNA viral load at Baseline[3]
<200 c/mL at Week 48	**303/321 (94.4%)**	**287/309 (92.9%)**	**1.5%**	**1.5%**

95% CI	(91.3%, 96.6%)[1]	(89.4%, 95.7%)[1]	(-2.3%, 5.3%)[2]	(-2.4%, 5.4%)

[1]: Exact CI was used; [2]: Asymptotic CI was used;
[3]: HIV RNA viral load: <100k or ≥100k c/mL was used as the stratification factor

Reviewer Comment
The lower bound of 95% confidence interval (CI) for rate difference between EFV 400 mg and EFV 600 mg was -2.3% and was -2.4% with an adjustment of baseline HIV-1 RNA viral load, which are both greater than -10% NI margin. This demonstrated that EFV400 mg is non-inferior to EFV 600 mg with NI margin of 10%. The proportions of subjects with plasma HIV-1 RNA <200 copies/mL in both arms were overall similar, 94.4% for the EFV 400mg group and 92.9% for the EFV 600mg group.

6.1.6 Other Endpoints

In the mITT population, an increase in CD4 count from baseline was noted in the EFV 400 mg group compared to the EFV 600 mg at Week 48 (183 cells/μL vs. 158 cells/μL, 95% CL: 6.6 - 44.4). However, the magnitude of these changes between the treatment groups is not clinically meaningful since mean baseline CD4 counts was 273 cells/μL in both treatment groups.

Table 8: Summary of Mean Changes in CD4+ from Baseline to Week 48

Treated Subjects	CD4 count		
Parameters analyzed	EFV400 (N=321)	EFV600(N=309)	Mean Change Difference[2]
CD4 count at Baseline	N=321	N=309	
(Mean (min, max))	272.8 (63.0, 526.5)	272.4 (37.7, 679.0)	
CD4 count at Week 48	N=311	N=295	
(Mean (min, max))	458.2 (79.0, 993.0)	435.3 (66.0, 942.0)	
Mean Change at Week 48 from Baseline[1]	183.0 (-68.5, 660.5)	157.5 (-121.5, 547.5)	25.5
95% CI of Mean Change	(169.4, 196.5)	(144.3, 170.7)	(6.6, 44.4)

[1]: LOCF was used to calculate the mean change from baseline to Week 48 (total 24 subjects missed Week 48 CD4 count);
[2]: A T-test with Pooled method was used to generate mean change difference and its 95% CI

6.1.7 Subpopulations

Subgroup analyses for stratification factor, HIV-1 RNA viral load at baseline, are summarized for the primary efficacy endpoint of HIV-1 RNA <50 copies/mL (Table 9) and for the secondary efficacy endpoint of HIV-1 RNA <200 copies/mL (Table 10).

Table 9: Primary Efficacy Endpoint (<50 c/mL) Results by Baseline HIV-1 RNA viral load at Week 48

Treated Subjects *Parameters analyzed*	<100,000 c/mL at Baseline			≥100,000 c/mL at Baseline		
	EFV400 (N=321)	EFV600 (N=309)	Rate Diff	EFV400 (N=321)	EFV600 (N=309)	Rate Diff
<50 c/mL at Week 48	**174/197 (88.3%)**	**170/197 (86.3%)**	**2.0%**	**102/124 (82.3%)**	**91/112 (81.3%)**	**1.0%**
95% CI	(83.0%, 92.5%)[1]	(80.7%, 90.8%)[1]	(-4.5%, 8.6%)[2]	(74.4%, 88.5%)[1]	(72.8%, 88.0%)[1]	(-8.9%, 10.9%)[2]

[1]: Exact CI was used; [2]: Asymptotic CI was used;
[3]: HIV RNA viral load: <100k or ≥100k c/mL was used as the stratification factor

Reviewer Comment
The primary efficacy endpoint results within two strata were similar to the overall results. The response rates in the strata of the HIV-1 RNA viral load ≥100,000 c/mL at Baseline were slightly lower than the overall results and the lower bound of 95% CI of -8.9% was also lower than that in the overall analysis.

Table 10: Secondary Efficacy Endpoint (<200 c/mL) Results by Baseline HIV-1 RNA viral load at Week 48

Treated Subjects *Parameters analyzed*	<100,000 c/mL at Baseline			≥100,000 c/mL at Baseline		
	EFV400 (N=321)	EFV600 (N=309)	Rate Diff	EFV400 (N=321)	EFV600 (N=309)	Rate Diff
<200 c/mL at Week 48	**187/197 (94.9%)**	**183/197 (92.9%)**	**2.0%**	**116/124 (93.6%)**	**104/112 (92.9%)**	**0.7%**
95% CI	(90.9%, 97.5%)[1]	(88.4%, 96.1%)[1]	(-2.7%, 6.7%)[2]	(87.7%, 97.2%)[1]	(86.4%, 96.9%)[1]	(-5.7%, 7.1%)[2]

[1]: Exact CI was used; [2]: Asymptotic CI was used;
[3]: HIV RNA viral load: <100k or ≥100k c/mL was used as the stratification factor

Reviewer Comment
The secondary efficacy endpoint results within two strata were similar to the overall results.

Subgroup analyses for some baseline demographic factors and the primary efficacy endpoint are summarized in Table 11.

Table 11: Subgroup analyses of Primary Efficacy Endpoint (<50 c/mL) - Results by Baseline Factors at Week 48

Efficacy Parameter	EFV400	EFV600	Total
Treated (ITT)			
N	276/321(86.0)	261/309(84.5)	537/630(85.2)
Gender			
Female	85 /100 (85.0)	87 /103 (84.5)	172 /203 (84.7)
Male	191 /221 (86.4)	174 /206 (84.5)	365 /427 (85.5)
Ethnicity			
African heritage	99 /118 (83.9)	96 /116 (82.8)	195 /234 (83.3)
Asian	92 /106 (86.8)	91 /103 (88.3)	183 /209 (87.6)
Caucasian	40 / 46 (87.0)	31 / 36 (86.1)	71 / 82 (86.6)
Hispanic or Latin	45 / 51 (88.2)	42 / 53 (79.2)	87 /104 (83.7)
Australian Aboriginal or Torres Strait or South Sea Islander	. / . (.)	1 / 1 (100)	1 / 1 (100)
Age Group 1 (35 years)			
<=35	147 /169 (87.0)	128 /157 (81.5)	275 /326 (84.4)
>35	129 /152 (84.9)	133 /152 (87.5)	262 /304 (86.2)
Age Group 2 (65 years)			
<65	275 /320 (85.9)	260 /307 (84.7)	535 /627 (85.3)
>=65	1 / 1 (100)	1 / 2 (50.0)	2 / 3 (66.7)
Baseline BMI Category 1 (kg/m^2)			
<=25	183 /215 (85.1)	174 /204 (85.3)	357 /419 (85.2)
25<=, <30	66 / 75 (88.0)	58 / 72 (80.6)	124 /147 (84.4)
>=30	26 / 30 (86.7)	29 / 33 (87.9)	55 / 63 (87.3)
missing	1 / 1 (100)	. / . (.)	1 / 1 (100)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	15 / 21 (71.4)	18 / 23 (78.3)	33 / 44 (75.0)
18.5<=,<25	168 /194 (86.6)	156 /181 (86.2)	324 /375 (86.4)
25<=, <30	66 / 75 (88.0)	58 / 72 (80.6)	124 /147 (84.4)
30<=, <35	20 / 24 (83.3)	18 / 21 (85.7)	38 / 45 (84.4)
>=35	6 / 6 (100)	11 / 12 (91.7)	17 / 18 (94.4)
missing	1 / 1 (100)	. / . (.)	1 / 1 (100)
Mode of Acquisition HIV			
Blood/blood product	. / 1 (0.00)	2 / 3 (66.7)	2 / 4 (50.0)
Heterosexual contact	131 /156 (84.0)	131 /155 (84.5)	262 /311 (84.2)
Homosexual/bisexual	122 /138 (88.4)	115 /134 (85.8)	237 /272 (87.1)

Injecting drug use	2 / 2 (100)	. / . (.)	2 / 2 (100)
Other;	21 / 24 (87.5)	13 / 17 (76.5)	34 / 41 (82.9)
CDC AIDS Category			
Category A	227 /264 (86.0)	224 /265 (84.5)	451 /529 (85.3)
Category B	41 / 46 (89.1)	28 / 33 (84.8)	69 / 79 (87.3)
Category C	8 / 11 (72.7)	9 / 11 (81.8)	17 / 22 (77.3)
HBV Surface Antigen			
Negative	178 /203 (87.7)	161 /194 (83.0)	339 /397 (85.4)
Positive	13 / 15 (86.7)	12 / 12 (100)	25 / 27 (92.6)
HCV Antibody			
Negative	184 /208 (88.5)	163 /194 (84.0)	347 /402 (86.3)
Positive	2 / 5 (40.0)	2 / 3 (66.7)	4 / 8 (50.0)
Country			
ARGENTINA	32 / 36 (88.9)	28 / 37 (75.7)	60 / 73 (82.2)
AUSTRALIA	19 / 22 (86.4)	18 / 19 (94.7)	37 / 41 (90.2)
CHILE	12 / 13 (92.3)	10 / 11 (90.9)	22 / 24 (91.7)
GERMANY	6 / 8 (75.0)	6 / 6 (100)	12 / 14 (85.7)
HONG KONG	3 / 3 (100)	3 / 3 (100)	6 / 6 (100)
ISRAEL	8 / 12 (66.7)	7 / 11 (63.6)	15 / 23 (65.2)
MALAYSIA	13 / 15 (86.7)	8 / 11 (72.7)	21 / 26 (80.8)
MEXICO	10 / 11 (90.9)	9 / 11 (81.8)	19 / 22 (86.4)
NIGERIA	26 / 31 (83.9)	22 / 28 (78.6)	48 / 59 (81.4)
SINGAPORE	18 / 20 (90.0)	19 / 20 (95.0)	37 / 40 (92.5)
SOUTH AFRICA	65 / 75 (86.7)	67 / 77 (87.0)	132 /152 (86.8)
THAILAND	39 / 45 (86.7)	42 / 47 (89.4)	81 / 92 (88.0)
UNITED KINGDOM	14 / 16 (87.5)	9 / 12 (75.0)	23 / 28 (82.1)

Reviewer Comment
None of baseline factors analyzed had a clinically or statistically significant impact on the primary efficacy endpoint results.

Subgroup analyses for some baseline demographic factors and the secondary efficacy endpoint of HIV-1 RNA <50 copies/mL are summarized in Table 12.

Table 12: Subgroup analyses of One of the Secondary Efficacy Endpoints (<200 c/mL) - Results by Baseline Factors at Week 48

Efficacy Parameter	EFV400	EFV600	Total
Treated (ITT)			
N	303/321(94.4)	287/309(92.9)	590/630(93.7)
Gender			
Female	91 /100 (91.0)	94 /103 (91.3)	185 /203 (91.1)
Male	212 /221 (95.9)	193 /206 (93.7)	405 /427 (94.8)
Ethnicity			
African heritage	107 /118 (90.7)	104 /116 (89.7)	211 /234 (90.2)
Asian	103 /106 (97.2)	100 /103 (97.1)	203 /209 (97.1)

Caucasian	44 / 46 (95.7)	33 / 36 (91.7)	77 / 82 (93.9)
Hispanic or Latin	49 / 51 (96.1)	49 / 53 (92.5)	98 /104 (94.2)
Australian Aboriginal or Torres Strait or South Sea Islander	. / . (.)	1 / 1 (100)	1 / 1 (100)
Age Group 1 (35 years)			
<=35	158 /169 (93.5)	142 /157 (90.4)	300 /326 (92.0)
>35	145 /152 (95.4)	145 /152 (95.4)	290 /304 (95.4)
Age Group 2 (65 years)			
<65	302 /320 (94.4)	285 /307 (92.8)	587 /627 (93.6)
>=65	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
Baseline BMI Category 1 (kg/m^2)			
<=25	203 /215 (94.4)	187 /204 (91.7)	390 /419 (93.1)
25<=, <30	70 / 75 (93.3)	68 / 72 (94.4)	138 /147 (93.9)
>=30	29 / 30 (96.7)	32 / 33 (97.0)	61 / 63 (96.8)
missing	1 / 1 (100)	. / . (.)	1 / 1 (100)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	20 / 21 (95.2)	19 / 23 (82.6)	39 / 44 (88.6)
18.5<=,<25	183 /194 (94.3)	168 /181 (92.8)	351 /375 (93.6)
25<=, <30	70 / 75 (93.3)	68 / 72 (94.4)	138 /147 (93.9)
30<=, <35	23 / 24 (95.8)	20 / 21 (95.2)	43 / 45 (95.6)
>=35	6 / 6 (100)	12 / 12 (100)	18 / 18 (100)
missing	1 / 1 (100)	. / . (.)	1 / 1 (100)
Mode of Acquisition HIV			
Blood/blood product	. / 1 (0.00)	3 / 3 (100)	3 / 4 (75.0)
Heterosexual contract	145 /156 (92.9)	144 /155 (92.9)	289 /311 (92.9)
Homosexual/bisexual	135 /138 (97.8)	126 /134 (94.0)	261 /272 (96.0)
Injecting drug use	2 / 2 (100)	. / . (.)	2 / 2 (100)
Other;	21 / 24 (87.5)	14 / 17 (82.4)	35 / 41 (85.4)
CDC AIDS Category			
Category A	252 /264 (95.5)	247 /265 (93.2)	499 /529 (94.3)
Category B	42 / 46 (91.3)	30 / 33 (90.9)	72 / 79 (91.1)
Category C	9 / 11 (81.8)	10 / 11 (90.9)	19 / 22 (86.4)
HBV Surface Antigen			
Negative	193 /203 (95.1)	180 /194 (92.8)	373 /397 (94.0)
Positive	14 / 15 (93.3)	12 / 12 (100)	26 / 27 (96.3)
HCV Antibody			
Negative	200 /208 (96.2)	182 /194 (93.8)	382 /402 (95.0)
Positive	2 / 5 (40.0)	2 / 3 (66.7)	4 / 8 (50.0)
Country			
ARGENTINA	35 / 36 (97.2)	33 / 37 (89.2)	68 / 73 (93.2)
AUSTRALIA	20 / 22 (90.9)	18 / 19 (94.7)	38 / 41 (92.7)
CHILE	13 / 13 (100)	11 / 11 (100)	24 / 24 (100)
GERMANY	8 / 8 (100)	6 / 6 (100)	14 / 14 (100)
HONG KONG	3 / 3 (100)	3 / 3 (100)	6 / 6 (100)
ISRAEL	10 / 12 (83.3)	7 / 11 (63.6)	17 / 23 (73.9)

MALAYSIA	15 / 15 (100)	9 / 11 (81.8)	24 / 26 (92.3)
MEXICO	10 / 11 (90.9)	10 / 11 (90.9)	20 / 22 (90.9)
NIGERIA	27 / 31 (87.1)	25 / 28 (89.3)	52 / 59 (88.1)
SINGAPORE	20 / 20 (100)	20 / 20 (100)	40 / 40 (100)
SOUTH AFRICA	70 / 75 (93.3)	72 / 77 (93.5)	142 /152 (93.4)
THAILAND	44 / 45 (97.8)	47 / 47 (100)	91 / 92 (98.9)
UNITED KINGDOM	15 / 16 (93.8)	11 / 12 (91.7)	26 / 28 (92.9)

Reviewer Comment
None of baseline factors analyzed had significant impact on the secondary efficacy endpoint results.

The subgroup analyses by sites for the primary and secondary efficacy endpoints are listed in the appendix (Section 9.6).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant used the ENCORE1 data to support the dosage recommendation for the proposed 400 mg QD dosing of EFV. Please see Section 6.1.4

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

(b) (4) the Applicant proposes (b) (4)

Reviewer Comment
(b) (4) Therefore, the labeling was revised to (b) (4)

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety results from ENCORE1 are consistent with the findings from prior clinical trials with EFV 600 mg, TDF, and FTC, as well as post-marketing experience with these approved products. Through Week 48, EFV 400 mg QD was not associated with an

increase in SAEs, Grade 3 or 4 AEs, or laboratory abnormalities compared to EFV 600 mg QD.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review is based upon data from the ENCORE1 study. Week 48 results were included in the submitted datasets. (b) (4)

(b) (4)
. Therefore, the labeling

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 15.0 was used for AE coding. Adverse events were summarized by MedDRA System Organ Class and Preferred Term. A treatment-emergent AE was defined as any AE that began on or after the treatment start date up to 30 days after the treatment stop date.

A serious adverse event (SAE) is any event that results in any one of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only data from ENCORE1 are presented in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation selected for marketing is the EFV/3TC/TDF (400/300/300 mg) tablet.

The EFV 400 mg dose was compared with the EFV 600 mg dose in the ENCORE1 study. Overall, 630 subjects (321 in the EFV 400mg group; 309 in the EFV 600 mg group) received at least one dose of study drug. Through Week 48, 570 subjects (295 in

the EFV 400 mg group; 275 in the EFV 600 mg group) were still receiving study drug. The reasons for stopping blinded EFV are summarized in Table 13.

Table 13: Reasons for discontinuing blinded EFV

	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects who discontinued EFV, n (%)	26 (8.1)	34 (11.0)
Adverse events (AEs)	13 (4.0)	17 (5.5)
Subject decision	4 (1.2)	3 (1.0)
Death	2 (0.6)	3 (1.0)
Pregnancy	2 (0.6)	3 (1.0)
Withdrew from study	2 (0.6)	2 (0.6)
Virologic failure	1 (0.3)	2 (0.6)
Physician decision	1 (0.3)	2 (0.6)
Missed doses > 30 days	0	2 (0.6)
Lost to follow-up	1 (0.3)	0

Reviewer Comment
Through Week 48, a lower proportion of subjects (8.1%) in the EFV 400 mg group discontinued study drug compared to the EFV 600 mg group (11%). The difference between treatment groups was not statistically significant.

Please refer to Section 6.1.2 for demographic information. Additional discussion about deaths (Section 7.3.1), AEs (Section 7.3.3), and pregnancies are provided in other sections of the review.

7.2.2 Explorations for Dose Response

Please see Section 6.1.4

7.2.3 Special Animal and/or In Vitro Testing

Not applicable. New nonclinical studies were not performed.

7.2.4 Routine Clinical Testing

Subjects underwent clinic visits at Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96 for physical examination, adverse event reporting, biochemistry, hematology, immunology, and local viral load (VL) quantification for clinical management. Plasma VL was also measured at one central reference laboratory with the Abbott m2000 Real Time HIV-1 Test (b) (4) lower limit of detection 40 copies/mL).

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profiles of the ARVs used in this study were taken into consideration during the safety review.

7.3 Major Safety Results

7.3.1 Deaths

There were five deaths through Week 48, two in the EFV 400mg group, and three in the EFV 600 mg group. These cases are summarized below:

1. Subject (b) (6) was a 58-year old Caucasian male randomized to the EFV 400 mg group. Study treatment started on (b) (6) he presented with diffuse high grade B-cell lymphoma which was HIV-associated. The event was coded as Grade 4 non-Hodgkin's lymphoma with onset date on (b) (6). He was hospitalized for chemotherapy on (b) (6) He died of multi-organ failure on (b) (6) Primary cause of death was documented as non-Hodgkin lymphoma. Death was assessed by the study investigator as probably not related to study drug.
2. Subject (b) (6) was a 42-year old Asian male randomized to the EFV 400 mg group. Study treatment started on 1 (b) (6). He presented with persistent serious Grade 3 dizziness on (b) (6) that changed to Grade 2 on (b) (6) The events of dizziness were assessed as probably related to study treatment. Following hospitalization, brain masses were observed and CNS lymphoma or infiltrative glioma was suspected. Brain biopsy could not be performed because of the location of the masses. Therapy with XRT 40Gy/20F was planned but only SRT 22Gy could be administered due to thrombocytopenia. Worsening of clinical status was observed after radiation therapy. On (b) (6), he presented with dyspnea and productive cough and patchy infiltration of both lungs was observed. Pneumonia and septicemia was suspected. No antibiotics were prescribed. He developed septic shock and died on (b) (6). The primary cause of death was suspected primary lymphoma of the brain. Death was assessed by the study investigator as probably not related to study drug.
3. Subject (b) (6) was a 31-year old Asian male randomized to the EFV 600 mg group. Study treatment started on (b) (6). He was hospitalized on (b) (6) following a week of fever, sore throat and diarrhea. On admission, he was unconscious, hypotensive, and showing signs of sepsis and renal and hepatic impairment. He died on (b) (6) following cardiac arrest. The primary cause of death was septic shock. Death was assessed by the study investigator as probably not related to study drug.
4. Subject (b) (6) was a 30-year old African male randomized to the EFV 600 mg group. Study treatment started on (b) (6). This subject had a protocol violation of having had twice daily treatments of TDF/FTC for 43 days instead of the prescribed dose of once daily. He presented with serious Grade 4 disseminated TB on (b) (6) which was downgrade

to non-serious Grade 2 on [redacted] Both AEs of TB were related to study treatment. He also presented with serious Grade 3 subdural hematoma from [redacted]. This recurred as serious Grade 4 subdural hematoma on [redacted] which was downgraded to non-serious Grade 2 subdural hematoma on [redacted] All AEs of subdural hematoma were assessed as not related to study drug. He was hospitalized due to CNS toxoplasmosis and respiratory dysfunction on [redacted]. Blood culture tested positive for *Acinetobacter*. Diagnosis was pneumonia due to *Acinetobacter* that resulted in death on [redacted] Death was assessed by the study investigator as probably not related to study drug.

5. Subject [redacted] was a 23-year old African male randomized to the EFV 600 mg group. Study treatment started on [redacted]. He died on [redacted] after ingestion of rat poison and his death was assessed as suicide. Toxicology report was not available. Death was assessed by the study investigator as possibly related to study treatment.

Reviewer comment

- For cases 1-4, this reviewer agrees with the investigator assessments that these deaths were probably not related to study drug.
- For case 5, although insufficient data was provided to conclusively determine causality, this reviewer agrees with the investigator assessment that the study drug could possibly have contributed to suicide.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were overall comparable for both groups. Through Week 48, SAEs occurred in 19 subjects (5.9%) in the EFV 400 mg group and 17 subjects (5.5%) in the EFV 600 mg group. Overall, the SOC categories were balanced between treatment groups. Most SAEs were assessed by investigators as not related to study drug. These SAEs are summarized in Table 14.

Table 14: Non-Fatal Serious Adverse Events through Week 48

	EFV 400 mg (N=321)	EFV 600 mg (N=309)
	N (%)	N (%)
Total # of subjects with SAE, n (%)	19 (5.9)	17 (5.5)
Infections and infestations	7 (2.2)	10 (3.2)
Vascular disorders	3 (0.9)	2 (0.6)
Gastrointestinal disorders	2 (0.6)	1 (0.3)
Blood and lymphatic disorders	2 (0.6)	0
Reproductive disorders	2 (0.6)	1 (0.3)
General system disorders	1 (0.3)	0
Immune system disorders	1 (0.3)	1 (0.3)
Injury, poisoning and procedural	1 (0.3)	0
Metabolism and nutritional disorders	1 (0.3)	0
Neoplastic disorders	1 (0.3)	0
Psychiatric disorders	1 (0.3)	0
Eye disorders	0	1 (0.3)
Hepatobiliary disorders	0	1 (0.3)
Nervous system disorders	0	1 (0.3)

Pregnancy, puerperium and perinatal	0	1 (0.3)
Renal and urinary disorders	0	2 (0.6)
Respiratory disorders	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (0.3)
Surgical and medical procedures	0	1 (0.3)

The number of SAEs considered by investigators as related to study drug (two in EFV 400 mg recipients, and four in EFV 600 mg recipients) was overall comparable for both groups. These cases are summarized below:

1. Subject (b) (6) was a 42-year old Asian male randomized to EFV 400 mg. This subject is discussed in Section 7.3.1; Grade 3 dizziness was assessed by investigators as definitely related to study treatment.
2. Subject (b) (6) was a 45-year-old African male randomized to EFV 400 mg. Study treatment started on (b) (6), he presented with serious Grade 4 Stevens-Johnson syndrome that was assessed by investigators as definitely related to study treatment. The event resolved on (b) (6). This subject completed Week 48.
3. Subject (b) (6) was a 52-year-old Hispanic male randomized to EFV 600 mg. Study treatment started on (b) (6) he presented with an SAE of Grade 3 nephrotic syndrome that was assessed by investigators as probably related to study treatment. The SAE was reported as ongoing. Other AEs that were reported included serious Grade 3 pneumonia, serious Grade 3 pleural effusions, and non-serious Grade 2 herpes zoster which were all assessed as not related to study treatment. This subject completed Week 48.
4. Subject (b) (6) was a 26-year-old Caucasian male randomized to EFV 600 mg. Study treatment started on (b) (6) he presented with non-serious Grade 2 diffuse maculopapular rash. On (b) (6), he presented with serious Grade 3 lip edema and the rash worsened to Grade 3 SAE on the same day. These two SAEs were assessed by investigators as definitely related to study treatment and resulted in change in ART. The lip edema resolved on (b) (6) and the maculo-papular rash on (b) (6). Other AEs reported were non-serious Grade 2 rash macular on (b) (6) assessed as definitely related and non-serious Grade 2 rash on (b) (6) both assessed as probably related to study treatment. Both AEs resolved. This subject completed Week 48.
5. Subject (b) (6) was a 35-year-old male African male randomized to EFV 600 mg. Study treatment started on (b) (6), he presented with an SAE of Grade 4 renal failure (serum creatinine of 6.99 mg/dL) that resulted in a change in ART. (Of note, baseline creatinine was 0.71 mg/dL). The SAE was assessed by investigators as probably related to study treatment. He completed Week 48 with a serum creatinine of 0.77 mg/dL.
6. Subject (b) (6) was a 33-year-old African female randomized to EFV 600 mg. Study treatment started on (b) (6). Pregnancy was documented on Week 4. Spontaneous abortion occurred on (b) (6). The SAE was assessed by investigators as possibly related to study treatment.

Reviewer comment

This reviewer agrees with the investigator assessments that these SAEs could be related to study drug. Of note, the renal SAEs were considered as possibly related to TDF.

7.3.3 Dropouts and/or Discontinuations

Through Week 48, AEs leading to discontinuation of blinded EFV were reported in 13 subjects (4%) in the EFV 400 mg group and 17 subjects (5.5%) in the EFV 600 mg group.

Table 15: AEs leading to discontinuation of blinded EFV through Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with AEs that led to discontinuation of EFV, n (%)	13 (4.0)	17 (5.5)
Rash	1 (0.3)	9 (2.9)
Stevens-Johnson syndrome	1 (0.3)	0
Dermatitis	1 (0.3)	0
Dermatitis allergic	0	1 (0.3)
Dizziness	1 (0.3)	1 (0.3)
Insomnia	1 (0.3)	0
Depression	1 (0.3)	1 (0.3)
Transaminases increased	3 (0.9)	1 (0.3)
Unspecified	1 (0.3)	0
Pulmonary tuberculosis[1]	2 (0.6)	0
Neutropenia[2]	1 (0.3)	0
Nephrotic syndrome[2]	0	1 (0.3)
Renal failure[2]	0	1 (0.3)
Gynecomastia	0	2 (0.6)

[1]Subjects were switched to open-label EFV (600 mg/day) while TB treatment was given. Blinded EFV was resumed after completing TB treatment.
[2]Blinded EFV was temporarily held (when AE was initially identified), then resumed.
Of note, TDF/FTC was discontinued due to AEs in a total of 6 subjects: one subject (with SJS) in the EFV 400 mg group vs. 6 subjects (2 with rash; 1 with nephrotic syndrome; 1 with renal failure; 1 with urosepsis; 1 with elevated transaminases) in the EFV 600 mg group

Reviewer Comment
Discontinuations due to AEs occurred more frequently at EFV 600 mg vs. EFV 400 mg (5.5% vs. 4%); the main difference between treatment groups was more discontinuations due to rash AEs at EFV 600 mg.

7.3.4 Significant Adverse Events

HIV-related opportunistic infections and other AIDS-defining illnesses
Over 48 weeks, new AIDS-defining events were reported in 11 subjects (3.4%) in the EFV 400 mg group and 5 subjects (1.6%) in the EFV 600 mg group. These AIDS-defining events are shown in Table 16.

Table 16: New CDC Class C AIDS-Defining Events (all grades, regardless of causality) through Week 48

System Organ Class Preferred Term	EFV 400 mg (n=321) N (%)	EFV 600 mg (n=309) N (%)
Total # of subjects with AE, n (%)	11 (3.4)	5 (1.6)
Infections and Infestations	4 (1.2)	5 (1.6)
Pulmonary tuberculosis	3 (0.9)	3 (1.0)
Extra-pulmonary tuberculosis	0	2 (0.6)
Cerebral toxoplasmosis	1 (0.3)	0
Neoplasms, benign, malignant, and unspecified	7 (2.2)	0
Kaposi's sarcoma	3 (0.9)	0
Non-Hodgkins lymphoma	3 (0.9)	0
Primary brain lymphoma	1 (0.3)	0

The incidence of AIDS-defining events was not statistically different between groups. Overall, no new safety issues regarding development of AIDS-defining events were observed through 48 weeks in ENCORE1.

7.3.5 Submission Specific Primary Safety Concerns

The safety profile of EFV was taken into consideration for this detailed review of specific safety concerns such as rash, nervous system disorders, and psychiatric disorders. The majority of these AEs were mild (Grade 1) to moderate (Grade 2). For Grade 2-4 AEs, rash and dizziness were the only two AEs with more than a 2% difference between treatment groups. Overall, no new safety signals or unexpected toxicities were observed.

Rash

Through Week 48, rash AEs occurred in 84 subjects (26.2%) in the EFV 400 mg group and 99 subjects (32%) in the EFV 600 mg group. Table 17 summarizes rash (all grades) that occurred in at least 1% of subjects (by preferred term) in either group regardless of causality.

Table 17: Grade 1-4 rash observed in ≥ 1% in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321) N (%)	EFV 600 mg (n=309) N (%)
# of subjects with Grade 1-4 AE, n (%)	84 (26.2)	99 (32.0)
Rash	41 (12.8)	57 (18.4)
Pruritus	6 (1.9)	8 (2.6)
Eczema	7 (2.2)	6 (1.9)
Dermatitis allergic	5 (1.6)	6 (1.9)
Rash papular	5 (1.6)	7 (2.3)
Rash maculo-papular	4 (1.2)	7 (2.3)
Rash pruritic	3 (0.9)	4 (1.3)
Rash macular	1 (0.3)	5 (1.6)

Rash generalized	4 (1.2)	1 (0.3)

Reviewer Comment
As illustrated in Table 17, the main difference (by preferred term) between treatment groups was that rash (18.4% vs. 12.8%) occurred more frequently at EFV 600 mg vs. EFV 400 mg. By preferred term, other rash AEs were generally similar in both treatment groups or were slightly higher at EFV 600 mg.

As summarized in Table 18, Grade 2-4 rash occurred in 29 subjects (9%) in the EFV 400 mg group and 8 subjects (12.9%) in the EFV 600 mg group through Week 48.

Table 18: Grade 2-4 rash observed in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 2-4 AE, n (%)	29 (9.0)	40 (12.9)
Rash	16 (5.0)	26 (8.4)
Rash maculo-papular	4 (1.2)	5 (1.6)
Rash generalized	2 (0.6)	1 (0.3)
Pruritus	2 (0.6)	1 (0.3)
Generalized erythema	2 (0.6)	0
Photosensitivity reaction	1 (0.3)	0
Rash morbilliform	1 (0.3)	0
Rash papular	1 (0.3)	0
Skin lesion	1 (0.3)	0
Rash erythematous	0	2 (0.6)
Rash macular	0	2 (0.6)
Rash pruritic	0	1 (0.3)
Rash vesicular	0	1 (0.3)
Dermatitis	0	1 (0.3)
Drug eruption	0	1 (0.3)
Dry skin	0	1 (0.3)
Eczema	0	1 (0.3)
Dermatitis allergic	3 (0.9)	2 (0.6)
Stevens-Johnson syndrome	1 (0.3)	1 (0.3)
Urticaria	0	2 (0.6)

As summarized in Table 19, Grade 3-4 rash occurred in 3 subjects (0.9%) in the EFV 400 mg group and 8 subjects (2.6%) in the EFV 600 mg group through Week 48.

Table 19: Grade 3-4 rash observed in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 3-4 AE, n (%)	3 (0.9)	8 (2.6)
Rash	0	2 (0.6)
Rash maculo-papular	1 (0.3)	3 (1.0)
Rash morbilliform	1 (0.3)	0

Drug eruption	0	1 (0.3)
Dry skin	0	1 (0.3)
Dermatitis allergic	0	1 (0.3)
Stevens-Johnson syndrome	1 (0.3)	0

Reviewer Comment
The majority of rash AEs were mild (Grade 1) to moderate (Grade 2). Overall, no new safety signals were identified through 48 weeks in ENCORE1.

Through Week 48, discontinuations due to rash occurred in 3 subjects (0.9%) in the EFV 400 mg group and 10 subjects (3.2%) in the EFV 600 mg group. Please see Section 7.3.3 for additional information on discontinuations due to AEs.

In summary, rash AEs were more common at EFV 600 mg compared to EFV 400 mg.

Nervous system disorders
FDA analyses differ from the Applicant's analyses because the Applicant did not include dizziness in its analyses of nervous system disorders.

Through Week 48, nervous system AEs occurred in 127 subjects (39.6%) in the EFV 400 mg group and 149 subjects (48.2%) in the EFV 600 mg group. Table 20 summarizes nervous system AEs (all grades) that occurred in at least 1% of subjects (by preferred term) in either group regardless of causality.

Table 20: Grade 1-4 nervous system AEs observed in ≥1% in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 1-4 AE, n (%)	127 (39.6)	149 (48.2)
Dizziness	85 (26.5)	108 (34.9)
Headache	35 (10.9)	34 (11.0)
Paresthesia	2 (0.6)	4 (1.3)
Hypoesthesia	2 (0.6)	3 (1.0)

Reviewer Comment
Dizziness occurred more frequently at EFV 600 mg vs. EFV 400 mg (34.9% vs. 26.5%); otherwise, the distribution of nervous system AEs was generally similar in both treatment groups.

As summarized in Table 21, the main difference between treatment groups was that Grade 2-4 dizziness occurred more frequently at EFV 600 mg vs. EFV 400 mg (9.1% vs. 5.6%).

Table 21: Grade 2-4 nervous system AEs in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 2-4 AE, n (%)	23 (7.2)	35 (11.3)
Dizziness	18 (5.6)	28 (9.1)
Headache	4 (1.2)	9 (2.9)

Convulsion	1 (0.3)	0
Balance disorder	0	1 (0.3)

As summarized in Table 22, Grade 3-4 nervous system AEs were relatively uncommon, occurring in 4 subjects (1.2%) in the EFV 400 mg group and 8 subjects (2.6%) in the EFV 600 mg group through Week 48.

Table 22: Grade 3-4 nervous system AEs in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 3-4 AE, n (%)	4 (1.2)	8 (2.6)
Dizziness	3 (0.9)	5 (1.6)
Headache	0	3 (1.0)
Convulsion	1 (0.3)	0

Reviewer Comment
The majority of nervous system AEs were mild (Grade 1) to moderate (Grade 2). Overall, no new safety signals were identified through 48 weeks in ENCORE1.

Through Week 48, discontinuations due to nervous system AEs occurred in 2 subjects (0.6%) in the EFV 400 mg group and 1 subject (0.3%) in the EFV 600 mg group. Please see Section 7.3.3 for additional information on discontinuations due to AEs.

In summary, dizziness was more common at EFV 600 mg compared to EFV 400 mg.

Psychiatric disorders
Through Week 48, psychiatric AEs occurred in 79 subjects (24.6%) in the EFV 400 mg group and 76 subjects (24.6%) in the EFV 600 mg group. Table 23 summarizes psychiatric AEs (all grades) that occurred in at least 1% of subjects (by preferred term) in either group regardless of causality.

Table 23: Grade 1-4 psychiatric AEs observed in ≥ 1% in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 1-4 AE, n (%)	79 (24.6)	76 (24.6)
Abnormal dreams	28 (8.7)	35 (11.3)
Insomnia	20 (6.2)	20 (6.5)
Depression	10 (3.1)	5 (1.6)
Somnolence	10 (3.1)	12 (3.8)
Sleep disorder	7 (2.2)	4 (1.3)
Nightmare	6 (1.9)	8 (2.6)
Anxiety	4 (1.2)	4 (1.3)

Reviewer Comment
Abnormal dreams occurred more frequently at EFV 600 mg vs. EFV 400 mg (11.3% vs. 8.7%); otherwise, the distribution of psychiatric AEs was generally similar in both treatment groups.

As summarized in Table 24, Grade 2-4 psychiatric AEs were overall comparable between treatment groups.

Table 24: Grade 2-4 psychiatric AEs observed in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 2-4 AE, n (%)	25 (7.8)	24 (7.8)
Insomnia	8 (2.5)	11 (3.6)
Abnormal dreams	5 (1.6)	6 (1.9)
Depression	6 (1.9)	4 (1.3)
Somnolence	2 (0.6)	3 (1.0)
Anxiety	4 (1.2)	0
Sleep disorder	3 (0.9)	0
Poor quality sleep	1 (0.3)	0
Nightmare	0	2 (0.6)
Confusional state	1 (0.3)	0
Hallucination	1 (0.3)	0
Depressed mood	1 (0.3)	1 (0.3)
Lethargy	1 (0.3)	1 (0.3)
Mood swings	0	1 (0.3)
Intentional self-injury	0	1 (0.3)
Libido decreased	1 (0.3)	0
Stress	0	1 (0.3)
Suicidal ideation	1 (0.3)	0

As summarized in Table 25, Grade 3-4 psychiatric AEs were relatively uncommon, occurring in 4 subjects (1.2%) in the EFV 400 mg group and 3 subjects (1%) in the EFV 600 mg group through Week 48.

Table 25: Grade 3-4 psychiatric AEs observed in either treatment group at Week 48

Preferred Term	EFV 400 mg (n=321)	EFV 600 mg (n=309)
	N (%)	N (%)
# of subjects with Grade 3-4 AE, n (%)	4 (1.2)	3 (1.0)
Depression	3 (0.9)	1* (0.3)
Insomnia	1 (0.3)	1 (0.3)
Lethargy	0	1 (0.3)
Intentional self-injury	0	1* (0.3)

*Occurred in the same subject

Reviewer Comment
The majority of psychiatric AEs were mild (Grade 1) to moderate (Grade 2). Overall, no new safety signals were identified through 48 weeks in ENCORE1.

Through Week 48, discontinuations due to psychiatric AEs occurred in 1 subject (0.3%) in the EFV 400 mg group and 1 subject (0.3%) in the EFV 600 mg group. Please see Section 7.3.3 for additional information on discontinuations due to AEs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Through Week 48, a total of 2355 AEs (all grades, regardless of causality) were reported in 559 subjects. The number of AEs was overall similar between treatment groups:

- 1173 AEs in 286 (89.1%) subjects in the EFV 400 mg group
- 1182 AEs in 273 (88.3%) subjects in the EFV 600 mg group

Table 26 summarizes all AEs that occurred in at least 4% of subjects (by preferred term) in either group regardless of causality. Multiple AEs were counted only once per subject for each preferred term.

Table 26: Common AEs (all grades) in ≥ 4% in either treatment group through Week 48

System Organ Class Preferred Term	EFV 400 mg (n=321) N (%)	EFV 600 mg (n=309) N (%)
# of subjects experiencing any AE, n (%)	286 (89.1)	273 (88.3)
Gastrointestinal AEs	92 (28.7)	98 (31.7)
Diarrhea	33 (10.3)	36 (11.7)
Nausea	14 (4.4)	22 (7.1)
Vomiting	9 (2.8)	15 (4.9)
General disorders	44 (13.7)	47 (15.2)
Pyrexia	13 (4.0)	14 (4.5)
Fatigue	10 (3.1)	14 (4.5)
Infections and Infestations	180 (56.1)	153 (49.5)
Upper respiratory tract infection	57 (17.8)	36 (11.7)
Nasopharyngitis	26 (8.1)	18 (5.8)
Influenza	18 (5.6)	17 (5.5)
Gastroenteritis	17 (5.3)	13 (4.2)
Nervous system disorders	127 (39.6)	154 (49.8)
Dizziness	85 (26.5)	107 (34.6)
Headache	35 (10.9)	34 (11.0)
Psychiatric disorders	79 (24.6)	76 (24.6)
Abnormal dreams	28 (8.7)	35 (11.3)
Insomnia	20 (6.2)	20 (6.5)
Respiratory system	37 (11.5)	31 (10.0)
Cough	19 (5.9)	19 (6.1)
Skin and Subcutaneous tissue	84 (26.2)	99 (32.0)
Rash	41 (12.8)	57 (18.4)

The majority of AEs were mild (Grade 1). Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 27.

Table 27: Selected treatment-emergent AEs (Grades 2 to 4) in ≥ 2% in either treatment group through Week 48

System Organ Class Preferred Term	EFV 400 mg (n=321) N (%)	EFV 600 mg (n=309) N (%)
# of subjects experiencing any Grade 2-4 AE, n (%)	148 (46.1)	145 (45.2)
Gastrointestinal AEs	25 (7.8)	28 (8.7)
Diarrhea	7 (2.2)	8 (2.5)
Vomiting	2 (0.6)	6 (1.9)
General disorders	18 (5.6)	8 (2.5)
Pyrexia	6 (1.9)	2 (0.6)
Infections and Infestations	60 (18.7)	51 (15.9)
Upper respiratory tract infection	9 (2.8)	4 (1.2)
Nasopharyngitis	8 (2.5)	6 (1.9)
Herpes zoster	8 (2.5)	4 (1.2)
Gastroenteritis	6 (1.9)	7 (2.2)
Nervous system disorders	23 (7.2)	35 (11.3)
Dizziness	18 (5.6)	28 (9.1)
Headache	4 (1.2)	9 (2.9)
Psychiatric disorders	25 (7.8)	24 (7.8)
Abnormal dreams	5 (1.6)	6 (1.9)
Insomnia	8 (2.5)	11 (3.6)
Respiratory system	4 (1.2)	2 (0.6)
Skin and Subcutaneous tissue	29 (9.0)	40 (12.9)
Rash	29 (9.0)	40 (12.9)

Reviewer Comment
Dizziness and rash were the only two Grade 2-4 AEs with more than a 2% difference between treatment groups. Please see Section 7.3.5 for additional analyses. Overall, no new safety signals were identified through 48 weeks in ENCORE1.

7.4.2 Laboratory Findings

Laboratory results were reviewed for each subject to identify abnormal values which met the definitions for Grade 3 and 4 events based on the DAIDS Toxicity Grading Scale.

Table 28: Grade 3-4 Laboratory Abnormalities in ≥ 2% in either treatment group through Week 48

Laboratory parameter	EFV 400 mg (n=321) N (%)	EFV 600 mg (n=309) N (%)
ALT	16 (5.0)	9 (2.9)
AST	7 (2.2)	6 (1.9)
Total bilirubin	1 (0.3)	9 (2.9)
Cholesterol	7 (2.2)	14 (4.5)
Neutrophils	5 (1.6)	9 (2.9)
Phosphorus	7 (2.2)	9 (2.9)

Reviewer comment
Overall, few Grade 3-4 laboratory abnormalities were reported through Week 48. In addition, the overall number of subjects reporting Grade 3-4 laboratory abnormalities at Week 48 was low (i.e. <2%) in both treatment groups for renal parameters, hematologic parameters, and glucose.

Lipids
Through Week 48, lipid changes were overall comparable between treatment groups:

- Of 624 subjects with median baseline total cholesterol of 159 mg/dL, mean total cholesterol increased by 17 mg/dL in the EFV 400 mg group and by 20 mg/dL in the EFV 600 mg group.
- Of 604 subjects with median baseline LDL cholesterol of 159 mg/dL, mean LDL cholesterol increased by 7 mg/dL in the EFV 400 mg group and by 9 mg/dL in the EFV 600 mg group.
- Of 609 subjects with median HDL cholesterol of 39 mg/dL, mean HDL cholesterol increased by 9 mg/dL in the EFV 400 mg group and by 10 mg/dL in the EFV 600 mg group.
- Of 624 subjects with median baseline triglycerides of 94 mg/dL, mean triglycerides increased by 7 mg/dL in the EFV 400 mg group and by 7 mg/dL in the EFV 600 mg group.

Renal
Through Week 48, changes in creatinine were overall comparable between treatment groups. Of 630 subjects with a median baseline creatinine of 0.8 mg/dL, mean serum creatinine decreased by 0.004 mg/dL in the EFV 400 mg group and increased by 0.01 mg/dL in the EFV 600 mg group. These changes were not clinically meaningful.
- Only one subject (in the EFV 600 mg group) reported a Grade 3/4 creatinine abnormality.

Reviewer comment
Overall, no new pattern of laboratory abnormalities appears evident from review of the datasets and supporting documents. FDA analysis of the laboratory data concurs with the Applicant's overall analysis.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse, temperature) and weight were measured at all visits. Clinically significant changes from baseline (Screening visit) were recorded as AEs. No clinically significant changes were noted.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained during the study.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The safety findings for EFV 400 mg compared to EFV 600 mg are described in the above sections of the safety review. EFV 400 mg QD dosing was not associated with an increase in SAEs, discontinuations due to AEs, Grade 3 or 4 AEs, or laboratory abnormalities compared to EFV 600 mg QD dosing.

7.5.2 Time Dependency for Adverse Events

Through Week 48, a lower proportion of subjects (8.1%) in the EFV 400 mg group discontinued study drug compared to the EFV 600 mg group (11.0%). The difference between treatment groups was not statistically significant.

7.5.3 Drug-Demographic Interactions

No significant drug-demographic interactions were appreciated in this study. The occurrence of AEs was similar between age groups and gender.

7.5.4 Drug-Disease Interactions

Treatment of HIV-1 infection with combination ART reduces viral load and maintains viral suppression.

7.5.5 Drug-Drug Interactions

Formal drug-drug interaction studies were not conducted. Please refer to the Clinical Pharmacology Review for a full discussion of the PK of this product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

New studies have not been performed and are not needed.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy and breastfeeding were exclusion criteria in ENCORE1. There were a total of six pregnancies through Week 48:

- Among EFV 400 mg recipients, there were two pregnancies: one resulted in a live male with no birth defects; one resulted in a live female with no birth defects.
- Among EFV 600 mg recipients, there were four pregnancies: one resulted in a spontaneous abortion; one resulted in an induced abortion; one resulted in a live female with no birth defects; and one resulted in a live infant but no other data was available.

7.6.3 Pediatrics and Assessment of Effects on Growth

New studies have not been performed and are not needed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Abrupt cessation/withdrawal of 3TC and/or TDF could cause a hepatic flare in patients co-infected with hepatitis B.

7.7 Additional Submissions / Safety Issues

No additional concerns.

8 Postmarket Experience

This FDC has not yet been approved for marketing in any country and there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

No literature references are attached to this review.

9.2 Labeling Recommendations

The proposed Package Insert (PI or label) is being reviewed by all disciplines. Labeling discussions are ongoing and the recommendations have not been finalized at the time of this review. Below are general clinical recommendations for proposed labeling:

1) The indication statement should be revised as follows:

(b) (4)

(b) (4)

2) (b) (4)

Therefore, the labeling was revised (b) (4)

3) In Section 5.8 (nervous system disorders), FDA analyses differ from the Applicant's proposed information because the ENCORE1 analyses did not include (b) (4) as a component of nervous system disorders.

4) The labeling was also revised to display the ENCORE1 safety and efficacy results in a similar format consistent with other HIV labeling. Additionally, for consistency with FDA guidance for development of antiretroviral drugs for treatment of HIV-1 infection (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf), efficacy results are evaluated using the primary endpoint of HIV-RNA < 50 copies/mL.

Please refer to the Cross DisciplineTeam Leader/Division Director Memo by Dr. Jeffrey Murray for detailed labeling recommendations.

9.3 Advisory Committee Meeting

No advisory Committee Meeting was held for this application.

9.4 Financial Disclosure

The ENCORE1 clinical investigators have no financial interests/arrangements with the Applicant.

Was a list of clinical investigators provided:	Yes √	No ☐ (Request list from applicant)
Total number of investigators identified: 37		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None *(note: The clinical study was not performed under a US IND and thus Forms FDA 3455 were not collected from clinical investigators.)*		
If there are 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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes √	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes √	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1 *(note: One Form 3454 was submitted by the University of New South Wales on behalf of the ENCORE1 clinical investigators.)*		
Is an attachment provided with the reason:	Yes √	No ☐ (Request explanation from applicant)

There are no financial issues that affect the approvability of this application.

9.5 Efficacy Analysis Memorandum for the Discrepancy

Reviewers found discrepancies in terms of the efficacy endpoints. Comments for the sponsor were sent on December 23, 2016, and the sponsor responded on January 27, 2017. However, the sponsor's responses did not adequately answer the questions raised by the reviewer. For completeness, a summary of these discrepancies along with the reviewer's final decision regarding these discrepancies is listed here. The overall conclusions remain unchanged.

1. Efficacy endpoints:

The efficacy review was based on the datasets submitted in SN0006 on Jul. 11, 2016. There were two datasets, VLD and BOTH, under the analysis subfolder for the viral load, VLD contained viral load data for the efficacy analyses, and BOTH contained both local and central viral load data.

The sponsor confirmed that raw central viral load data was not submitted in SN0006. When the reviewer evaluated the datasets submitted in SN0005 on May 31, 2016, there was a dataset named **VLD** under the analysis subfolder. This dataset contained the

central viral load data even though the sample date variable is not available. The sponsor confirmed and stated that the Week 48 viral load data for some subjects who missed Week 48 visits were imputed by their Week 36 viral load data.

The reviewers found Week 48 visit viral load data for six subjects ([redacted] (b) (6)) in the **VLD** dataset under SN0005 as listed below:

	SUBJECTI (b) (6)	RAND	VLD	week
1		2	240470	48
2		2	39	48
3		2	45	48
4		2	39	48
5		1	39	48
6		1	94	48

- For the first four subjects [redacted] (b) (6) the VL values for Week 48 were the same as the VL values for Week 36, and their VL values for Week 60 were missing. The VL of Week 48 may have been carried over from Week 36. These four outcomes were counted as failures since there were no VL data within the analysis window.
- For subject [redacted] (b) (6) the VL value at Week 48 was the same as the VL at Week 36 with a value of 39. However, the Week 60 VL data was available, and VL value was 40. The subject was counted as a success.
- For subject [redacted] (b) (6) the VL at Week 48 was 94 and the VL at Week 36 was 39. These values contradict the applicant's explanation of carry-over values. This subject was counted as a failure.

Additionally, there were three subjects, [redacted] (b) (6) who were hard-coded to failure for the primary efficacy endpoint, in the SAS program named **VLD_SAS.txt**. The applicant responded that the hard coding was according to the protocol. However, the reviewer found the explanation to be inadequate as the protocol did not include any provision for hard coded efficacy results.

The VLs for these three subjects are:

- [redacted] (b) (6) had VL=139 at Week 48 and VL=3291 at Week 60. The subject was classified as failure for <50 c/mL while Success for <200 c/mL;
- [redacted] (b) (6) had VL=524 at Week 48 and VL=87 at Week 60. The subject was classified as failure for <50 c/mL while Success for <200 c/mL;
- [redacted] (b) (6) had VL=50 at Week 48 (local VL=40) and VL=40 at Week 60. The subject was classified as success for <50 c/mL while Success for <200 c/mL;

As a result, for the efficacy endpoint of the proportion of subjects with plasma HIV RNA < 50 c/mL at Week 48 in the mITT population, there is difference with respect to one subject between the reviewer's and sponsor's primary efficacy results as shown below:

- Subject (b) (6) the VL at Week 48 was 50 and 40 at Week 60, will be counted as a success;

For Subject (b) (6) the VL at Week 48 was 50, which was counted as a success by the applicant. The reviewer did not have any concern with the applicant's conclusion for Subject (b) (6)

For the efficacy endpoint of the proportion of subjects with plasma HIV RNA < 200 c/mL at Week 48 in the mITT population, there were differences for three subjects between the reviewer's and sponsor's efficacy results. One subject was already listed above in addition to two more subjects listed below:

- Subject (b) (6), the VL at Week 48 was 94and counted as a success;
- Subject the VL at Week 48 was 139and counted as a success for <200 c/mL;

2. Disposition:

There were 7 subjects who were hard-coded to lost to follow-up in the code submitted in disposition_sas.txt in the disposition analysis. However, 5 of these 7 subjects had discontinuation reason as "participate withdrew consent". The sponsor did not adequately answer questions regarding hard coding, and hence the reviewer's results are used in the review. The difference was that those five subjects were classified as "withdrew consent" instead of "lost-to-follow".

The sponsor's disposition table is provided below for comparison with the FDA reviewer's disposition table in the review (see Table 4, Section 6.1.3):

Subgroup	EFV400	EFV600	Total
N	321	309	630
Attended Wk48	311(96.9%)	295(95.5%)	606(96.2%)
Did not Attended Wk4	10(3.1%)	14(4.5%)	24(3.8%)
Reasons of NOT completed treatment			
Died	2(0.6%)	3(1.0%)	5(0.8%)
Lost to follow up	4(1.2%)	3(1.0%)	7(1.1%)
Missing week 48	1(0.3%)	5(1.6%)	6(1.0%)
Withdrew	3(0.9%)	3(1.0%)	6(1.0%)

9.6 Subgroup Analyses of Primary/Secondary Efficacy Endpoint by Sites

Overall, no clinically meaningful discrepancies were identified by site (Tables 29 and 30 generated by the FDA reviewer).

Table 29: Primary Efficacy Endpoint (<50 c/mL) Results by Sites at Week 48

Efficacy Parameter	EFV400	EFV600	Total
Treated (ITT)			
N	276/321(86.0)	261/309(84.5)	537/630(85.2)
Site			
(0102)	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
(0103)	2 / 2 (100)	2 / 2 (100)	4 / 4 (100)
(0111)	2 / 3 (66.7)	2 / 2 (100)	4 / 5 (80.0)
(0112)	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
(0121)	2 / 2 (100)	. / . (.)	2 / 2 (100)
(0123)	4 / 5 (80.0)	4 / 4 (100)	8 / 9 (88.9)
(0127)	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
(0131)	2 / 3 (66.7)	3 / 3 (100)	5 / 6 (83.3)
(0152)	4 / 4 (100)	2 / 3 (66.7)	6 / 7 (85.7)
(0201)	2 / 2 (100)	4 / 5 (80.0)	6 / 7 (85.7)
(0206)	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
(0207)	9 / 11 (81.8)	6 / 11 (54.5)	15 / 22 (68.2)
(0208)	. / . (.)	2 / 2 (100)	2 / 2 (100)
(0209)	5 / 6 (83.3)	4 / 6 (66.7)	9 / 12 (75.0)
(0210)	7 / 7 (100)	5 / 5 (100)	12 / 12 (100)
(0215)	2 / 3 (66.7)	2 / 3 (66.7)	4 / 6 (66.7)
(0217)	5 / 5 (100)	4 / 4 (100)	9 / 9 (100)
(0301)	10 / 10 (100)	9 / 10 (90.0)	19 / 20 (95.0)
(0302)	2 / 3 (66.7)	1 / 1 (100)	3 / 4 (75.0)
(0401)	3 / 3 (100)	1 / 3 (33.3)	4 / 6 (66.7)
(0402)	7 / 8 (87.5)	8 / 8 (100)	15 / 16 (93.8)
(0601)	8 / 10 (80.0)	6 / 7 (85.7)	14 / 17 (82.4)
(0602)	6 / 6 (100)	3 / 5 (60.0)	9 / 11 (81.8)
(0802)	5 / 7 (71.4)	5 / 5 (100)	10 / 12 (83.3)
(0803)	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
(0901)	8 / 10 (80.0)	3 / 6 (50.0)	11 / 16 (68.8)
(0903)	5 / 5 (100)	5 / 5 (100)	10 / 10 (100)
(1001)	3 / 3 (100)	3 / 3 (100)	6 / 6 (100)
(1201)	29 / 33 (87.9)	33 / 36 (91.7)	62 / 69 (89.9)
(1202)	10 / 12 (83.3)	9 / 11 (81.8)	19 / 23 (82.6)
(1207)	11 / 14 (78.6)	13 / 16 (81.3)	24 / 30 (80.0)
(1301)	18 / 20 (90.0)	19 / 20 (95.0)	37 / 40 (92.5)
(1401)	8 / 12 (66.7)	7 / 11 (63.6)	15 / 23 (65.2)
(2001)	23 / 24 (95.8)	25 / 26 (96.2)	48 / 50 (96.0)
(2002)	19 / 20 (95.0)	17 / 20 (85.0)	36 / 40 (90.0)
(2003)	23 / 31 (74.2)	25 / 31 (80.6)	48 / 62 (77.4)
(2101)	16 / 20 (80.0)	15 / 19 (78.9)	31 / 39 (79.5)
(2103)	10 / 11 (90.9)	7 / 9 (77.8)	17 / 20 (85.0)

Table 30: One of Secondary Efficacy Endpoint (<200 c/mL) Results by Sites at Week 48

Efficacy Parameter	EFV400	EFV600	Total
Treated (ITT)			
N	303/321(94.4)	287/309(92.9)	590/630(93.7)
Site			
(0102)	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
(0103)	2 / 2 (100)	2 / 2 (100)	4 / 4 (100)
(0111)	2 / 3 (66.7)	2 / 2 (100)	4 / 5 (80.0)
(0112)	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
(0121)	2 / 2 (100)	. / . (.)	2 / 2 (100)
(0123)	4 / 5 (80.0)	4 / 4 (100)	8 / 9 (88.9)
(0127)	1 / 1 (100)	2 / 2 (100)	3 / 3 (100)
(0131)	3 / 3 (100)	3 / 3 (100)	6 / 6 (100)
(0152)	4 / 4 (100)	2 / 3 (66.7)	6 / 7 (85.7)
(0201)	2 / 2 (100)	5 / 5 (100)	7 / 7 (100)
(0206)	2 / 2 (100)	1 / 1 (100)	3 / 3 (100)
(0207)	11 / 11 (100)	9 / 11 (81.8)	20 / 22 (90.9)
(0208)	. / . (.)	2 / 2 (100)	2 / 2 (100)
(0209)	5 / 6 (83.3)	5 / 6 (83.3)	10 / 12 (83.3)
(0210)	7 / 7 (100)	5 / 5 (100)	12 / 12 (100)
(0215)	3 / 3 (100)	2 / 3 (66.7)	5 / 6 (83.3)
(0217)	5 / 5 (100)	4 / 4 (100)	9 / 9 (100)
(0301)	10 / 10 (100)	10 / 10 (100)	20 / 20 (100)
(0302)	3 / 3 (100)	1 / 1 (100)	4 / 4 (100)
(0401)	3 / 3 (100)	2 / 3 (66.7)	5 / 6 (83.3)
(0402)	7 / 8 (87.5)	8 / 8 (100)	15 / 16 (93.8)
(0601)	9 / 10 (90.0)	6 / 7 (85.7)	15 / 17 (88.2)
(0602)	6 / 6 (100)	5 / 5 (100)	11 / 11 (100)
(0802)	7 / 7 (100)	5 / 5 (100)	12 / 12 (100)
(0803)	1 / 1 (100)	1 / 1 (100)	2 / 2 (100)
(0901)	10 / 10 (100)	4 / 6 (66.7)	14 / 16 (87.5)
(0903)	5 / 5 (100)	5 / 5 (100)	10 / 10 (100)
(1001)	3 / 3 (100)	3 / 3 (100)	6 / 6 (100)
(1201)	32 / 33 (97.0)	36 / 36 (100)	68 / 69 (98.6)
(1202)	12 / 12 (100)	11 / 11 (100)	23 / 23 (100)
(1207)	13 / 14 (92.9)	15 / 16 (93.8)	28 / 30 (93.3)
(1301)	20 / 20 (100)	20 / 20 (100)	40 / 40 (100)
(1401)	10 / 12 (83.3)	7 / 11 (63.6)	17 / 23 (73.9)
(2001)	23 / 24 (95.8)	25 / 26 (96.2)	48 / 50 (96.0)
(2002)	20 / 20 (100)	18 / 20 (90.0)	38 / 40 (95.0)
(2003)	27 / 31 (87.1)	29 / 31 (93.5)	56 / 62 (90.3)
(2101)	17 / 20 (85.0)	17 / 19 (89.5)	34 / 39 (87.2)
(2103)	10 / 11 (90.9)	8 / 9 (88.9)	18 / 20 (90.0)

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