CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical and Biometrics Review

Date	June 20, 2011
From	Yodit Belew, M.D. / Fraser Smith, Ph.D.
Subject	Clinical Reviewer / Biometrics Reviewer
NDA/BLA # Supplement#	202123 (000)
Applicant	Gilead Sciences
Date of Submission	February 10, 2011
PDUFA Goal Date	August 10, 2011
Proprietary Name / Established (USAN) names	Complera Emtricitabine/Rilpivirine/tenofovir DF FDC (FTC/RPV/TDF)
Dosage forms / Strength	Single tablet containing 200mg/25mg/300mg of FTC/RPV/TDF
Proposed Indication(s)	A complete regimen for the treatment of HIV-1 infection in treatment-naïve adult patients
Recommended:	Approval

1. Introduction

Rilpivirine, an NNRTI developed by Tibotec Inc., was recently approved under NDA 202022 for the treatment of HIV-1 infection in treatment naive adult patients. Gilead has co-formulated rilpivirine with two NRTIs to create a fixed dose combination (FDC) drug product containing emtricitabine/rilpivirine/tenofovir DF (FTC/RPV/TDF). Of note, FTC/TDF is the preferred NRTI regimen by the DHHS treatment guidelines. Gilead submitted NDA 202123 containing two BA/BE studies and one relative BA study. No new clinical safety and efficacy trials were conducted by Gilead using the FDC product. Cross reference was made to the clinical trials (TMC278-C209 and TMC278-C215) conducted by Tibotec to the support the safety and efficacy of rilpivirine which is contained in this FDC drug product. Therefore, the clinical safety and efficacy data are the same for NDAs 202022 and 202123. The safety and efficacy results presented in this review are for subset of subjects who received tenofovir and emtricitabine as background regimen. This clinical review presents the main findings for rilpivirine (RPV) in combination with FTC/TDF, highlighting safety, efficacy and overall risk/benefit assessment to support my recommendation for approval for NDA 202123. References are also made to Gilead's emtricitabine and tenofovir NDAs to support safety and efficacy of FTC/TDF when used with other ARVs.

Although the fixed drug product under review contains three antiretroviral agents, limited discussions are included for emtricitabine and tenofovir as these NRTIs have been approved for market for several years. Emtricitabine was approved on July 2003 (Gilead's NDAs 21-500 for the capsule formulation) and on 28 September 2005 (Gilead's NDA 21-896 for an oral solution); Tenofovir was approved on 26 October 2001 (Gilead's NDA 21-356 for tablet formulation). Emtricitabine and tenofovir were also approved on 2 August 2004 for the treatment of HIV-1 infection in a FDC tablet product (Truvada®) (Gilead's NDA 21-752). Prescribers are familiar with the adverse reactions associated with the individual drugs. On the contrary, rilpivirine was approved for marketing on May 20, 2011, where knowledge of rilpivirine among prescribers is likely limited. Therefore, this clinical review focuses on the safety and efficacy of rilpivirine, when used in combination with tenofovir and emtricitabine. Please refer to the individual drug products reviews of tenofovir and emtricitabine for additional safety information.

Aside from the new BA/BE and BA studies linking the two formulations (FDC vs. individual drug products), no new additional clinical pharmacology data were submitted. As rilpivirine was bioequivalent when administered as a FDC product compared to the individual rilpivirine tablet formulation under fed conditions (400 kcal with 13 grams of fat),, reference is made to NDA 202022 for details on the

pharmacokinetics and pharmacodynamics of rilpivirine. Please refer to NDAs 21500 and 21356 for additional information on the pharmacokinetics of emtricitabine and tenofovir, respectively.

Reference is also made to the individual drug NDAs for details regarding pharmacology/toxicology as no new data are submitted under this NDA.

2. Background

The estimated number of people infected with HIV or AIDS worldwide is approximately 33 million, which pleads for continuing the need for development of new treatments. Currently available HIV treatment includes six different antiretroviral drug classes- comprised of over 25 single and fixed dose combinations. The drug classes include: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 receptor antagonists, and integrase inhibitors.

Emtricitabine, an NRTI, is a synthetic analog of the naturally occurring nucleotide, 2′-deoxycytidine, a pyrimidine nucleoside. Tenofovir DF, the oral prodrug of TFV, is an NtRTI. Both have been approved for treatment of HIV infection in combination with other ARVs.

Rilpivirine, an NNRTI developed by Tibotec, Inc is indicated for treatment of HIV-1 infection in combination with other ARV in antiretroviral treatment-naïve adult patients. Rilpivirine was the fifth and the latest NNRTI to be approved for treatment of HIV infection. Previously approved NNRTIs include efavirenz, nevirapine etravirine and delavirdine. This class of ARV has been used in clinical practice for over a decade. Adverse events from NNRTIs include neuropsychiatric events, liver toxicity, and rash. Teratogenicity is also a known side effect of efavirenz. Because NNRTIs are also substrates of CYP3A4 enzymes, these agents can interact with commonly prescribed drugs.

Rilpivirine was approved for treatment of HIV infection in treatment naïve adults on May 20, 2011. The approval was primarily supported by three clinical trials: one Phase 2 dose-finding and two Phase 3 trials, all conducted in treatment-naïve subjects. The Phase 2 trial (C204) is a dose comparison and active-control trial for 96 weeks, with long-term extension phase at the marketed dose (25 mg once daily) for up to 192 weeks. The two phase 3 trials (C209 and C215) are ongoing, randomized, double-blind, double-dummy, active controlled international trials and are identical in design. The active comparator in both trials is efavirenz. The two trials differ in the background regimen: C209 included a fixed regimen of tenofovir/emtricitabine; whereas, C215 included either abacavir/lamivudine, zidovudine/lamivudine or tenofovir/emtricitabine. The safety data from these three trials includes approximately 780 subjects treated at the marketed dose for at least 48 weeks in duration. Trials in treatment-experienced patients were not conducted and therefore, the indication is restricted to the treatment-naïve population.

Gilead has co-formulated FDC drug product using FTC/RPV/TDF. This new fixed-dose combination tablet represents a new complete regimen administered as a single tablet, taken once daily with a meal, for the treatment of HIV-1 infection in treatment naïve adults.

This NDA contains two referenced Phase 3 trials, conducted by Tibotec Inc. (C209 and C215). The safety and efficacy data submitted in support of traditional approval is from two 48 week trials in treatment naïve adults. Please refer to sections 7 and 8 for further details.

The FDA's draft guidance for industry on fixed dose combination and co-packaged drug products for treatment of HIV encourages sponsors to submit applications to the FDA for approval of fixed dose combination (FDC) and co-packaged versions of previously approved antiretroviral therapies. The guidance also states that priority review would likely be applicable to these products. This NDA received a priority 6 month review because the FDC represents a one tablet, once daily complete ARV regimen.

3. CMC

At the time of the completion of the clinical review for this NDA, establishment of the dissolution acceptance criteria was still under negotiation with the Applicant. In addition, inspection of drug manufacturing sites has not yet been completed and it is unclear at this time if all sites will have satisfactory status post inspections. Please refer to CMC review for additional details.

4. Nonclinical Pharmacology/Toxicology

Extensive programs of nonclinical studies with FTC, RPV, and TDF have been previously conducted. In view of the nonclinical safety profiles for each of these compounds, additional nonclinical combination safety studies with FTC, RPV and TDF are not considered necessary to support this application. Therefore, no new nonclinical pharmacology/toxicology data were submitted.

The preclinical evaluation of rilpivirine included over 55 trials to assess the safety pharmacology, pharmacokinetics, general toxicology, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and local tolerance in mice, rats, rabbits, dogs and cynomolgus monkeys. Please refer to NDA 202022 for full details.

Emtricitabine and tenofovir DF have been marketed since 2003 and 2001, respectively. Please refer to the individual drugs' NDAs for further details.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Stanley Au's Clinical Pharmacology Review for details.

Absorption, Food effects and Bioavailability

BA/BE Studies Using the FDC (FTC/RPV/TDF):

The Applicant conducted BA/BE studies to support the FDC drug product. Please refer to individual studies below for details. At the time of this clinical review, the long-term stability data of rilpivirine (when in combination with emtricitabine and tenofovir) has not yet been submitted.

Comparative BA and Bioequivalence Studies, Fed Conditions: Studies 101 and 103
The primary objective of Study 101 was to evaluate the bioequivalence of two fixed-dose combination tablets (each containing emtricitabine 200 mg, rilpivirine 25 mg, and tenofovir DF 300 mg) compared to a 200-mg capsule of emtricitabine, a 25-mg tablet of rilpivirine, and a 300-mg tablet of tenofovir DF taken concurrently under fed conditions. The results demonstrated that while emtricitabine and tenofovir exposures met the bioequivalence criterion in each FDC test formulation (FTC/RPV/TDF FDC Formulation 1 and FTC/RPV/TDF FDC Formulation 2) versus the individual drugs, rilpivirine exposures did not. Because the bioequivalence criterion could not be achieved for all 3 components of the FDC formulations, the study concludes that FTC/RPV/TDF FDC Formulation 1 and FTC/RPV/TDF FDC Formulation 2 are not bioequivalent to the reference treatment (individual components FTC+RPV+TDF administered concurrently).

The primary objective of Study 103 was to evaluate the bioequivalence of two fixed-dose combination (FDC) tablets, each containing emtricitabine (FTC) 200 mg, rilpivirine (RPV) 25 mg, and tenofovir disoproxil fumarate (TDF) 300 mg (FTC/RPV/TDF), compared to a 200-mg strength capsule of FTC, a 25-mg strength tablet of RPV, and a 300-mg strength tablet of TDF taken concurrently under fed conditions. The study demonstrated that the FTC/RPV/TDF FDC test formulation 3 is bioequivalent to concurrent administration of the individual components under fed conditions.

Relative BA Study, Fasted Condition: Study 108

The primary objective of Study 108 was to evaluate the relative BA of a FDC tablet (containing FTC 200 mg, RPV 25 mg, and TDF 300 mg) compared to a 200-mg strength capsule of FTC, a 25-mg tablet of RPV, and a 300-mg tablet of TDF taken concurrently under fasted conditions. The FDC tablet provided modestly higher exposures (~ 25% higher) of RPV compared to the individual components administered concurrently under fasted conditions; FTC and TFV exposures were comparable.

Individual drug products

Rilpivirine: The absorption of rilpivirine is pH-dependent; therefore medications that alter gastric pH can decrease rilpivirine exposures. Rilpivirine exposures are increased in the presence of food and the type of meal (high fat or standard meal) results in similar increased exposures. The exposure to rilpivirine is approximately 40% lower when taken in a fasted condition as compared to a normal caloric meal or high-fat high-caloric meal. Therefore, rilpivirine must be taken with food. This recommendation was used during the phase 3 trials.

Tenofovir: When comparing fasted to fed conditions, administration of tenofovir following a high-fat meal increases the oral bioavailability, with an increase in AUC of approximately 40% and an increase in Cmax of approximately 14%. However, a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to administration of the drug under fasted conditions.

Emtricitabine: Emtriva capsules and oral solution may be taken with or without food.

In summary, based on the individual drug profiles and the FDC drug profile, labeling recommendations for the FDC product is to administer with food.

Metabolism, Elimination, Half-life

Rilpivirine: CYP3A is the primary system responsible rilpivirine metabolism. CYP 2C19 also potentially contributes to metabolism of rilpivirine. Rilpivirine is eliminated via feces (85%) and urine (6%). The half-life of rilpivirine is approximately 50 hours thereby supporting once daily dosing. Please refer to reviews from NDA 202022 for additional details.

Tenofovir is eliminated primarily by renal excretion via glomerular filtration and tubular secretion. After intravenous administration of tenofovir in subjects with normal renal function, approximately 70% to 80% of the dose is recovered in urine as unchanged tenofovir within 72 hours of dosing.

Emtricitabine is also eliminated primarily by renal excretion through a combination of glomerular filtration and active tubular secretion. Approximately 65-70% of an oral dose of emtricitabine is recovered in urine as unchanged drug in subjects with normal renal function. Metabolism is a minor elimination pathway for FTC. Approximately 13% of an oral dose was recovered as metabolites, 12.9% in the urine and 0.01% in feces.

Dose Selection

The FDC product contains the approved doses of emtricitabine 200mg, rilpivirine 25 mg and tenofovir DF 300 mg [each tablet contains 200 mg of emtricitabine, 27.5 mg of rilpivirine hydrochloride (equivalent to 25 mg of rilpivirine), and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil) as active ingredients].

Drug-drug interactions (DDI)

Please refer to Dr. Stanley Au's Clinical Pharmacology Review for details. In summary no new DDI studies were conducted using the FDC drug product. Summaries are provided highlighting the major DDI for the individual drugs:

Rilpivirine

Rilpivirine is primarily metabolized by CYP 3A, and drugs that induce or inhibit CYP3A may affect the rilpivirine exposures. Co-administration of rilpivirine with other drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance and cross resistance to the class of NNRTIs. Likewise, co-administration of rilpivirine and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance. Given these issues, several drugs are contraindicated including:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampin, rifapentine
- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone (more than a single dose)
- St John's wort (*Hypericum perforatum*)

Rilpivirine at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes. Please refer to NDA 202022 Clinical Pharmacology Review by Dr. Au's for further details.

Given the effect on QTc interval at supratherapeutic doses (75 mg and 300 mg), rilpivirine should be used with caution when given with a drug with a known risk of Torsade de Pointes.

Tenofovir and Emtricitabine are considered to have a low potential for cytochrome P450-mediated interactions based on the results of in vitro experiments and the known renal elimination pathways of both agents. Since both agents are primarily renally excreted, there is potential for interaction with other drugs that are similarly eliminated. Drugs that decrease renal function may also increase serum concentrations of these agents.

In summary, based on various DDI studies for the individual drugs the following recommendation are included in the FTC/RPV/TDF FDC label:

- Use of the FDC tablet is contraindicated with drugs that significantly decrease rilpivirine plasma concentrations, which may result in loss of virologic response and possible resistance and cross-resistance
- Use of the FDC tablet should be used with caution with drugs that increase gastric pH
- Use of the FDC tablet should be used with caution when given with a drug with a known risk of Torsade de Pointes
- Use of the FDC tablet should be avoided with current or recent use of nephrotoxic drugs

FDC drug product
This FDC drug product is indicated in HIV-1 infected, treatment *naïve* population only and provides a complete, one-pill, once-daily regimen for the treatment of HIV-1 infection. Therefore, it is highly unlikely that it would be co-administered with other HIV antiretroviral medications. Thus information regarding potential drug-drug interactions with other antiretroviral medications does not need to be included in the

FDC label. Instead, a statement referring providers to prescribing information for the individual drug products- rilpivirine, tenofovir and emtricitabine has been recommended to be included in the label.

Thorough QT study or other QT assessment

Rilpivirine
Rilpivirine prolongs the QT interval at doses of 75 mg or higher. At the recommended dose of 25 mg once daily, the maximum mean time-matched difference in QTcF interval from placebo was 4.8 milliseconds, which is below the threshold of regulatory concern. At supratherapeutic doses of 75 mg and 300 mg once daily, the maximum mean time-matched differences in QTcF interval from placebo was 10.7 and 23.3 milliseconds, respectively. The potential QTc prolongation, hepatic impairment and drug-drug interaction issues with concomitantly administered drugs metabolized by CYP enzymes are reflected in the rilpivirine label.

Tenofovir and Emtricitabine have no known effect on the QTc interval.

Critical intrinsic factors: age, gender, hepatic insufficiency and renal impairment.

Rilpivirine
Rilpivirine exposures were not affected by age, gender, race, body weight or co-infection with HBV or HCV. Of note only three subjects greater than 65 years of age were enrolled in the phase 3 trials; therefore definitive conclusions can not be made with regard to age over 65 years. No data are available for severe hepatic impairment. In subjects with mild hepatic impairment rilpivirine Cmax and AUC increased by 27% and 47%, respectively. Based on exposure-safety data, no dose adjustment is necessary for mild or moderate hepatic impairment. Based on population PK analysis, minimal changes in rilpivirine exposures were observed in subjects with mild renal impairment; only seven subjects in the phase 3 trials had moderate renal impairment. In addition, rilpivirine is minimally excreted renally. Rilpivirine is not expected to have clinically significant impact for subjects with moderate renal impairment; therefore no dose adjustment is required.

Tenofovir and Emtricitabine: The pharmacokinetics of FTC and TDF are similar in male and female subjects. The pharmacokinetics of FTC or TFV have not been evaluated in subjects > 65 years old. In subjects with mild renal impairment, the pharmacokinetics of TFV and FTC are not substantially altered to warrant dose adjustment. Emtricitabine is not significantly metabolized by liver enzymes; the pharmacokinetics of FTC have not been studied in hepatically-impaired subjects. The pharmacokinetics of tenofovir were studied in non-HIV-1 infected subjects with varying degrees of hepatic impairment (Child-Pugh classification). Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment compared with unimpaired subjects.

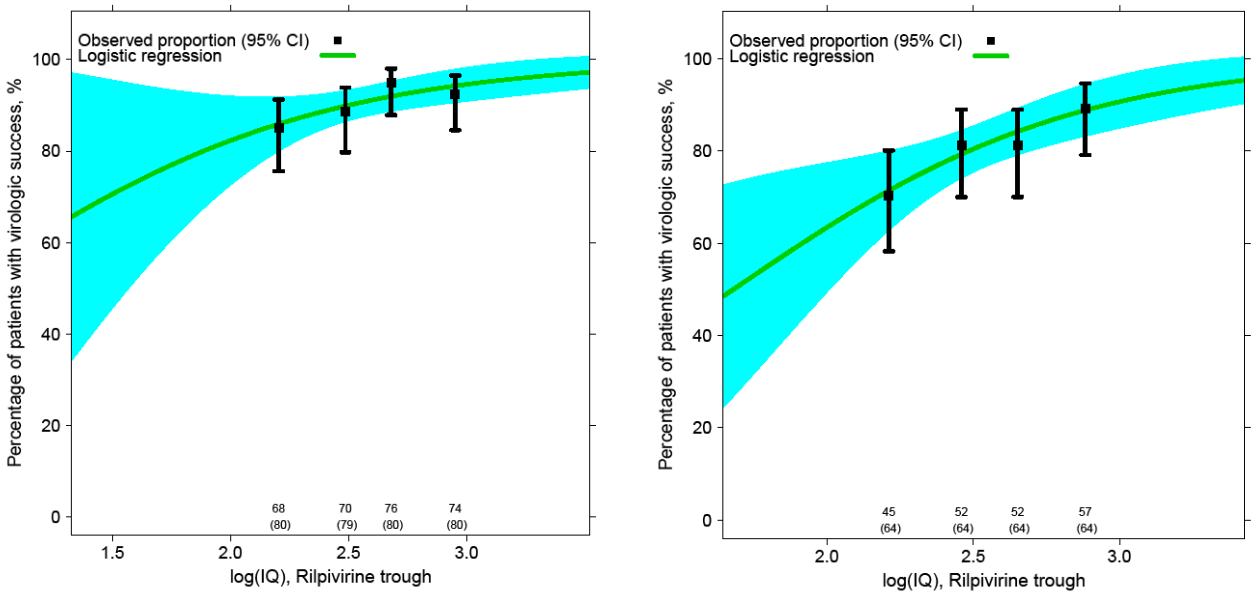
In summary, because the FDC drug product cannot be dose adjusted, any dose adjustment requirement for any of the individual drug products should be reflected on the FDC drug product. Therefore, the labeling recommendations for the FDC drug product FTC/RPV/TDF will include information that it should not be prescribed for patients requiring dosage adjustment such as those with moderate, severe or end stage renal impairment (creatinine clearance below 50 mL per minute).

Exposure-response and Exposure-safety analyses

Rilpivirine
Please refer to reviews of NDA 202022 for details on the exposure-response and exposure-safety analyses. Exposure-response analysis was conducted by the FDA to evaluate the relationship between baseline viral load, exposure (C_{trough}) and virologic success (Figure 1). Subjects with self-reported compliance <90% were removed from the exposure-response analysis as these patients are assumed to have lower rilpivirine exposure that is driven by a failure to properly follow the dosing schedule as opposed to pharmacokinetic variability. The analysis demonstrated that for subjects with baseline HIV-1

RNA >100,000 copies/mL, an increase in exposure would result in a greater percentage increase in patients achieving virologic success; alternatively, subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL would attain less benefit from an exposure increase. Although an exposure-response relationship was observed, therapeutic drug monitoring and dose adjustment are not recommended as rilpivirine has a narrow therapeutic window due to its known effect on QT interval at higher exposures. However, conditions that may result in decreased rilpivirine exposure (intake without food, co-administration with exposure-lowering drugs including drugs that lower gastric pH) should be minimized to prevent underdosing. This information is contained in the Contraindications Section of the label.

Figure 1: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus $\log_{10}$(IQ) for Patients with Baseline Viral Load <100,000 (left) and ≥100,000 Copies/mL (right) from the Phase 3 (C209 and C215) trials.



Additionally, no exposure–response relationship was seen for psychiatric, skin, dizziness or hepatobiliary events.

The labeling for the FDC drug product should contain the same contraindications as those listed for the individual drug, rilpivirine.

6. Clinical Microbiology

Rilpivirine

Please refer to clinical and virology reviews of NDA 202022 for additional details. In addition to the important genotypic and phenotypic changes that emerged in rilpivirine-treated subjects with virologic failure, cross-resistance to the NNRTI class is likely after virologic failure with rilpivirine. The emergence of resistance was greater in the rilpivirine group compared to the EFV group- 41% (38/92) of the virologic failures in the rilpivirine group had genotypic and phenotypic evidence of rilpivirine resistance compared to 25% (15/60) of the virologic failures in the EFV group who developed efavirenz resistance. Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine-containing regimen- 38 rilpivirine failure subjects had evidence of rilpivirine resistance. Of these patients, 89% (n=34) were resistant to etravirine and efavirenz, and 63% (n=24) were resistant to nevirapine. In the EFV group, none of the 15 EFV-resistant virologic failures were resistant to etravirine or rilpivirine at

failure; all were resistant to nevirapine. In addition, phenotypic resistance to a background (BR) drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in 48% (44/92) of the subjects in the rilpivirine group compared to 15% (9/60) in the EFV group.

These data suggest the ability to use a subsequent NNRTI, specifically etravirine whose indication is for subjects with HIV-1 strains resistant to an NNRTI and other ARVs, is limited. This significant information is included in the label (Use and Indication Section and Microbiology Section).

Tenofovir: Please refer to NDA 21-356 and to the USPI for additional details. In treatment naïve subjects treated with tenofovir +lamivudine + efavirenz (Study 901), genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently. The K65R substitution occurred in 8/47 (17%) analyzed patient isolates. Of the 8 subjects whose virus developed K65R, 7 occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to tenofovir were not identified in this study. In Study 934 of treatment-naïve subjects (tenofovir + emtricitabine + efavirenz), genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently. The M184V substitution, associated with resistance to emtricitabine, was observed in 2/19 analyzed subject isolates. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis. The K65R substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine

Emtricitabine: Please refer to NDA 21-500 and to the USPI for additional details. Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study of treatment-naive patients treated with emtricitabine, didanosine, and efavirenz (Study 301A), viral isolates from 37.5% of patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene. In a clinical study of treatment-naive patients treated with either emtricitabine, tenofovir, and efavirenz (Study 934), resistance analysis was performed on HIV isolates from all virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 48 or early discontinuations. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17%) analyzed patient isolates in the emtricitabine plus tenofovir-treated group. Through 48 weeks of Study 934, no patients have developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis. Cross-resistance among certain nucleoside analog reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine).

The FDC drug product should reflect all the pertinent microbiology points discussed above.

7. Clinical/Statistical- Efficacy

No efficacy trial was conducted using the FDC drug product. The efficacy of rilpivirine, the anchor drug for the FDC, was established based on the pooled efficacy analyses from trials C209 and C215. Please refer to NDA 202022 for details on trial design attributes, demographics, baseline characteristics and results. This review focuses on the efficacy results on the subset of subjects who received FTC/TDF as background regimen.

Briefly, The long-term (≥ 48 Weeks) safety and efficacy of rilpivirine was evaluated in HIV-1 infected, treatment naïve adults in two Phase 3 trials and one Phase 2 trial. In all trials, efavirenz (EFV) was used as the active comparator. The Phase 3 trials were identical in study design with exception of the background regimen (BR). Therefore, pooled analysis of efficacy was conducted. In trial TMC278-C209, only tenofovir (TDF) + emtricitabine (FTC) were allowed for construction of the background regimen. In TMC278-C215, three options were available: TDF/FTC, zidovudine (AZT)/lamivudine (3TC), or abacavir (ABC)/3TC. The BR could be taken as individual drugs or as a FDC product, if available. Most (60%) of subjects in C215 received TDF/FTC; 30% received AZT/3TC, and 10% received ABC/3TC. Overall, 80% of subjects enrolled in the two Phase 3 trials received TDF/FTC as background regimen. Both trials were stratified by baseline viral load (strata were ≤100,000; >100,000 to ≤500,000; and >500,000 copies/ml). Stratification by background regimen was also included for trial C215.

The primary efficacy endpoint was defined as HIV-1 RNA <50 copies/mL at Week 48. The FDA's snapshot algorithm was utilized for calculating the primary endpoint. In the pooled Phase 3 trials, the proportion of subjects with viral load <50 copies/mL was 83% for rilpivirine and 80% for EFV. Although the overall proportion of non-responders was comparable between the two groups, more subjects discontinued due to virologic failure in the rilpivirine group (5% vs. 2%), while more subjects discontinued due to adverse events in the EFV group (2% vs. 7%). Among subjects with baseline HIV-1 RNA >100,000 copies/mL, virologic failure rate was higher in rilpivirine treated group when compared to EFV group, 22% vs. 13%, respectively.

Demographics and Baseline Characteristics

The intent to treat population (ITT) for the pooled Phase 3 trials included 1368 subjects, 686 of whom received rilpivirine and 682 received EFV. Baseline characteristics, including gender, race and age were comparable between the two groups. The majority of the participants were male (75%) and Caucasians (60%). Hispanic ethnicity was represented equally between the two groups, 13% in the rilpivirine group and 14% in the EFV group. Most subjects were recruited in the USA. The median baseline viral load was 90,450 copies/mL in the rilpivirine group and 104,500 copies/mL in the EFV group.

Table 1 summarizes the demographic and baseline characteristics of the subset of subjects who received FTC/TDF as background regimen.

Table 1 Demographics and Baseline Characteristics of Subjects Receiving FTC/TDF

	C209		C215		Pooled	
	Rilpivirine N=346	EFV N=344	Rilpivirine N=204	EFV N=202	Rilpivirine N=550	EFV N=546
Gender n (%)						
Male	268 (77)	275 (80)	161 (79)	156 (77)	429 (78)	431 (79)
Female	78 (23)	69 (20)	43 (21)	46 (23)	121 (22)	115 (21)
Race n (%)						
White	214 (62)	206 (60)	134 (66)	128 (63)	348 (64)	334 (61)
Black	89 (26)	80 (23)	45 (22)	48 (24)	134(24)	128(23)
Asian	33 (10)	48 (14)	21 (10)	22 (11)	54 (10)	70 (13)
Other	10 (2)	10 (2)	4 (2)	4(2)	12 (2)	14 (3)
Age (years)*						
Median (min, max)	36 (18-78)	36 (19-67)	36 (20-62)	38 (19-69)	36 (18-78)	36 (19-69)
Plasma HIV- 1 RNA n (%)						
Median (min, max)	94950 (156-3300000)	105000 (1010-3360000)	90700 (1480-20800000)	117000 (1140-2830000)	93850 (156-20800000)	108500 (1010-3360000)
≤100,000	181(52)	163(47)	107(52)	93 (46)	288(52)	256(47)

>100,000-≤500,000	131(38)	134(39)	78(38)	85(42)	209(38)	219(40)
>500,000	34(10)	47(12)	19(9)	24(12)	53(10)	71(13)
CD4+ Cell Count						
Median (min, max)	240 (1-888)	257 (1-757)	267 (2-744)	272 (1-857)	247 (1-888)	261 (1-857)
Clinical stage of HIV infection at screening						
CDC Category A	249(72)	242(70)	141(69)	139(69)	390(71)	382(70)
CDC Category B	83(24)	79(23)	48(24)	51(25)	131(24)	130(24)
CDC Category C	14(4)	23(7)	15(7)	12(6)	29 (5)	35(6)

*Investigators at German sites were not required to enter birth date information (as per the local regulations). Therefore age was not calculated for some subjects, all of whom were from C215 (30 subjects from rilpivirine arm and 28 subjects from EFV arm).
Source: Dataset DMAD

Statistical Methodology

The efficacy analysis for the subset of subjects who received FTC/TDF as background regimen was conducted jointly with the Division of Biostatistics. Below is a summary of trials C209 and C215, conducted by Dr. Frasier Smith, statistical reviewer. I concur with his analysis and conclusions in supporting the establishment of the efficacy of rilpivirine when used in combination with FTC plus TDF.

Statistical methodology for the Primary Efficacy Analysis used by the Statistical Reviewer

The primary efficacy parameter was the proportion of subjects with plasma viral load < 50 copies/ml at Week 48 (Snapshot Algorithm). A non-inferiority margin for rilpivirine compared with control was provided for a maximum allowable difference of 12%. A p-value for superiority of rilpivirine compared with control was also provided where non-inferiority was achieved.

The primary efficacy variable in the primary population (ITT) was also compared between rilpivirine and control at the Week 48 time point, adjusted using baseline log10 plasma viral load as a dichotomous categorical variable (≤100,000 copies/mL vs. >100,000 copies/mL). The adjusted risk difference for rilpivirine relative to control was calculated along with the associated 95% CI based on the stratum-adjusted Mantel-Haenszel (MH) proportions for the rilpivirine and control arm using a continuity-corrected estimate of the variance of the stratum-adjusted difference in proportions.

Virologic failure rates were also compared in the subset of patients with baseline HIV RNA viral loads > 100,000 copies/mL using Fisher's exact test.

Results and Conclusions

Trial C209 and C215 Combined

Snapshot results for the label for NDA 202123 were nearly the same as results for NDA 202022 except for a slightly smaller number of subjects in each treatment arm due to the exclusion of subjects in study TMC278-C215 who were not using Truvada as their optimized background regimen.

The efficacy results of this trial demonstrated non-inferiority of rilpivirine vs. control in regard to virologic response, viral load results < 50 copies/mL at Week 48 (primary efficacy parameter) with a pre-defined non-inferiority margin of 12%. The results of the primary efficacy analysis were supported by primary and secondary efficacy results from NDA 202022.

Using the snapshot algorithm the proportion of virologic response at week 48 was 83% for the rilpivirine treatment group and 81% for the control group. The unadjusted risk difference between the proportion of rilpivirine and EFV responders was +1.8% with a 95% confidence interval of (-2.8%, +6.4%). The

adjusted risk difference between the proportion of rilpivirine and EFV responders was +1.1% with a 95% confidence interval of (-3.4%, +5.7%).

Since the lower bound of the 95% C.I. was > -12%, non-inferiority of rilpivirine to EFV was concluded for the primary endpoint. The non-inferiority conclusion was also supported by numerous analyses in NDA 202022.

Table 2: Virologic Outcome of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 (Pooled subjects with background regimen TDF/FTC) at Week 48

	Rilpivirine + TDF/FTC N=550	**Efavirenz + TDF/FTC N=546**
HIV-1 RNA < 50 copies/mL*	454 (83%)	441 (81%)
Virologic failure†	71 (13%)	43 (8%)
No virologic data at Week 48 window		
Reasons		
Discontinued study due to adverse event or death‡	12 (2%)	40 (7%)
Discontinued study for other reasons and last available HIV-1 RNA < 50 copies/mL (or missing)§	10 (2%)	20 (4%)
Missing data during window but on study	3 (1%)	2 (< 1%)
HIV-1 RNA < 50 copies/mL by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	257/288 (89%)	219/256 (86%)
> 100,000 to ≤ 500,000	162/209 (78%)	171/219 (78%)
> 500,000	35/53 (66%)	51/71 (72%)
Virologic failure† by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	14/288 (5%)	7/256 (3%)
> 100,000 to ≤ 500,000	41/209 (20%)	23/219 (11%)
> 500,000	16/53 (30%)	13/71 (18%)

N = total number of subjects per treatment group
† Includes subjects who had ≥ 50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL, and subjects who had a switch in background regimen that was not permitted by the protocol.
‡ Includes subjects who discontinued due to an adverse event or death if this resulted in no on-treatment virologic data in the Week 48 window.
§ Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.
Note: Analysis was based on the last observed viral load data within the Week 48 window (Week 44-54).

Analysis based on the sponsor's Snapshot algorithm.

Compared to subjects in the efavirenz treatment arm, virologic failure rates were significantly higher in rilpivirine subjects for the subgroup of subjects with baseline viral loads > 100,000 copies/mL (p=0.004).

This finding is similar to what was seen for the overall population enrolled into the Phase 3 trials, C209 and C215 (Table 3). Rilpivirine was non-inferior to EFV, regardless of background regimen. The proportions of subjects with viral load <50 copies/mL in rilpivirine and EFV groups were 83% and 80%, respectively. More subjects discontinued rilpivirine due to virologic failure; conversely, more subjects

discontinued EFV due to adverse events. Virologic response to rilpivirine appears to be influenced primarily by baseline HIV-1 RNA. The response rate for subjects with higher baseline viral load (HIV-1 RNA >100,000 copies/mL) was lower than the rate observed in subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL. The response rate was even lower in a subgroup of subjects with baseline HIV-1 RNA >500,000 copies/mL. However the number of subjects with baseline HIV-1 RNA >500,000 copies/mL is insufficient to make definitive statistical conclusions.

Table 3: Virologic Outcome of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 (Pooled Data) at Week 48

	Rilpivirine + BR N=686	**Efavirenz + BR N=682**
HIV-1 RNA < 50 copies/mL*	83%	80%
Virologic failure†	13%	9%
No virologic data at Week 48 window		
Reasons		
Discontinued study due to adverse event or death‡	2%	7%
Discontinued study for other reasons and last available HIV-1 RNA < 50 copies/mL (or missing)§	2%	3%
Missing data during window but on study	1%	< 1%
HIV-1 RNA < 50 copies/mL by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	89%	83%
> 100,000 to ≤ 500,000	78%	78%
> 500,000	65%	73%
Virologic failure† by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	5%	5%
> 100,000 to ≤ 500,000	20%	11%
> 500,000	29%	17%

N = total number of subjects per treatment group * CI = Predicted difference (95% CI) of response rates is 2.0 (-2.1; 6.1) † Includes subjects who had ≥ 50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL, and subjects who had a switch in background regimen that was not permitted by the protocol. ‡ Includes subjects who discontinued due to an adverse event or death if this resulted in no on-treatment virologic data in the Week 48 window. § Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc. Note: Analysis was based on the last observed viral load data within the Week 48 window (Week 44-54).

In summary, rilpivirine, when used in combination with TDF/FTC, is efficacious for treatment of HIV-1 infection in treatment naïve subjects. However, the efficacy results are influenced by baseline viral load. These facts should be considered when treatment is initiated with FTC/RPV/TDF FDC drug product. Therefore, the FDC drug product Package Insert reflects these limitations under the Usage and Indications Section, Contraindications Section, Warnings and Precautions Section and Clinical Studies Section.

Furthermore, the development of cross-resistance to the NNRTI class among rilpivirine treated virologic failure subjects is also communicated in the Usage and Indications Section and Microbiology Section.

8. Safety

Emtricitabine and tenofovir have been marketed for several years. The safety profiles of these drugs are well known when used in combination with other ARVs. Rilpivirine is a new ARV, approved in May 2011 and the focus of the safety review for this NDA will highlight adverse reactions associated with rilpivirine. Pooled safety data from the Phase 3 controlled trials (C209 and C215) were used to support approval of rilpivirine. Safety results from subset of subjects who received FTC/TDF as background regimen are presented in this NDA. Please refer to NDA 202022 review for extensive discussions on the safety and tolerability of rilpivirine when used in combination with ARVs.

Please refer to emtricitabine and tenofovir NDAs for discussions on the safety and tolerability of these NRTIs.

General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Rilpivirine

For the overall population enrolled, the number of subjects who discontinued treatment with rilpivirine or efavirenz due to an adverse drug reaction, regardless of severity, was 2% and 4%, respectively. Among subjects receiving FTC/TDF as background N(t)RTI, discontinuation due to AEs remained higher in the efavirenz group (8% vs. 3%.) The most common adverse drug reactions leading to discontinuation were psychiatric disorders 1% in the rilpivirine group and 2% in the efavirenz group.

In the overall population enrolled, a total of five subjects died during the 48 week treatment period in C209 and C215, one in the rilpivirine group (bronchopneumonia) and four in the efavirenz group. The death in the rilpivirine group did not appear to be drug related; FTC/TDF was used to construct the background regimen. See NDA 202022 for detailed discussion.

Among subjects treated with FTC/TDF, the most common SAE was Infection/Infestation (2% in each group). Serious hepatobililary disorders and renal disorders were reported more frequently in the rilpivirine group compared to the efavirenz group. Five rilpivirine treated subjects experienced a hepatobiliary event compared to one efavirenz treated subject. Cholecystitis/cholethiasis have been included in the rilpivirine label, under less common adverse reactions. Three subjects were reported to have serious renal adverse events (acute renal failure, ureter calculus, and membranous glomerulonephritis) while no serious renal adverse events were reported for the efavirenz group. Refer to the sections below for discussion on renal events, hepatotoxicity and laboratory results.

Among subjects treated with FTC/TDF, the majority of adverse events were grade 1 or 2 in severity. Among subjects receiving either rilpivirine or efavirenz in combination with FTC/TDF, similar proportions of subjects experienced at least 1 AE during treatment with rilpivirine (90%) or efavirenz (92%). The most commonly reported adverse events (all cause, all severity) with rilpivirine were headache (14%), diarrhea (13%), nausea (12%) and nasopharyngitis (12%). Events considered at least possibly, probably or likely related to drug and at least moderate in severity are summarized in the table below.

In summary, the treatment-emergent adverse drug reactions in the subset of subjects who received FTC/TDF as background regimen were similar between treatment groups or within 1-2% difference. Dizziness, abnormal dreams and rash were reported more frequently in the efavirenz group. The majority of these events did not lead to discontinuation.

The incidence of ADRs is also similar between the subset of subjects who received FTC/TDF versus the overall population enrolled into C209 and C215.

Table 4 Selected Treatment-Emergent Adverse Drug Reactions of at least Moderate Intensity* (Grades 2-4) Occurring in at Least 2% of Antiretroviral Treatment-Naïve HIV-1 Infected Adult Subjects

	Rilpivirine + (TDF/FTC) N=550	Efavirenz + (TDF/FTC) N=546	Rilpivirine + BR N=686	Efavirenz + BR N=682
Gastrointestinal Disorders				
Nausea	4 (<1%)	13(2%)	1%	3%
Abdominal pain	2(<1%)	3(<1%)	1%	2%
Vomiting	2(<1%)	6(1%)	1%	2%
General Disorders and Administration Site				
Conditions				
Fatigue	4(<1%)	5(<1%)	1%	2%
Nervous System Disorders				
Headache	9(2%)	12(2%)	3%	3%
Dizziness	4(<1%)	37(7%)	1%	7%
Psychiatric Disorders				
Depressive disorders†	8(1%)	12(2%)	4%	3%
Insomnia	11(2%)	12(2%)	3%	3%
Abnormal dreams	6(1%)	15(3%)	1%	4%
Skin and Subcutaneous Tissue Disorders				
Rash	11(2%)	49(9%)	3%	11%

N=total number of subjects per treatment group, BR=background regimen
Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
† includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation

Special Safety Concerns:

Based on the preclinical profile and known toxicities for the NNRTI drug class, the safety evaluation for rilpivirine included rash, neuropsychiatric disorders, hepatobiliary disorders, renal disorders, adrenal disorders and cardiac events.

Rash (in subjects who received FTC/TDF as background regimen)

The group term 'rash' was defined to contain any preferred terms containing 'rash' (e.g. rash vesicular, rash erythematous, rash generalized, rash macular, rash maculopapular, drug rash), 'drug eruption', 'blister', 'exfoliation', 'bullous dermatitis' 'dermatitis, 'erythema', urticaria, pruritis, pruritis generalized, and prurigo. The majority of the rashes were grade 1 or 2 in severity and only three rilpivirine treated subjects had a grade 3 rash compared to six in the efavirenz group. No grade 4 rash in the rilpivirine group was reported. Most of the rashes in the rilpivirine group occurred within the first four weeks of treatment, with median duration of 18 days. Rilpivirine had less rash compared to efavirenz (13% vs. 25% for all cause, all severity; 2% vs. 9% for $\geq$ grade 2 and treatment related). All of the above events were reported with similar incidence in the overall population enrolled in the two Phase 3 trials (i.e. regardless of background regimen). An exposure-response relationship was not seen for rash in the rilpivirine group and only one rilpivirine treated subject discontinued the phase 3 trial for rash (vs. 11 efavirenz treated subjects).

Neurologic and psychiatric disorders (in subjects who received FTC/TDF as background regimen)

Neuropsychiatric events have been commonly reported with use of NNRTIs (e.g. efavirenz). More subjects treated with efavirenz (47%) developed a neurologic event (all cause, all severity) compared to rilpivirine (31%). The major difference for this system organ class was dizziness. The incidence of dizziness (all cause, all severity) was approximately 3 times higher in the efavirenz group (28%) compared to the rilpivirine group (10%). Headache (all cause, all severity) was similar between treatment groups (approximately 14% in each group). Somnolence (all cause, all severity) was 3% in the rilpivirine group compared to 6% in the efavirenz group. The incidence reported for neurological disorders are similar to what was reported for the overall population enrolled in C209 and C215.

Psychiatric events (all cause, all severity) were reported in 25% for rilpivirine and 32% of efavirenz treated subjects. The main differences between the two treatment groups were abnormal dreams (7% vs. 11%) and anxiety (3% vs. 6%). Unlike abnormal dreams and anxiety disorders, the incidence of depressive disorders (all cause, all severity) was higher in the rilpivirine group (8% vs. 6% in the EFV group). The grouped term 'depressive disorders' includes depression, major depression, depressed mood, dysphoria, mood altered, negative thoughts, suicidal thoughts and suicidal ideation. One subject in the rilpivirine group had a grade 4 event- major depression which led to treatment discontinuation. [Of note, another rilpivirine treated subject who did not receive FTC/TDF also had a grade 4 event (suicide attempt)]. An additional subject treated with rilpivirine plus FTC/TDF attempted suicide and was discontinued from treatment. Discontinuation due to depressive disorders was similar between the two groups (4 subjects in each group). An exposure-response relationship was not observed for depressive disorder events. The incidence of psychiatric events reported in subset of subjects who received FTC/TDF as background regimen was similar to the overall population enrolled in C209 and C215.

Hepato-biliary events (in subjects who received FTC/TDF as background regimen)

NNRTIs have been associated with hepatotoxicity, especially nevirapine which has a Box Warning for this event. Therefore, the hepatic related events and laboratory abnormalities were selected as adverse events of special interest and reviewed in detail. Treatment emergent adverse hepatic reactions were similar between the two treatment groups (2% each). The events reported in the rilpivirine group include hepatomegaly, cholelithiasis, biliary colic, acute cholecystitis, hepatic pain and hepatitis. Grade 3 and 4 events occurred <1% in each group (2 subjects in rilpivirine group and 5 subjects in efavirenz group). No Hy's Law cases were identified. An exposure-response relationship was not seen for hepatic events.

Apparent imbalance in biliary events was observed between the two groups, with greater incidence occurring in the rilpivirine group (7 rilpivirine vs. 2 efavirenz). No exposure-response relationship was established for these events. Nonetheless, excluding a causal relationship between cholelithiasis and rilpivirine is very difficult as no analysis of the stones has been provided.

Based on the analysis of the laboratory datasets, the incidence of grade 3 and 4 increases in ALT and AST were 2% or less for rilpivirine. The incidence of grade 1 and 2 ALT and AST elevations were numerically higher in the efavirenz group compared to the rilpivirine group.

In summary, the incidence of hepatobiliary events observed in the subset of subjects treated with FTC/TDF as background regimen is similar to what was observed in the overall pooled analysis of C209 and C215.

Renal events (in subjects who received FTC/TDF as background regimen)

An early, preclinical signal of renal effect was observed for rilpivirine when administered at high doses. The AE analysis was performed by selecting all preferred AE terms in system organ class 'renal or

urinary disorders'. Additionally, renal AEs were the further analyzed based on preferred AE terms, 'renal failure', 'acute renal failure', 'chronic renal failure', 'glomerulonephritis', 'increase blood creatinine', 'renal colic', 'nephrolithiasis', 'calculus', 'hematuria', 'proteinuria', Glycosuria, and 'chromaturia.

Overall, the incidence of 'renal and urinary' AEs (regardless of severity, causality) was 8% in the rilpivirine group vs. 6% in the EFV group. The incidence of 'renal' AEs was numerically higher in the rilpivirine group (e.g. renal colic and glomerulonephritis). A case of membranous glomerulonephritis and a case of mesagnioproliferative glomerulonephritis were reported with rilpivirine. A biopsy in the case of membranous glomerulonephritis suggested a drug-related event. The incidence of 'renal failure' was 0.5% in the rilpivirine group and 0.4% in the efavirenz group. . No cases required dialysis or led to death. With the exception of glomerulonephritis, all cases of renal AEs in the rilpivirine group had resolved.

Serum Creatinine *(in all subjects enrolled in C209 and C215)*
An increase in serum creatinine (SCr) was observed with use of rilpivirine. This increase was regardless of background regimen used to construct complete regimen for HIV treatment. Please refer to NDA 202022 Clinical Review, Pharmacometrics Review and Division of Renal and Cardiovascular Consultation Review for details. The analysis presented for SCr is not limited to FDC/TDF background due to the limited number of subjects available for analysis. At Week 24, the mean SCr change from baseline was 0.19 mg/dL (0-0.7) for rilpivirine and 0.13 mg/dL (0 - 5.4) for efavirenz. The mean maximum SCr was 1.04 mg/dL (0.53-1.8) for rilpivirine compared to 0.97 (0.6, -6.2) for efavirenz. Table 5 also summarizes the results for the final reported SCr while receiving drug and at a follow-up visit after treatment discontinuation. Note, few subjects had follow-up SCr readings at the time of the analysis.

Table 5 Serum Creatinine at Baseline, Last Visit While on Treatment and at Follow-up Visit

All Subjects		
	Rilpivirine + BR N= 686	Efavirenz + BR N=673
Mean baseline serum creatinine (mg/dL)	0.85	0.85
Mean last visit serum creatinine while on treatment (mg/dL)	0.94	0.87
Difference between mean last visit serum creatinine (mg/dL)	0.09	0.02
Sub-group of Subjects with Follow-up Readings		
	Rilpivirine + BR N= 61	Efavirenz + BR N=61
Mean baseline serum creatinine (mg/dL)	0.86	0.86
Mean last visit serum creatinine while on treatment(mg/dL)	0.95	0.88
Difference between mean last visit serum creatinine (mg/dL)	0.09	0.02
Mean follow-up serum creatinine (mg/dL)	0.92	0.85
Difference between mean baseline and follow-up serum creatinine (mg/dL)	0.06	-0.01

Source: Consultation Review for NDA 202022 by Dr. Melanie Blank

Tibotec hypothesized the mechanism for the SCr changes was due to inhibition of creatinine tubular secretion and not frank nephrotoxicity. Tibotec conducted a cystatin C substudy in trial C215 to show no decline in eGFR when cystain C levels are used to estimate renal function. Overall eGFRcyst C did not decrease in either treatment group. On the contrary, an increase in mean eGFRcyst C at weeks 2 and 24 were seen; however, the increase was greater in the efavirenz group. This difference weakened the hypothesis that SCr was increased only due to tubular secretion.

Additional pharmacometrics analyses evaluated the effect of rilpivirine on creatinine clearance. The effect of rilpivirine on CrCL depended on the baseline CrCl- smaller changes were noted in subjects with lower baseline CrCL compared to those with normal baseline CrCl (Table 6). Subjects with moderate renal

function did not worsen over time and few patients transitioned to mild or moderate renal impairment during the trial. Almost all patients returned to baseline after treatment was stopped (2-4 weeks follow-up period). Again, the analysis presented for CrCL is not limited to FDC/TDF background due to limited number of subjects available for analysis. As previously stated, the background regimen used did not appear to impact these results.

Table 6 Mean Maximum Change in CrCL Grouped by Baseline Renal Function for Patients Treated with Rilpivirine 25 mg q.d. from C209 and C215

CrCL Category, mL/min	Count, n	Mean max change in CrCL, mL/min	Percent of Patients with two consecutive CrCL measurements indicating transition to worse renal function category
30-59 (moderate)	7	-5.9	0 (0/7)
60-90 (mild)	80	-12.5	9 (7/80)
>90 (normal)	596	-22.2	15 (87/596)

Source: Pharmacometrics Review NDA 202022 by Dr. Jeffry Florian

Adrenal events (in all subjects enrolled in C209 and C215)

During the pre-clinical studies, adrenal effects characterized by increased serum progesterone and decreased cortisol levels were observed in rats, dogs, monkeys and likely mice. The clinical data from C209 and C215 were reviewed in consultation with the Division of Metabolic and Endocrinology Products (DMEP). Please refer to the review by DMEP for NDA 202022 for additional details.

Briefly, an analysis was performed to evaluate trends in ACTH-stimulated cortisol values in patients who either had low levels at baseline or developed low levels during the course of the study. As a whole, subjects who had an abnormal ACTH stimulation test at baseline did not appear to have a worsening of their hypocortisolism over the 48-weeks in the Phase 3 trials, and in fact most had normal values for the remainder of the study. The results were less clear for subjects who had normal ACTH-stimulated cortisol values at baseline, but who subsequently had abnormal values later in the trial. Twenty three subjects (3.4% of the rilpivirine group) were identified to have a pattern of steady worsening of adrenal function over the course of the study. The majority of these patients (15/23, 65%) had mild, albeit sustained, decreases in ACTH-stimulated cortisol levels over a 48-week course while on rilpivirine. Of the 8 subjects who developed more profound hypocortisolism (drop in ACTH-stimulated cortisol of >200 nmol//L), one was discontinued from the trial due to new-onset irritability, anxiety, and sleep disturbances, which may be consistent with the clinical effects of adrenal insufficiency.

In summary, adrenal suppression was identified early in the pre-clinical developmental stage. The clinical data from the Phase 3 trials did not conclusively identify a clear case of adrenal insufficiency, but the laboratory data suggested a small change in mean basal cortisol level. Therefore, because HIV-1 infected patients are at risk population for adrenal insufficiency (independent of exposure to rilpivirine), the Package Insert (Adverse Events Section) includes information with regards to potential effect of rilpivirine on adrenal function.

QTc Interval

Rilpivirine has a positive effect on the QTc interval at supra-therapeutic (e.g. 75 mg, 300mg qd) doses. Therefore, cardiac events were considered adverse events of special interest due to the positive thorough QT study. A “worse-case scenario” analysis conducted by the Clinical Pharmacology group evaluated potential drug-drug interactions that may increase the exposure of a 25mg rilpivirine dose. Refer to Clinical Pharmacology and Pharmacometrics review for details. Based on these evaluations, rilpivirine at the 25 mg dose should not lead to exposure that could potentially prolong the QTc interval beyond 10 msec. However, in the Warnings and Precautions, Drug Interactions subsection, reference is

made to exercise caution when co-administering rilpivirine with a drug with a known risk of Torsade de Pointes.

Laboratory

The following are selected laboratory toxicities to be included in the FDC label. Overall, the incidence reported for this subgroup of subjects is similar to what was reported for the overall population enrolled in trials C209 and C215. Refer to NDA 202022 for additional analysis.

n(%)	Rilpivirine + TDF/FTC N=550	Efavirenz + TDF/FTC N=546	Rilpivirine + BR N=686	Efavirenz+ BR N=682
AST worst grade toxicity (%)				
G1	13	17	15	18
G2	3	6	3	6
G3	2	2	2	2
G4	<1	<1	<1	1
ALT worst grade toxicity (%)				
G1	16	19	15	17
G2	4	6	4	7
G3	1	2	1	2
G4	1	1	1	1
TB worst grade toxicity (%)				
G1	5	<1	5	<1
G2	2	<1	3	<1
G3	<1	<1	1	<1

Source: NDA 202022 Datasets

Please refer to Gilead's NDA for tenofovir and emtricitabine for laboratory findings during clinical trials. As reflected in the USPIs, the following laboratory abnormalities have been previously reported in patients treated with emtricitabine or tenofovir with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities included increased bilirubin (>2.5 x ULN), increased or decreased serum glucose (<40 or >250 mg/dL), increased creatine kinase (M:>990 U/L; F:>845 U/L), increased serum amylase (>175 U/L), increased hematuria (>75 RBC/HPF), increased alkaline phosphatase (>550 U/L), decreased neutrophils (<750/mm3), and increased glycosuria (≥3+).

Safety Summary

Rilpivirine Among the principle safety issues identified for rilpivirine include prolongation of the QT interval at supratheraputic doses; increase in serum creatinine over time; and a small decrease in basal cortisol and attenuation of cortisol response to ACTH. Similar to other NNRTIs, rilpivirine is also associated with psychiatric adverse reactions, including depressive disorders, insomnia and abnormal dreams. Despite these limitations, rilpivirine appears to have some advantage over efavirenz for the following reasons: fewer subjects discontinued treatment due to adverse events, and fewer subjects developed rash, dizziness and somnolence. Fewer grade 1-4 increases in ALT and AST were also seen in rilpivirine treated subjects compared to efavirenz. The adverse reactions identified with use of rilpivirine can be managed with routine HIV care. Additional safety monitoring with postmarketing surveillance is in effect.

Emtricitabine and Tenofovir have been approved for several years and their safety profiles have been well established. Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir with other antiretroviral agents in clinical trials include arthralgia, increased cough, dyspepsia, fever, vomiting, myalgia, pain, abdominal pain, back pain, paresthesia, sinusitis, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia,

rhinitis, and nasopharyngitis. Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

As highlighted in the labels, lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue these drugs.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir. Creatinine clearance should be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients who are at risk for renal impairment.

With use of tenofovir, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip. BMD monitoring should be considered for HIV-1 infected patients who have a history of pathologic bone fracture or other risk factors for osteoperosis or bone loss. The effects of tenofovir -associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have also been reported.

In conclusion, the safety of the individual drugs for this FDC drug product has been established. No unique new safety signal is expected due to new formulation (i.e. FDC). Continued postmarketing pharmacovigilance with the use of the new formulation is recommended.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Pediatric trials with rilpivirine, as well as with tenofovir are ongoing. A deferral has been requested for studies in pediatric patients using the FDC product until dosing recommendation are available for the individual drugs across the age groups.

Rilpivirine Tibotec was issued a written request to evaluate rilpivirine from birth to < 18 years of age. The goal of the trials is to match the pharmacokinetics in children compared to adults and provide supporting safety and activity data. Please also refer to PMR discussion. As mentioned in section 4, the adrenal findings may be of concern for pediatric development and could led to changes in growth, pubertal status, breast development, menarache or evidence of hirsutism or delayed adrenarche. In the ongoing and planned trials in children, endocrine monitoring is included and is closely monitored to document any of these changes.

Tenofovir has been approved for use in pediatric patients 12 years of age and above. Study results in pediatric patients 2 to 12 years of age are currently pending.

Emtricitabine has been approved for use in children 3 months of age and older. There is an outstanding PMC to evaluate emtricitabine in children birth to 3 months of age.

11. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

12. Labeling

- **Physician Labeling**

The following section was successfully negotiated during the review of this NDA:

Section 6.0 Adverse Reactions
The Division proposed that the ADR table use similar criteria used during the labeling for rilpivirine. Specifically, the ADR table should include ADRs of grade 2 and above, considered treatment related (i.e. related to rilpivirine), and occurred in at least 2% of either rilpivirine or efavirenz-treated subjects. A paragraph describing adverse reactions associated with use of emtricitabine or tenofovir during previous clinical trial would be included following the ADR table to provide a complete adverse reaction information for all 3 individual drugs contained in the FDC drug product.

The laboratory toxicity table has also been revised to present results for each grade (1-4).

The following sections are currently under negotiation with the Applicant:

Section 6 ADR table
The unique subject ID numbers have been requested for subjects who were included in the 'depression' ADRs.

Section 7 Drug interactions and Section 12.3 Pharmacokinetics
The Division believes that because the FDC is indicated for treatment naïve population only and because it provides a complete regimen for the treatment of HIV-1 infection, it is highly unlikely that it would be co-administered with other HIV antiretroviral medications. Therefore information regarding potential drug-drug interactions with other antiretroviral medications does not need to be included. Instead, a statement should be included referring providers to prescribing informations for the individual drug products-rilpivirine, tenofovir and emtricitabine.

- **Patient Labeling**
  The Package Insert and Patient Labeling are currently being reviewed by DDMAC and OSE.

13. Outstanding Issues

The following non-clinical items need to be resolved prior to approval of this NDA:

- CMC:
  - Agreement on the dissolution acceptance criteria
  - Completion of inspection of the drug manufacturing sites
- Clinical Pharmacology
  - Submission and acceptance of long-term stability data of rilpivirine (when in combination with emtricitabine and tenofovir)

14. Recommendations/Risk Benefit Assessment

I recommend the approval of this NDA, pending the resolution of all outstanding CMC and clinical pharmacology issues. The referenced individual NDAs for rilpivirine, emtricitabine and tenofovir provide sufficient evidence to recommend emtricitabine/rilpivirine/tenofovir fixed dose combination once daily for the treatment of HIV-1 infection in antiretroviral treatment-naïve patients.

Results from the phase 3 trials (C209 and C215) confirm rilpivirine is non-inferior to efavirenz. Overall the proportion of subjects who received FTC/TDF and with HIV RNA < 50 copies/mL at Week 48 was 83% for rilpivirine and 81% for efavirenz containing regimens. More subjects discontinued rilpivirine due to virologic failure; conversely, more subjects discontinued EFV due to adverse events.
At Week 48, 13% of rilpivirine subjects experienced virologic failure, compared with 8% in the efavirenz arm and 5% of rilpivirine subjects discontinued due to virologic failure compared to 1% of efavirenz subjects. However 7% of efavirenz subjects discontinued due to an AE or death compared with only 2% in the rilpivirine group. Virologic response to rilpivirine appears to be influenced by baseline HIV-1 RNA. At Week 48, in subjects with baseline HIV RNA $\leq$ 100,000 copies/mL the virologic failure rate was 5% for rilpivirine and 3% for efavirenz. The virologic failure rates for rilpivirine were 20% and 30% for baseline HIV RNA strata > 100,000 - $\leq$ 500,000 copies/mL and > 500,000 copies/mL, respectively compared to 11% and 18% in the efavirenz group. Furthermore, there is an increased frequency in overall resistance and cross resistance to the NNRTI class and lamivudine/emtricitabine observed with rilpivirine use. These facts should be considered when treatment is initiated with rilpivirine.

Despite the higher virologic failure rate in subjects with baseline HIV RNA > 100,000 copies/mL, the majority of the subjects maintained HIV RNA <50 copies/mL (78% in those with baseline HIV RNA >100,000 to $\leq$ 500,000 copies/mL and 66% in those with baseline HIV RNA >500,000 copies/mL). Rilpivirine can be a viable treatment option for this population and clinicians and patients should understand the limitations as outlined in the labeling before initiating treatment.

Safety differences identified between rilpivirine and efavirenz include: an increased incidence of hyperbilirubinemia (grade 1 and 2), an increase in mean serum creatinine, and a small change in mean basal cortisol level- all of which were observed with higher incidence in the rilpivirine group. None of these events require additional laboratory monitoring. Rilpivirine at supratherapeutic doses (75 and 300 mg) has a positive effect on QTc but the marketed 25 mg dose had a maximum mean time-matched difference in QTc interval of 4.8 msec, which is below the threshold of regulatory concern. Overall rilpivirine appears to have some advantage over efavirenz with regards to discontinuations due to adverse events and for the development of rash, dizziness and somnolence; however, no apparent advantage for the psychiatric disorders of depression, insomnia and abnormal dreams.

Rilpivirine may be a more desirable NNTRI for certain subpopulations. This may be particularly true for women of child bearing age who may prefer to be on a regimen with no known reproductive toxicity.

Patients with history of hyperlipidemia may also prefer a rilpivirine based regimen parameters (refer to rilpivirine NDA for details).

This FDC drug product is not indicated for treatment-experienced patients or for pediatric patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities are required for this application.

Recommendation for other Postmarketing Requirements and Commitments

- The following PMRs have been recommended:

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and antiviral activity study of FTC/RPV/TDF FDC with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Protocol Submission: August 2015
Trial Completion: January 2018
Final Report Submission: July 2018

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from birth to less than 12 years of age. Conduct a pediatric safety and antiviral activity study of FTC/RPV/TDF FDC with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Protocol Submission: September 2019
Trial Completion: January 2022
Final Report Submission: July 2022

APPENDIX: COMPUTATION OF STRATUM-ADJUSTED 95% CONFIDENCE INTERVALS

The calculation of the difference of proportions and its confidence intervals is based on stratum-adjusted Mantel-Haenszel (MH) proportions. This difference is weighted by the harmonic mean of sample size per arm for each stratum. Mathematically, if n_{1h} and n_{2h} are the sample sizes of the two comparison arms 1 and 2 in stratum h, then the weight

$$w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$$

is used for stratum h in calculating the overall difference.

Let $d_h = p_{1h} - p_{2h}$ be the difference in the proportion of virologic responders of arm 1 and arm 2 in stratum h, then the stratum-adjusted MH proportion is

$$d = \frac{\sum w_h d_h}{\sum w_h}.$$

Its continuity-corrected variance can be estimated by

$$\frac{\sum w_h^2 \left(\frac{p^*_{1h}(1 - p^*_{1h})}{n_{1h} - 1} + \frac{p^*_{2h}(1 - p^*_{2h})}{n_{2h} - 1} \right)}{(\sum w_h)^2}$$

where $p^*_{1h} = \frac{m_{1h} + 0.5}{n_{1h} + 1}$ and $p^*_{2h} = \frac{m_{2h} + 0.5}{n_{2h} + 1}$ and m_{1h} and m_{2h} are the number of virologic responders in treatment groups 1 and 2.

More weight is given to large and balanced strata than small or unbalanced strata. In the extreme case where one of the comparison arms has no patients, the weight is 0 and the stratum has no contribution in the evaluation.

NB: In Koch et al, the variance is estimated to be

$$\frac{\sum w_h^2 \left(\frac{p_{1h}(1 - p_{1h})}{n_{1h} - 1} + \frac{p_{2h}(1 - p_{2h})}{n_{2h} - 1} \right)}{(\sum w_h)^2}$$

where $p_{1h} = \frac{m_{1h}}{n_{1h}}$ and $p_{2h} = \frac{m_{2h}}{n_{2h}}$.

Reference:

Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E.. and Uryniak, T.J. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.

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/s/

YODIT BELEW
07/15/2011

FRASER B SMITH
07/15/2011

GUOXING SOON
07/15/2011

KIMBERLY A STRUBLE
07/15/2011

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 202123 Applicant: Gilead Sciences Stamp Date: February 10, 2010

Drug Names: emtricitibine/rilpivirine/tenofovir (COMPLERA) **NDA/BLA Type: Priority**

On initial overview of the NDA/BLA application for filing:

Content parameter	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2. On it's face, is the clinical section of the application organized in a manner to allow substantive review to begin?	x			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			No new phase 3 clinical trials were conducted under this NDA to assess the safety and efficacy of emtricitabine/rilpivirine/tenofovir, a FDC drug product, for treatment of HIV-1 infection. Under Section 1.4 (Reference Section), letters of Authorization to Tibotec NDA (202022) are provided. This FDC drug product contains emtricitabine/rilpivirine/tenofovir. Emtricitabine and tenofovir have both been previously studied and approved for treatment of HIV-1 infection in combination with other ART. Rilpivirine is currently under review, under NDA 202022. Two phase 3 clinical trials (C209 and C215) were conducted to assess safety and efficacy of rilpivirine in combination with other ART. Emtricitabine + tenofovir were used to construct the background regimen in study C209. In study C215, most (~66%) received emtricitabine + tenofovir as background regimen. Please refer to NDA 202022 review for safety, efficacy and risk-benefits information for rilpivirine when used in combination with other ART for treatment of HIV-1 infection. In modules 2 and 5, the study reports provided supporting the efficacy and safety of emtricitabine/rilpivirine/tenofovir are the study results from C209 and C215 (excluding those subjects who did not receive emtricitabine + tenofovir).

4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5. Are all documents submitted in English, or are English translations provided when necessary?	x			
6. Is the clinical section legible so that substantive review can begin?	x			
LABELING				
7. Has the applicant submitted design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	x			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9. Has the applicant submitted the integrated summary of safety (ISS)?	x			The ISS is based on study report from C209 and C215.
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	x			The ISE is based on study report from C209 and C215
11. Has the applicant submitted a benefit-risk analysis for the product?	x			clinical-overview.pdf section 2.5.7
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug:	x			505(b)(1)
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			x	Reference is made to Phase 1 and Phase 3 studies conducted by Tibotec (NDA 202022, module 2.7.2.3.2)
EFFICACY				
14. Do there appear to be the requisite number of adequate and well controlled studies in the application?	x			**Referenced efficacy studies:** C209 and C215 **Indication:** treatment of HIV infection In addition, BA/BE studies which were conducted in support of this FDC drug product application.
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. populations/practice of medicine in the submission?			x	

SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			The two referenced Phase 3 studies are C209 and C215. In addition, safety data from 2 BA/BE studies and 1 BA study using the FDC product have been submitted: GS-US-264-0101- a randomized, single-center, single dose, 3-way crossover study to evaluate the safety and BE of 2 formulations of the FDC tablets vs. individual drugs. There were 48 healthy adult subjects enrolled and received 3 single doses, 1 each of treatment on Days 1,15, 29 GS-US-264-0103- a randomized single-center, single-dose, 3-way crossover study to evaluate the safety and BE of 2 formulations of the FDC tablets vs. individual drugs. There were 36 healthy adult subjects enrolled and received 3 single doses, 1 each of treatment on Days 1,15, 29 GS-US-264-0108: a randomized single-center, single-dose, 2-way crossover study to evaluate the safety and BA of FDC tablet vs. individual drugs. There were 16 healthy adult subjects enrolled and received 2 single doses, 1 each of treatment on Days 1,15
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?			x	Reference is made to Tibotec NDA for information pertaining to QT prolongation effect.
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?			x	
21. For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22. For drugs not chronically administered (intermittent or short coursers), have the requisite number of patients been exposed as requested by the Division?			x	
23. Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		x		
24. Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in	x			

the class to which the new drug belongs?				
25. Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES				
26. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			x	
27. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			x	
PEDIATRIC USE				
28. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		x		A deferral plan has been submitted but lacks the date(s) for which the pediatric studies would be due.
ABUSE LIABILITY				
29. If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES				
30. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS				
31. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		x		The applicant submitted study report and data via Global Submit (eCTD). AEs and laboratory datasets (.xpt) have been submitted for JMP analysis for studies 103 and 108 but not for study 101
32. Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33. Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34. Are all datasets to support the critical safety analyses available and complete?			x	
35. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?			x	
CASE REPORT FORMS				
36. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE				
38. Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE				
39. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATIONS FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please submit Individual Subject Data Listing (which includes Data Tabulation Dataset in .xpt format) for study GS-US-264-0101.

Please revise the 'Pediatric Study Deferral Request' to include anticipated dates for study protocol submission(s), study(ies) completion and study report(s) submission.

Yodit Belew, M.D.	3/16/11
Reviewing Medical Officer	Date
Kim Struble, Pharm.D.	3/16/11
Clinical Team Leader	Date

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/s/

YODIT BELEW
03/17/2011

KIMBERLY A STRUBLE
03/22/2011