

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 31, 2011
From	Kimberly A Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202022 (000)
Applicant	Tibotec
Date of Submission	July 23, 2010
PDUFA Goal Date	May 23, 2010
Proprietary Name / Established (USAN) names	Proprietary Name is pending Rilpivirine (RPV)
Dosage forms / Strength	25 mg tablets
Proposed Indication(s)	In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients
Recommended:	Approval

1. Introduction

This cross discipline team leader review presents the main findings for rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1). This review highlights the safety and efficacy, virology, clinical pharmacology findings and overall risk/benefit assessment to support my recommendation for approval for this NDA. Brief comments regarding chemistry/manufacturing and controls and pharmacology/toxicology are also presented.

2. Background

Approximately 33.4 million people worldwide are living with HIV/AIDS; therefore, a continuing need for new treatments still exists. To date, six different antiretroviral drug classes are available comprising of over 25 single and fixed dose combinations for the treatment of HIV infection. The drug classes include: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, CCR5 coreceptor antagonists, and integrase strand transfer inhibitors.

Rilpivirine is an NNRTI developed by Tibotec, Inc and is a new therapeutic option for antiretroviral treatment-naïve adult patients. NNRTIs are a well-characterized class of antiretroviral (ARV) agents with over 10 years of clinical experience. Rilpivirine is the fifth agent in the NNRTI drug class preceded by nevirapine, delaviridine, efavirenz and etravirine. The hallmark safety issue with the class of NNRTI agents is rash, including severe life-threatening skin reactions. Additionally, nevirapine has a box Warning for severe life-threatening hepatic toxicity. Efavirenz labeling includes a Warning on psychiatric symptoms and nervous system symptoms. Rilpivirine was developed in efforts to provide improved safety and tolerability over currently approved NNRTIs while preserving potent antiviral efficacy and offer a convenient dosing regimen.

This NDA was submitted in support of traditional approval and not accelerated approval because the clinical development included two phase 3 trials conducted for 48 weeks in duration. Typically applications for accelerated approval for treatment of HIV infection are based on 24 week data and “provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of available therapy, or improved patient response over available therapy). Traditional approval is applicable for HIV applications with trials conducted for at least 48

weeks. Additionally, the Division's policy to grant an indication for the treatment-naïve population is based on at least 48 weeks of safety and efficacy data at the to-be-marketed dose. The data submitted are in support of a treatment-naïve indication. Trials in treatment-experienced patients were not conducted and therefore, the indication is restricted to the treatment-naïve population. To date, Tibotec has no plans to evaluate rilpivirine in treatment-experienced patients.

This NDA received a standard 10 month review and was not presented at the Antiviral Products Advisory Committee because rilpivirine is the fifth member of the NNRTI drug class. An advisory committee meeting was not warranted for the following reasons [Reference is made to the Draft Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings, August 2008]:

- Rilpivirine is neither first-of-a-kind, first-in-class medical product nor a medical product for a significant new indication. Rilpivirine is the fifth NNRTI and over 29 agents (single and fixed dose combinations) are approved for the treatment of HIV infection, thus not a new indication.
- Rilpivirine is not a novel product or use of new technology
- The review team's preliminary assessment based on the pre NDA package of the risk/benefit ratio is not controversial and risks and benefits appear similar to the approved NNRTI class. The safety concerns appear typical for the NNRTI drug class and HIV drugs in general.
- The review team has not identified any significant questions or concerns about how the trials conducted nor identified any significant difference of scientific opinion on the preliminary trial results.
- Finally, the efficacy and safety results and labeling have similar issues the divisions has dealt with in past applications can be addressed within the Agency and do not require outside expertise.

The clinical development package submitted to support the safety and efficacy of rilpivirine consists primarily of data from three 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 a long-term extension phase at the to-be-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 regimens: 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 are acceptable and include approximately 780 subjects treated at the to-be-marketed dose for at least 48 weeks in duration. Please refer to sections 7 and 8 for further details.

3. CMC/Device

All CMC issues are adequately addressed. The long-term stability of the drug product was demonstrated under ICH and WHO conditions. The CMC inspections were satisfactory. The recommendation regarding CMC is for approval.

4. Nonclinical Pharmacology/Toxicology

The preclinical evaluation of rilpivirine included over 55 studies 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.

- **General nonclinical pharmacology/toxicology considerations**

The main findings in animal studies were adrenal, thyroid, renal, and coagulation effects.

The adrenal effects were characterized by increased serum progesterone and decreased cortisol levels were observed in rats, dogs, monkeys and likely mice. The potential mechanism is likely inhibition of

steroidogenesis at the level of 21-hydroxylase (CYP21) and 12-hydroxylase (CYP17, monkeys). In dogs, premature activation and overstimulation of the ovaries may be related to inhibition of steroidogenesis. The effects on dog ovaries were seen at 8-25 times higher than the recommended 25 mg human dose. Given these findings, the endocrine monitoring was included in the clinical trials to evaluate adrenal function including ACTH stimulation testing, basal and stimulated cortisol measurements, 17-hydroxy progesterone, aldosterone, androstenedione, and testosterone. Please refer to section 8 below for clinical safety evaluation and conclusions from the consult review from the Division of Metabolic and Endocrine Products.

The noted thyroid effects in rats were likely due to a rodent-specific mechanism and did not have any clinical consequence during development.

The renal effects were seen in mice and dogs. In mice, minimal to moderate nephropathy was seen at systemic exposures greater than 200-fold the human exposures for the 25 mg dose. In dogs, the findings included acute interstitial nephritis in two males and minimal to slight corticomedullary mineralization in all females. These effects were seen at exposures more than 25-fold the exposure for the 25 mg human dose. In the phase 3 trials, renal parameters including serum creatinine, creatinine clearance, estimated glomerular filtration rate (eGFR) and cystatin-C were measured. Please refer to section 8 below for clinical safety evaluation and conclusions from the consult review from the Division of Cardio Renal Products.

In male rats, slight to moderate increases in coagulation parameters (APTT and prothrombin time) were observed. No clinically relevant effects on coagulation were seen in clinical trials or any indication of bone marrow suppression.

- ***Carcinogenicity and Mutagenesis***

Two year carcinogenicity studies in rats and mice were conducted.

Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats although in rats the increase did not reach statistical significance. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine was not considered to be related to statistically significant increases in the incidence of other benign or malignant neoplasms in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent-specific, associated with liver enzyme induction. A similar mechanism has not been shown to exist in humans; hence, these tumors may not be relevant for humans. The follicular cell findings are considered to be rat-specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

Rilpivirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

- ***Reproductive toxicology***

No effects on mating or fertility were seen at exposures approximately 400 times higher than the exposure in humans. In the rat and rabbit offspring, minimal effects on bone ossification were seen and other developmental endpoints noted were not considered toxicologically significant. In humans, few pregnancies were reported during the clinical trials. The pregnancies led to live births with no reported congenital anomalies to date.

- **Other notable issues (resolved or outstanding)**

The adrenal findings may be of concern for pediatric development and could lead to changes in growth, pubertal status, breast development, menarche 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. The current labeling for rilpivirine states the safety and effectiveness in pediatric patients [REDACTED] (b) (4). The indication is limited to adults only at this time.

5. Clinical Pharmacology/Biopharmaceutics

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, elimination, half-life, food effects, bioavailability**

The absorption of rilpivirine is pH-dependent; therefore medications that alter gastric pH can decrease rilpivirine exposures. CYP3A is the primary system responsible rilpivirine metabolism. CYP 2C19 also potentially contributes to rilpivirine's metabolism. Rilpivirine is eliminated via feces (85%) and urine (6%). The half-life of rilpivirine is approximately 50 hours thereby supporting once daily dosing. 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.

- **Dose Selection:**

Results from animal studies suggested rilpivirine had a long elimination half-life to warrant once daily dosing in humans. The animal findings were confirmed in phase 1 healthy volunteer trials, where multiple doses up to 150 mg once daily had an acceptable safety profile and reached sufficient exposures to inhibit viral replication over the dosing interval. In the phase 2a 7-day trial, doses of 25 mg, 75 mg and 150 mg qd were evaluated and did not show any difference in the antiviral activity between doses. Therefore, Tibotec evaluated all three doses in the phase 2b dose finding trial. Through 48 weeks no dose-response relationship was observed for the dose ranged evaluated. The proportion of subjects with HIV-1 RNA < 50 copies/mL for the 25 mg, 75 mg and 150 mg once daily group was 79%, 80% and 77% respectively compared to 81% for the control, efavirenz. No difference in response rates was seen between doses for patients with various baseline viral loads (< 100,000 copies/mL, 100,000-300,000 copies/mL and > 300,000 copies/mL). Although the 25 mg cohort had a numerically lower response rate for patients with baseline viral load > 300,000 copies/mL (68% vs 71-73%), this group also had a numerically higher response rate in patients with baseline viral load < 100,000 copies/mL (84% vs 79-81%). Given the small sample size in each stratum, definitive conclusions can not be made. Additionally, no dose-safety relationships were seen. A trend for more AEs leading to discontinuation was observed in the 150 mg group (11%) compared to the 25 mg group (7%) and 75 mg group (8%). Rash was more commonly observed in the 150 mg group (12% vs 5-6%). Given these data, Tibotec chose the 75 mg once daily dose for phase 3 trials.

Prior to the start of phase 3, data from the TQT trial (C131) became available. In this trial the 75 mg and 300 mg once daily dose were compared to moxifloxacin. At steady state (day 11), nearly all the 90% CI for rilpivirine 75 mg crossed the 10 ms threshold for QTcF. Additionally a gender difference was observed suggesting the differences in QTcF interval for females is higher than for males. Furthermore, Tibotec used the change in QTcF interval (day 11) at various plasma concentrations to predict the QTcF interval for the 25 mg once daily dose. This model predicted, for the anticipated mean C_{max} for rilpivirine after 25 mg once daily, the upper limit of the 90% CI of the difference from baseline in QTcF interval would be below 10 ms for the overall population. Subsequently another QT/QTc trial evaluated the effect of 25 mg once daily on the QT interval. Moxifloxacin was the control. The highest upper limit

of the 90% CI of the time-matched change from baseline in QTcF interval (and vs placebo) for rilpivirine 25 mg did not exceed 10 ms. The maximum mean time-matched change from baseline in QTcF was < 5 ms. This finding was also confirmed in trial C152 comparing rilpivirine 25 mg once daily and efavirenz 600 mg once daily. Again the QTcF interval did not cross 10 ms for rilpivirine 25 mg.

Tibotec then reviewed the Week 96 data from the phase 2b trial. The proportion of patients with HIV-1 RNA < 50 copies/mL was maintained for the dose groups (25 mg: 76%, 75 mg 72%, 150 mg 71%). A dose response was not seen and Tibotec concluded the exposures following rilpivirine 25 mg once daily were sufficient to further evaluate in phase 3 trials. The Division did suggest Tibotec consider evaluating 25 and 50 mg once daily in phase 3 trials; however, Tibotec declined.

Given the week 48 and 96 virologic response rate data and safety findings in conjunction with the TQTc results from 3 trials, selection of the 25 mg dose was reasonable at the time for phase 3. However, in hindsight, when the review team focused on virologic failure rates during the review for the phase 3 trials, we observed statistically significant higher failure rates with rilpivirine compared to efavirenz. Similar findings were seen with the phase 2 data, and differences were noted between the dose groups for virologic failure. Based on the pharmacometric review, 50 mg may result in less virologic failure for patients with baseline HIV-1 RNA > 100,000 copies/mL. Please refer to section 7 for a complete discussion of the efficacy

- **Drug-drug interactions**

Rilpivirine is primarily metabolized by CYP 3A, and drugs that induce or inhibit CYP3A may affect the rilpivirine exposures. Co-administration of rilpivirine and other concomitantly administered 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 were contraindicated and include:

- 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 Dr. Au's review for further details regarding other established and predicted drug interactions.

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.

Based on in vitro data, rilpivirine may act as a P-gp inhibitor. Therefore, a PMR was proposed to Tibotec to conduct a trial evaluating the inhibitory effects of rilpivirine on digoxin, a P-gp substrate.

- **Thorough QT study or other QT assessment**

As stated above in the dose selection section, rilpivirine effects on ECG were evaluated in three trials. In summary, 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 were taken into consideration for the labeled recommendations in special populations and drug-drug interactions.

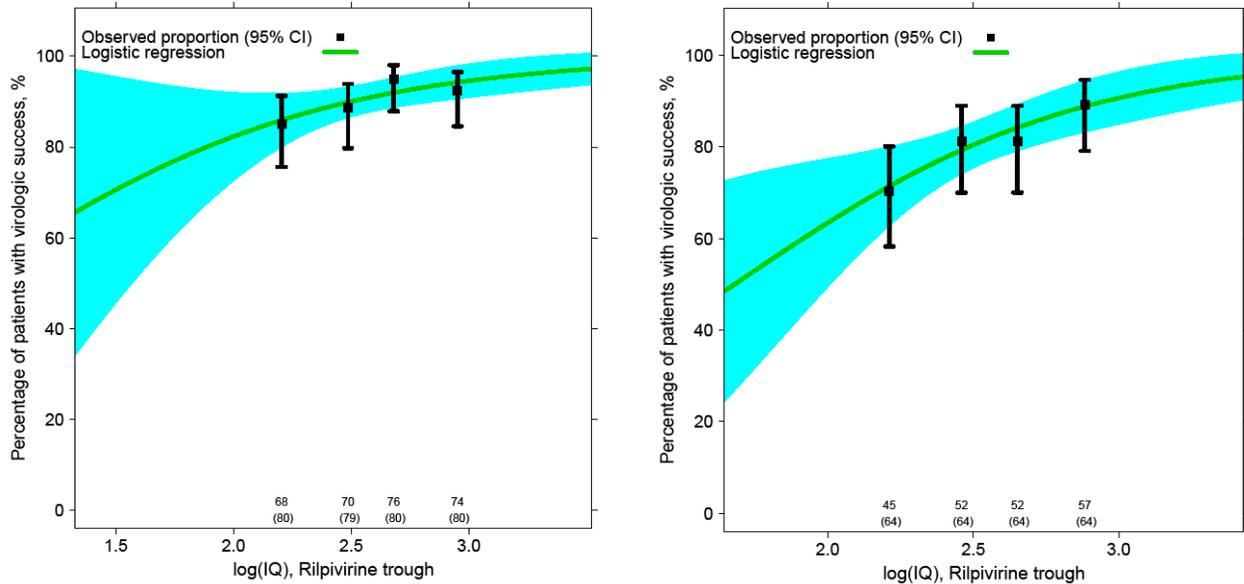
- **Critical intrinsic factors: age, gender, hepatic insufficiency and renal impairment.**

Rilpivirine exposures were not affected by age, gender, race, body weight or coinfection 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 C_{max} and AUC increased by 27% and 47%, respectively. Based on exposure-safety data, no dose adjustment is necessary for mild or moderate hepatic impairment. Additionally, in the population PK analysis conducted by FDA, minimal changes in rilpivirine exposures were seen in subjects with mild renal impairment compared to subjects with normal renal function. Only seven subjects in the phase 3 trials had moderate renal impairment. Additionally, the Clinical Pharmacology team concluded an 130% increase in rilpivirine exposure [AUC_(0-24h)] does not require a dosage adjustment for rilpivirine and also we anticipate the majority of subjects will not have severe renal impairment or end stage renal disease. Given these data, and the fact only 6% of rilpivirine is renally excreted and based on FDA guidance, a formal renal impairment trial is not warranted. No dose adjustments are needed in patients with mild renal impairment. The impact of rilpivirine exposures is not expected to be of clinical relevance for subjects with moderate renal impairment; therefore no dose adjustment is required. However, increased monitoring for adverse events should be done for patients with severe renal impairment or end-stage renal disease.

- **Exposure-response and Exposure-safety analyses**

Dr. Florian's review details the exposure-response and exposure-safety analyses. An exposure response relationship between rilpivirine C_{0h} and AUC and virologic success (HIV-1 RNA < 50 copies/mL) was seen. Median exposure values for C_{0h} and AUC_T were 80 ng/mL and 2397 (ng·h/mL) and correspond to 87% of patients achieving virologic success. A similar finding was seen for IQ ratio (ratio of C_{0h} to IC₅₀). Median exposure values for log₁₀ (IQ) was 2.57 and corresponds to 88% of patients achieving virologic success. The above analyses by baseline HIV RNA support the basis for the usage statement in the Indications and Usage section of the label and our recommendations for a PMC to evaluate a higher dose of rilpivirine in patients with baseline HIV RNA > 100,000 copies/ml. As stated in Dr. Florian's review and shown in the figure below, "the exposure-response relationship is flat for patients with viral load <100,000 copies/mL (percentage of patients achieving virologic success was 89% in the lowest exposure quartile compared to 94% in the highest exposure quartile). By comparison, a more pronounced relationship was seen for patients with baseline viral load ≥100,000 copies/mL (percentage of patients achieving virologic success was 68% in the lowest exposure quartile compared to 92% in the highest exposure quartile). Those patients who were virologic failures were not limited to patients with lower rilpivirine trough exposures or with higher IC₅₀ values. Instead, baseline viral load appears to be the primary factor in determining response in patients treated with rilpivirine." Please refer to section 7 for further details.

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 \geq 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.

6. Clinical Virology

Please refer to section 7 for an integrated review of the clinical efficacy and clinical virology findings. 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. Of the 38 rilpivirine subjects with virologic failure and evidence of rilpivirine resistance, 89% were resistant to etravirine and efavirenz and 63% were resistant to nevirapine. None of the efavirenz treated subjects were resistant to etravirine at failure. 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.

The review team is still in negotiations with Tibotec on the microbiology subsection of the label concerning this issue.

7. Clinical/Statistical- Efficacy

This section summarizes the pooled efficacy analyses from trials C209 and C215 to support our efficacy determination to support approval of rilpivirine. Additionally, the clinical virology data with respect to virologic failures are presented in this section. Please refer to reviews by Drs. Yodit Belew (clinical), Lei Nei (biometrics) and Lisa Naeger (virology) for further details.

Trial Design Attributes:

The pivotal trials to support efficacy were two Phase 3 (C209 and C215) non-inferiority trials. Both trials were identical in design with the exception of the background regimen. In trial C209 the background

regimen was fixed to tenofovir/emtricitabine. In trial C215 investigators selected the background from abacavir/lamivudine, zidovudine/lamivudine or tenofovir/emtricitabine. Both trials are ongoing 96-week, randomized, double-blind, double-dummy, active-controlled non-inferiority trials in HIV-1 infected treatment-naïve adults. Rilpivirine 25 mg once daily was compared to efavirenz 600 mg once daily, each in combination with either a fixed or investigator selected background regimen. Randomization was stratified by screening HIV RNA ($\leq 100,000$; $> 100,000 - \leq 500,000$ and $> 500,000$ copies/mL).

The active control, efavirenz, was appropriate and the preferred agent by the DHHS treatment guideline panel. Per FDA, the primary endpoint was proportion of subjects with HIV RNA < 50 copies/mL by the snapshot method.

The selected non-inferiority margin of 12% was acceptable. In DAVP's guidance on HIV drug development, the non-inferiority margin for comparing a third drug in regimens for HIV treatment-naïve patients is 10-12%. This margin is an "M2 delta", meaning the clinical treatment effect one wants to preserve compared to active controls. Based on well-controlled superiority trials, an "M1 delta" (the margin needed to assure that the new drug would be better than placebo) for assessing comparability to a PI or NNRTI is very large (upwards of 45%--using lower confidence bounds). Very few individuals (approximately 2%) receiving only two nucleoside analogues achieve HIV RNA < 400 copies/mL. Even fewer achieve HIV RNA < 50 copies/mL. Based on this information a non-inferiority margin of 10-12% is considered acceptable.

Results:

The baseline demographics and subject characteristics were balanced between the rilpivirine and efavirenz treated groups. Overall 76% enrolled were male, 61% white, 24% Black/African American, 11% Asian and 3% other or not permitted to ask about race per local regulations. FDA encourages adequate representation of females in all phases of drug development. Twenty-four percent females is roughly average for the most recent treatment-naïve trials submitted to the Division for review. The median baseline plasma HIV RNA was $5.0 \log_{10}$ copies/mL and the median CD4+ cell count for rilpivirine and efavirenz treatment groups was 249 and 260 cells/mm³, respectively. Overall 80% of subjects received tenofovir/emtricitabine as the background regimen compared to 15% who received zidovudine/lamivudine and 5% who received abacavir/lamivudine.

The Week 48 data from these two trials were pooled and provide the key efficacy results as presented below. Trials C209 and C215 met the primary non-inferiority objective. The pooled virologic success (HIV RNA < 50 copies/mL) at Week 48 was 83% for rilpivirine and 80% for efavirenz. The difference of response rate (95% CI) is 2.0 (-2.1; 6.1).

Virologic Outcome of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 (Pooled Data) at Week 48		
	TRADE NAME™ + BR N=686	Efavirenz + BR N=682
Virologic success HIV-1 RNA < 50 copies/mL*	83%	80%
Virologic failure†	13%	9%
No virologic data at Week 48 window		
<u>Reasons</u>		
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%

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: The analysis was based on the last observed viral load data within the Week 48 window (Week 44-54)

One important finding for the pooled analyses was more rilpivirine treated subjects with HIV RNA greater than 100,000 copies/mL at the start of treatment experienced virologic failure compared to patients with HIV RNA less than or equal to 100,000 copies/mL at the start of therapy. Please refer to the table below.

Virologic Response (< 50 copies/mL) by baseline HIV RNA

	≤100,000 copies/mL		>100,000 copies/mL	
	TMC278	EFV	TMC278	EFV
Pooled results	89% (327/368)	83% (273/330)	75% (237/318)	77% (270/352)

The overall response rates and response rates by baseline HIV RNA (≤ 100,000 and > 100,000 copies/mL) appear similar between the regimens; however, this is driven by differences in discontinuation rates due to AEs and virologic failure between the regimens. The primary endpoint is a composite endpoint and takes both virologic changes and safety into account. This is why rilpivirine and efavirenz response rates appear similar because more efavirenz related subjects discontinued the trial for AEs; whereas more rilpivirine-treated subjects experienced virologic failure. Given these points, the review team investigated the virologic failure rates based on the protocol specified baseline HIV RNA stratification (≤ 100,000 copies/mL, > 100,000 and ≤ 500,000 and > 500,000 copies/mL). Based on the statistical review, the difference in virologic failures is statistically significant for two higher baseline HIV RNA strata's shown in the table below.

The rate of virologic failure ^(a)	TRADE NAME™ + BR N=686		Efavirenz + BR N=682	
	N	Proportion of Subjects with HIV-1 RNA < 50 copies/ml at Week 48* n (%)	N	Proportion of Subjects with HIV-1 RNA < 50 copies/ml at Week 48* n (%)
Baseline Plasma Viral Load (copies/ml), Snapshot algorithm				
≤ 100,000 (p=.86) ^(b)	368	5.2% (19/368)	330	5.5% (18/330)
> 100,000 (p=.002) ^(b)	318	21.7% (69/318)	352	12.5% (44/352)
≤ 100,000 (p=.87) ^(b)	368	5.2% (19/368)	330	5.5% (18/330)
> 100,000 and ≤ 500,000 (p=0.007) ^(b)	249	19.7% (49/249)	270	11.1% (30/270)
> 500,000 (p=0.08) ^(b)	69	29.0% (20/69)	82	17.1%(14/82)

^(a)virologic failure 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.

^(b)p is the statistical significance level (p-value) showing the difference between TMC278 and EFV in each subgroup. The p-value is calculated using chi-square test.

Consequently, the observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of treatment resistance and cross-resistance to the NNRTI class compared to efavirenz [Please refer to section 6 above for discussion on cross-resistance]. Additionally, more NRTI resistance was seen with rilpivirine. Fifty-three percent of rilpivirine treated subjects developed the M184I or V substitution compared to 22% of the efavirenz treated subjects. The M184I NRTI substitution frequently occurred with the most common rilpivirine resistance-associated substitution, E138K/G, and contributed to rilpivirine resistance. The table below summarizes the frequent emergent RT substitutions among virologic failures from the two phase 3 trials.

Proportion of Frequently Emergent Reverse Transcriptase Substitutions in Virologic Failures from the Combined Phase 3 Studies		
	C209 and C215 N = 1368	
	Rilpivirine N = 686	EFV Control N = 682
Virologic Failures (As-Treated)	92/652 (14%)	60/604 (10%)
Evaluable Post-Baseline Resistance Data	75	37
Emergent NNRTI Substitutions in Virologic Failures with Post-Baseline Data		
V90I	12% (9/75)	3% (1/37)
K101E/P/T	19% (14/75)	3% (1/37)
K103N	0	32% (12/37)
E138K/G	36% (27/75)	0
E138K+ M184I*	27% (20/75)	0
V179I/D/L	5% (4/75)	3% (1/37)
Y181C/I	9% (7/75)	0
V189I	8% (6/75)	3% (1/37)
H221Y	8% (6/75)	0
Emergent NRTI Substitutions in Virologic Failures with Post-Baseline Data		
M184I or V	53% (40/75)	22% (8/37)
K65R/N	9% (7/75)	5% (2/37)

* This combination of NRTI and NNRTI substitutions is a subset of those with the E138K

Overall, these analyses show rilpivirine is inferior to efavirenz in subjects with baseline HIV RNA > 100,000 copies/mL. Despite this finding, approximately 75% of subjects with baseline HIV RNA > 100,000 copies/mL achieved and maintained HIV RNA < 50 copies/mL. Rilpivirine still remains an option for this subpopulation and clinicians and patients should take these findings into consideration when selecting a rilpivirine based treatment.

These findings are an important risk/benefit assessment for clinicians when selecting a rilpivirine based regimen for treatment-naïve patients. As a result the label states the following:

The following points should be considered when initiating therapy with TRADE NAME™:

- More TRADE NAME™ treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy [see *Clinical Studies (14)*].
- The observed virologic failure rate in TRADE NAME™ treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz [see *Microbiology (12.4)*].
- More subjects treated with TRADE NAME™ developed lamivudine/emtricitabine associated resistance compared to efavirenz [see *Microbiology (12.4)*].

Additionally, the differences in virologic failure rates were also observed in the phase 2b dose finding trial (C204). Based on Dr. Nie’s analyses presented below at weeks 48 and 96 a trend is seen for higher virologic failure rates in subjects with baseline HIV RNA > 100,000 copies/mL receiving rilpivirine 25 mg compared to 75 and 300 mg and EFV.

Virologic Failure^(a) Rates in C204:

Baseline viral load measurements	25 mg	75 mg	150 mg	EFV
Week 48				
≤ 100,000 copies/mL	16% (10/61) p=1.0 ^(b)	17% (10/59) p=1.0	19% (11/58) p=0.81	16% (9/56)
> 100,000 copies/mL	31% (10/32) p=0.08	22% (8/36) p=0.35	12% (4/33) p=1.0	12% (4/33)
Week 96				
≤ 100,000 copies/mL	13% (8/61) p=0.61	20% (12/59) p=0.81	19% (11/58) p=1.0	18% (10/56)
> 100,000 copies/mL	31%(10/32) p=0.08	14% (5/36) p=1.0	15% (5/33) p=1.0	12% (4/33)

^(a) virologic failure 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, subject who switched the ATV background regimen. ^(b) the p-value is computed based the Fisher is exact test of the difference between the TMC arms and the EFV arm. generated by [Leiprogram\Snapshot\snapshot_C204_week4896_withsiwtchdata100Kcut.sas](#) and [Leiprogram\support.sas](#)

The pharmacometrics team also provided perspective from their exposure-response model as shown in section 5. Subjects with higher baseline HIV RNA may benefit from 50 mg once daily. This dose may improve virologic success rates, minimize development of resistance and maintain exposures below the regulatory QTc threshold. Evaluation of 50 mg once daily in patients with higher baseline viral load is further supported because subjects with higher baseline HIV RNA had lower exposures compared to subjects with baseline HIV RNA < 100,000 copies/mL.

Based on the totality of the virology, pharmacokinetic and clinical data, I recommend Tibotec consider evaluating 50 mg once daily in patients with baseline HIV RNA > 100,000 copies/mL compared to efavirenz.

The median CD4+ cell count increase from baseline was 192 cells/mm³ for rilpivirine treated subjects and 176 cells/mm³ for efavirenz-treated subjects

8. Safety

This section focuses on the pooled safety data from the Phase 3 controlled trials (C209 and C215). Overall, Dr. Belew’s independent analyses of the safety data confirmed Tibotec’s findings with few exceptions. The differences were mainly due to group of preferred terms and not considered clinically significant as the overall percent differences between FDA and the applicant’s analyses were minimal and generally < 2%. For example, the FDA analyses included additional terms to derive the overall incidence of rash and depressive disorders. Tibotec agreed to the pooled terms and are reflected in labeling.

Adequacy of Safety Database:

The safety database was sufficient and included more than the minimal requirements (500 patients for approximately 48 weeks) as outlined the Guidance for Industry: Antiretroviral Dugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval. Overall 1712 subjects were treated with rilpivirine during the development phase, of which 1052 were HIV-1 infected subjects. The table below provides an overview of exposure to rilpivirine. A total of 1368 subjects were included in the two phase 3 trials, of which 686 received rilpivirine 25 mg once daily. The median duration of exposure for patients in the rilpivirine arm and efavirenz arm was 55.7 and 55.6 weeks, respectively.

Exposure in HIV-infected, treatment-naïve subjects in Phase 3 trials	N
C209	346
C215	340
<i>Total number of HIV-1 infected, treatment-naïve subjects treated with rilpivirine in Phase 3 trials</i>	686
Exposure in HIV-1 infected, treatment-naïve subjects in Phase 2b trial	N
C204	279
<i>Total number of HIV-1 infected, treatment-naïve subjects treated with rilpivirine in Phase 2b trial</i>	279
Exposure in HIV-1 infected subjects in Phase 2a trials	N
C201	36
C202	36
<i>Total number of HIV-1 infected subjects treated with rilpivirine in Phase 2a</i>	72
Exposure in HIV-1 infected subjects in Phase 1 trials	N
C101	15
<i>Total number of HIV-1 infected subjects in Phase 1 trials</i>	15
Total number of HIV-1 infected subjects treated with rilpivirine	1052
Exposure in non-HIV-1 infected subjects in Phase 1	N
<i>Total number of subjects in 8 pooled single dose Phase 1 trials</i>	184
<i>Total number of subjects in 19 pooled multiple dose Phase 1 trials</i>	431
C121 – multiple dose trial	13
C130 – multiple dose trial	32
<i>Total number of non-HIV infected subjects in Phase 1 trials</i>	660
Total number of subjects treated with rilpivirine	1712

(adapted from applicant Table 8: tcm278-20100700-clc-saf.pdf)

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

Overall, five rilpivirine treated subjects died in the phase 2b and phase 3 trials combined. A total of five subjects died in the phase 3 trials, one in the rilpivirine group (bronchopneumonia) and four in the efavirenz group. The death in the rilpivirine group did not appear drug related. Four subjects receiving rilpivirine died in the phase 2b trial (traffic accident, "natural causes", anemia/dehydration/lung infection and metabolic acidosis, and intestinal infarction).

Overall, 100 subjects experienced a serious adverse event (SAE), 6.6% in the rilpivirine group and 8.1% in the efavirenz group. The most common SAE was Infection/Infestation (3% in each group). All SAEs occurred similarly between the treatment groups, with the exception of hepatobiliary disorders. Six rilpivirine treated subjects experienced an event compared to one efavirenz treated subject. The events were cholecystitis (3), cholethiasis (2) and hyperbilirubinemia (1). Additionally, more subjects on rilpivirine developed grade 1 increase in total bilirubin (5%) compared to efavirenz (<1%). Based on these data, cholecystitis/cholethiasis could be related to rilpivirine and we recommend this is included in the less common adverse event section of the label. Please refer to the sections below for more details on hepatotoxicity and laboratory results.

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. The most common adverse drug reactions leading to discontinuation were psychiatric disorders 1% in the rilpivirine group and 2% in the efavirenz group.

The majority of adverse events were grade 1 or 2 in severity. The most commonly reported adverse events (all cause, all severity) with rilpivirine were headache (14%), nausea (13%), diarrhea (11%) and nasopharyngitis (10%). The events at least possibly, probably or likely related to drug and at least moderate in severity are summarized in the table below.

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		
System Organ Class, Preferred Term, %	Pooled Data from the TMC278-C209 and TMC278-C215 Trials	
	Rilpivirine + BR N=686	Efavirenz + BR N=682
Gastrointestinal Disorders		
Nausea	1%	3%
Abdominal pain	1%	2%
Vomiting	1%	2%
General Disorders and Administration Site Conditions		
Fatigue	1%	2%
Nervous System Disorders		
Headache	3%	3%
Dizziness	1%	7%
Psychiatric Disorders		
Depressive disorders [†]	4%	3%
Insomnia	3%	3%
Abnormal dreams	1%	4%
Skin and Subcutaneous Tissue Disorders		
Rash	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		

In general, the treatment-emergent adverse drug reactions were similar between treatment groups or within 1-2% difference. Notable differences include more dizziness, abnormal dreams and rash in the efavirenz group. The majority of these events did not lead to discontinuation.

- **Special Safety Concerns:**

Based on the preclinical profile and known toxicities for the NNRTI drug class, the safety evaluation focused on rash, neurologic and psychiatric disorders, hepatic and biliary disorders, renal and adrenal toxicity and cardiac events.

Rash

The hallmark toxicity for NNRTI class is rash. Therefore, rash was closely monitored throughout drug development and detailed analyses were conducted during this review to determine if additional labeling such as Warnings and Precautions were warranted. Rilpivirine had less rash compared to efavirenz (17% vs 31% for all cause, all severity and 3% vs 11% for related and moderate). The majority of the rash was 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. An exposure-response relationship was not seen for rash in the rilpivirine group. Most of the rashes in the rilpivirine group occurred within the first four weeks of treatment and the median duration was 18 days.

Based on the lower rates of rash with rilpivirine compared to efavirenz and severity (mild to moderate) and only one rilpivirine treated subject discontinued the phase 3 trial for rash compared to 10 efavirenz treated subjects, a warning and precaution for rash is not warranted. The label includes sufficient information with respect to rash in the Adverse Reactions section.

Neurologic and psychiatric disorders

Other commonly reported adverse events with NNRTIs, specifically efavirenz, are nervous system and psychiatric disorders. More subjects treated with efavirenz (45%) developed a neurologic event (all cause, all severity) compared to rilpivirine (27%). 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 (29%) compared to the rilpivirine group (10%). Headache (all cause, all severity) was similar between treatment groups (approximately 7% in each group). Somnolence (all cause, all severity) was 4% in the rilpivirine group compared to 8% in the efavirenz group. In general the incidence of psychiatric events was similar (24% for rilpivirine and 29% for efavirenz). The main differences were abnormal dreams (9% vs 14%) and anxiety. Fewer rilpivirine treated subjects (2%) developed anxiety (all cause, all severity) compared to efavirenz treated subjects (5%).

The difference in depressive disorders, including depression, major depression, depressed mood, dysphoria, mood altered, negative thoughts, suicidal thoughts and suicidal ideation (all cause, all severity) were similar (8% rilpivirine vs 7% efavirenz). Two subjects in the rilpivirine group had a grade 4 event and included major depression and suicide attempt. Another subject attempted suicide and both events led to discontinuation. Discontinuation due to depressive disorders was similar between the two groups. An exposure-response relationship was not observed for these events. Efavirenz is known to have psychiatric adverse events and the efavirenz package insert includes a Warning and Precaution statement. Therefore, based on these findings the label includes a WARNING AND PRECAUTION for depression disorders.

Hepato-biliary events

The class of NNRTIs has known hepatotoxicity issues, particularly nevirapine and to lesser degree efavirenz and etravirine. Therefore, the treatment emergent events and laboratory abnormalities were reviewed in detail. Treatment emergent adverse hepatic reactions were similar between regimens (2% each). Grade 3/4 events occurred <1% in each group. No Hy's Law cases were identified. The incidence of grade 3 and 4 increases in ALT and AST were 2% or less for rilpivirine. Numerically higher rates of grade 1 and 2 ALT and AST elevations were seen with efavirenz compared to rilpivirine. An exposure-response relationship was not seen for hepatic events.

More biliary events occurred in the rilpivirine group (8 rilpivirine vs 2 efavirenz). No exposure-response relationship was established for these events. Assessing causality is difficult because gall stones were not available to analyze. However, given the imbalance between the groups for biliary events and bilirubin changes, mention of cholecystitis and cholelithiasis in the label is warranted. Additionally, a Warning and Precaution for hepatotoxicity is not warranted. The laboratory subsection includes sufficient comparative information on the incidence of ALT, AST and total bilirubin changes. Additionally, the label includes a subsection on subjects co-infected with HBV or HCV. In each treatment group, the incidence of ALT/AST increases was higher in co-infected subjects than those not co-infected. This finding is observed in most HIV treatment trials.

Renal

As discussed in section 4 renal effects were noted in mice and dogs at high doses. Based on the animal findings renal events and serum creatinine changes were closely monitored in trials. We consulted with the Division of Cardio Renal Products to review the renal data and provide recommendations for labeling. At the preNDA meeting, the Division became aware of the rise in serum creatinine (SCr) in the first two weeks of treatment which predominately plateaued and appeared to stabilize by Week 2-4. The increases in Scr were numerically greater with rilpivirine compared to

efavirenz and this finding was seen irrespective of background treatment (tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine). To further evaluate these findings Tibotec conducted a cystatin C substudy to evaluate GFR. We determined these data were critical to the safety review and required these data were submitted with the NDA and not the safety update.

According to Dr. Blank's review the mean 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. The SCr changes during the trial were minor and few subjects had large increases. Overall 5% of subjects receiving rilpivirine developed a Grade 1 increase compared to <1% in the efavirenz group. No cases of grade 3 or 4 increases in SCr were seen in the rilpivirine and <1% grade 4 increase was seen in the efavirenz group. Each group had <1% of subjects developing a grade 2 increase.

Additionally, four subjects in the rilpivirine group had an AE of renal failure compared to three subjects in the efavirenz group. No cases required dialysis or led to death. Two of the 4 cases in rilpivirine resolved while on treatment and may be due in part to tenofovir use. Of note, a case of membranous glomerulonephritis and a case of glomerulonephritis mesangioproliferative was reported with rilpivirine. We concluded these events should be listed in less common adverse drug reactions due to investigator assessment of potential causal relationship; nephritis was also observed in animals. A biopsy indicative of possible drug-related lesions was submitted by the investigator. Tibotec disagreed and felt these events were not related because the event persisted after drug discontinuation. Tibotec also stated proteinuria was present at baseline to suggest pre-existing nephropathy; thereby prompting their decision to change the assessment to doubtful. We believe some permanent damage could be the explanation for the ongoing event and does not rule out a potential causal effect. At the time of this review, we are still negotiating the inclusion of these two events in the label. We stand by our assessment these events are possibly related given the investigator assessment and biopsy results.

Dr. Blank recommended the term nephrolithiasis is included in the label due to the imbalance in events between groups (8 events (1.2%) vs 4 events (0.6%). Additionally the incidence of urinary crystals was 12% in rilpivirine compared to 9% for efavirenz and according to Dr. Blank may support the observed difference in kidney stones. Of note no stone was available for analysis. Tibotec's reanalysis found four of the seven subjects in the rilpivirine group had a medical history of renal stones compared to one of the four subjects in the efavirenz group. In a subsequent analysis by Tibotec, the incidence of on treatment samples of urinary crystals was similar in the two groups. The review team concluded Tibotec's assessment was appropriate and inclusion of renal stones was not warranted. FDA will monitor these events in phase 4 trials and post-marketing.

Tibotec hypothesized the mechanism for the SCr changes were compatible with interference with creatinine tubular secretion and not frank nephrotoxicity. Tibotec conducted a cystatin C substudy in trial C215 to show no decline in eGFR when cystatin C levels are used to estimate renal function. Overall eGFRcyst C did not decrease in either treatment group. Of note an increase in mean eGFRcyst C at weeks 2 and 24 was seen and was greater in the efavirenz group, a finding that was not expected. Dr. Blank concluded this subgroup analysis did not provide sufficient support that the increase in SCr with rilpivirine is solely related to interference with tubular secretion of creatinine. Her alternate explanation for the difference in eGFRcyst C between baseline and Week 24 is efavirenz decreased inflammation more than rilpivirine. Therefore, Dr. Blank recommends a PMC to differentiate the effects of rilpivirine on GFR and tubular secretion either through a cimetidine mechanistic trial or measuring GFR in a trial in HIV infected patients or healthy volunteers.

The pharmacometric review by Dr. Florian further investigated the effect rilpivirine treatment on creatinine clearance. He concluded rilpivirine affects CrCL depending on baseline status with smaller changes in patients with lower baseline CrCL and vice versa. Almost all patients returned to baseline after treatment was stopped (2-4 weeks follow-up period). He then evaluated the relationship between on treatment maximum change in CrCL and baseline CrCL. The results are shown in the table below. Importantly those with moderate renal function did not worsen over time and few patients transitioned to mild or moderate renal impairment during the trial.

Mean Maximum Change in CrCL Grouped by Baseline Renal Function for Patients Treated with Rilpivirine 25 mg q.d. from C209 and C215			
Baseline CrCL Category, mL/min	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)

To assess the hypothesis rilpivirine inhibits tubular secretion of creatinine, patients on cimetidine or trimethoprim were identified. The theory is if tubular secretion is the predominant mechanism of rilpivirine induced increases in SCr then no increase in mean SCr levels should be apparent after maximum cimetidine/trimethoprim inhibition of tubular secretion is reached. For the 11 subjects who received cimetidine or trimethoprim the mean maximum decrease in CrCL was -8 mL/min compared to -20 mL/min in the overall patient population with similar baseline CrCL. I agree with Dr. Florian's assessment that this "analysis supports the sponsor's proposed mechanism of action of rilpivirine inhibition of tubular secretion of creatinine. This analysis does not rule out small changes on CrCL resulting from rilpivirine treatment, however, further investigation of the mechanism of action of rilpivirine on inhibition of tubular secretion of creatinine does not seem necessary due to the small effect size."

Therefore, a PMC was not requested. Additional renal monitoring other than routine HIV care is not warranted at this time. FDA will monitor renal events in phase 4 trials and during post-marketing use.

Adrenal:

The adrenal effects characterized by increased serum progesterone and decreased cortisol levels were observed in rats, dogs, monkeys and likely mice. Therefore, during development adrenal function was closely monitored. The Division of Metabolic and Endocrine Products (DMEP) provided input into the monitoring scheme during development. DMEP was consulted during this review to provide input on the totality of the adrenal related safety data and provide labeling recommendations if needed.

In summary, DMEP observed a small decrease in mean basal cortisol levels with rilpivirine compared to efavirenz. At Week 48, the mean change from baseline in basal cortisol was -13.1 nmol/L for rilpivirine compared to +9.0 nmol/L for efavirenz. The mean change from baseline in ACTH-stimulated cortisol levels was attenuated in the rilpivirine group (+16.5 nmol/L) compared to efavirenz (+58.1 nmol/L). DMEP concluded these differences were minimal and not likely clinically significant. Also 17-OHP and aldosterone levels indicated 21-hydroxylase is not affected by rilpivirine.

DMEP conducted additional analyses and found for those subjects with abnormal ACTH stimulation test at baseline did not worsen over 48 weeks. Twenty-three patients with normal ACTH-stimulated cortisol values at baseline had a pattern of worsening adrenal function over 48 weeks. Of note the majority (15/23; 65%) experienced mild sustained decreases over 48 weeks. No investigator coded discontinuations for adrenal insufficiency were observed. One subject who discontinued the trial due to new -onset irritability, anxiety and sleep disturbances may be consistent with the clinical effects of

adrenal insufficiency. This also could be a manifestation of psychiatric disorders as anxiety and sleep disturbances were also noted with rilpivirine treatment as discussed above.

I agree with DMEP's conclusions. The clinical data from the Phase 3 trials did not conclusively identify a clear case of adrenal insufficiency. The laboratory data suggested a small change in mean basal cortisol level. Therefore, because HIV-1 infected patients are an at risk population for adrenal insufficiency (independent of exposure to rilpivirine), the Adverse Reactions Section includes information with regards to potential effects of rilpivirine on adrenal function.

Cardiac:

As discussed in section 5, rilpivirine did have an effect on ECG. We had some concern the exposures of rilpivirine 25 mg in the presence of a drug interaction could approach exposures of rilpivirine 75 mg or beyond. Therefore, careful review of cardiac events during the phase 3 trials was conducted. Of note, please refer to the Clinical Pharmacology review for "worse-case scenario" presentation of potential drug interactions. In these situations, QTc interval would not likely exceed 10 msec. Therefore, a specific Warning and Precaution is not warranted for QTc effects. The labeling includes reference to the QTc effects in section 12.3. However, reference is made in the Warnings and Precautions, Drug Interactions subsection, rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade-de-Pointes.

Overall, numerically more efavirenz-treated subjects experienced conduction related AE or rate/rhythm cardiac related AE compared to rilpivirine. Of note, one subject in the rilpivirine group did discontinue treatment as mandated per protocol for a QTcF 457 ms, (an increase by 77 ms from baseline).

Overall rilpivirine appears to have some advantage over efavirenz in terms of 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. As shown in Dr. Belew's review and the product labeling, rilpivirine may have an advantage over efavirenz in terms of mean change from baseline for lipid parameters. Minimal changes in total cholesterol, LDL and triglycerides were seen through Week 48; however the clinical impact of such findings has not been demonstrated. Fewer grade 1-4 increases in ALT and AST were seen in rilpivirine treated subjects compared to efavirenz. Whereas, more rilpivirine treated subjects had grade 1 and 2 increases in total bilirubin compared to efavirenz. Other notable differences for rilpivirine treatment compared to efavirenz or other NNRTIs are renal and adrenal changes. Minor changes in adrenal and renal function did not warrant additional monitoring or Warnings and Precautions. I recommend these events are closely monitored by OSE during postmarketing.

9. Advisory Committee Meeting

Not applicable. See Background section 2 for rationale for not convening an advisory committee meeting.

10. Pediatrics

Pediatric trials with rilpivirine are ongoing. 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 lead to changes in growth, pubertal status, breast development, menarche 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.

11. Other Relevant Regulatory Issues

No additional regulatory issues were identified other than those highlighted throughout this review. All inspections (CMC and DSI) were satisfactory and do not preclude an approval action. The renal and endocrine consults were received and addressed in this review and in the clinical and clinical pharmacology review. We clearly outline the rationale for our alternative recommendations.

12. Labeling

- Proprietary name

Tibotec submitted three trade names and OSE/DMEPA and DDMAC found objections for all three names. At the time of this review, Tibotec is meeting with DMEPA to discuss the findings and proposed a fourth proprietary name. If the name is submitted soon, DMEPA may be able to review the new trade names in time for the May 23, 2011 action date.

- Address important issues raised by brief discussion of DDMAC and OSE Division comments.

The package insert and patient labeling are currently being reviewed by DDMAC and OSE.

- Physician labeling

All labeling issues with respect to Indications and Usage, Contraindications, Warnings and Precautions and Clinical Studies Section were successfully negotiated at the time of this review. The outstanding issues include addition of membranous glomerulonephritis, mesangioproliferative glomerulonephritis, cholecystitis and cholelithiasis to the Less Common Adverse Drug Reactions subsection of the label. The review team feels strongly based on the investigator assessment and case reports these events could be possibly related to rilpivirine and warrant inclusion in the label. Revisions to the microbiology section are still needed and relate to statements about emergence of resistance to background drugs during therapy and cross resistance to NNRTI class after virologic failure.

- Highlight of major issues discussed, resolved, or not resolved at the time of completion of the CDTL review.

The major issues discussed and resolved during the review process were the disproportionate virologic failure rates between rilpivirine and efavirenz. Despite similar response rates between groups for the overall patient population and by baseline HIV RNA, more virologic failure was seen with rilpivirine, whereas more discontinuations due to AEs were seen with efavirenz. The consequence of virologic failure seen with rilpivirine leads to a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. Additionally, lamivudine/emtricitabine associated resistance occurred more frequently with rilpivirine (53%) compared to efavirenz (22%). Tibotec agreed to the recommendations in the Indications and Usage, Microbiology and Clinical Studies section.

Another issue was including severe depressive disorders as a Warning and Precaution statement. The efavirenz label already includes a Warning and Precaution regarding neuropsychiatric events. The proportion of subjects experiencing a depressive disorder was similar between treatment groups. Suicide attempt and ideation was seen in the rilpivirine group. As a result, the review team negotiated successfully the inclusion of this Warning and Precaution.

13. Recommendations/Risk Benefit Assessment

I agree with the review team's assessments and recommend approval of this NDA. The data submitted provide sufficient evidence to recommend rilpivirine 25 mg once daily for the treatment of HIV-1 infection in antiretroviral treatment-naïve patients. Rilpivirine is not indicated for treatment-experienced patients or for pediatric patients. Results from the phase 3 trials confirm rilpivirine is non-inferior to efavirenz. Overall the proportion of subjects with HIV RNA < 50 copies/mL was 83% for rilpivirine and 80% for efavirenz containing regimens. The difference (95% CI) of response rates is 2.0 (-2.1; 6.1). Of note, the two treatment regimens reached similar results for different reasons. At Week 48, 13% of rilpivirine subjects experienced virologic failure, compared with 9% in the efavirenz arm. However 7% of efavirenz subjects discontinued due to an AE or death compared with only 2% in the rilpivirine group. Another important efficacy finding was the difference in virologic failure rates by baseline HIV RNA. In subjects with baseline HIV RNA \leq 100,000 copies/mL the virologic failure rate was 5% for both rilpivirine and efavirenz. At Week 48, the virologic failure rates for rilpivirine rose to 20% and 27% for baseline HIV RNA strata > 100,000 - \leq 500,000 copies/mL and > 500,000 copies/mL, respectively compared to 11% and 17% in the efavirenz group. The long term implications of this difference are an important factor when deciding to use rilpivirine. An increased frequency in overall resistance and cross resistance to the NNRTI class and lamivudine/emtricitabine was observed in the rilpivirine group which could negatively affect future treatment options. The increase in adverse events with efavirenz was primarily related to psychiatric disorders and rash events and is typically transient.

Given these issues, the review team recommended a PMR to submit the final study reports for the 96 week data (safety, efficacy and resistance evaluation) from the ongoing Phase 3 trials. In addition, a PMC to conduct a trial to evaluate the virologic failure rates at a higher dose of rilpivirine (50 mg) in subjects with baseline HIV RNA > 100,000 copies/mL compared to efavirenz was recommended. Based on the supporting phase 2b data and pharmacometric analyses, a higher dose such as 50 mg may minimize virologic failure and development of resistance and remain below the regulatory threshold of concern for QTc prolongation for higher rilpivirine exposures. This trial can provide useful efficacy data to further optimize the dose for subjects with higher baseline viral loads.

Despite the higher virologic failure rate in patients with baseline HIV RNA > 100,000 copies/mL, approximately 75% of subjects achieved and maintained HIV RNA < 50 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.

Overall rilpivirine appears to have some advantage over efavirenz in terms of 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 was found. Rilpivirine may have an advantage over efavirenz in terms of mean change from baseline for lipid parameters. Minimal changes in total cholesterol, LDL and triglycerides were seen through Week 48; however the clinical impact of such findings has not been demonstrated. Fewer grade 1-4 increases in ALT and AST were seen in rilpivirine treated subjects compared to efavirenz. Other benefits of rilpivirine is the ability to use in women of child bearing potential given the pregnancy category B rating; compared to the category D rating for efavirenz. Additionally, drug interactions for treatment-naïve subjects appear more manageable compared to efavirenz and nevirapine.

Some safety differences were noted with rilpivirine and include the following. More rilpivirine treated subjects had grade 1 and 2 increases in total bilirubin compared to efavirenz. Other notable differences for rilpivirine treatment compared to efavirenz or other NNRTIs are renal and adrenal changes. Minor changes in adrenal and renal function were observed which do not require additional monitoring during treatment. Rilpivirine at supratherapeutic doses (75 and 300 mg) did have an affect on QTcF; whereas the recommended 25 mg dose had a maximum mean time-matched difference on the QTcF interval from placebo of 4.8 msec which is below the threshold of regulatory concern.

Cross Discipline Team Leader Review

- 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. Submit final study reports for Week 96 data analyses (safety, efficacy and resistance evaluation) from the ongoing Phase 3 studies TMC278-C209 and TMC278-C215.

The Division proposed October 2012 as the due date for the submission of the final study report.

2. 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 rilpivirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Study completion by: September 2013
Final report submission by: June 2010

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

Protocol submission by: March 2011
Study completion by: September 2017
Final report submission by: January 2018

4. Digoxin Study: Conduct a clinical trial in healthy subjects to evaluate the effect of rilpivirine at steady state on the single dose pharmacokinetics of digoxin. The pharmacokinetics of digoxin when coadministered with rilpivirine (test arm) will be compared to the pharmacokinetics of digoxin by itself (reference arm). The primary digoxin pharmacokinetic parameters that will be evaluated are $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} .

Negotiation with Tibotec is planned for the study completion and final report submission due dates.

The following PMC is recommended. Negotiation with Tibotec is planned.

1. Conduct a trial to evaluate the virologic failure rates with rilpivirine 50 mg once daily compared to efavirenz in subjects with baseline HIV RNA > 100,000 copies/mL.

Negotiation with Tibotec is planned for the study completion and final report submission due dates.

- Recommended Comments to Applicant

No additional comments for Tibotec at this time. Final label comments and PMR/PMC recommendations were sent to Tibotec and a teleconference is scheduled to discuss.

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/s/

KIMBERLY A STRUBLE
04/06/2011