CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 202022 Applicant: Tibotec Stamp Date: July 23, 2010

Drug Name: rilpivirine (TMC278) (b) (4) NDA/BLA Type: Type 1 (Traditional)

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			tmc278-c209-crr.pdf tmc278-c215-crr.pdf
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		Included in Module 2 as Summary of Clinical Safety- summary and tables presented as pooled and for individual studies (tmc278-20100700-cls-saf.pdf
10. Has the applicant submitted the integrated summary of efficacy (ISE)?		x		Included in Module 2 as Summary of Clinical Efficacy- summary and tables presented as pooled and for individual studies (tmc278-20100700-cls-eff.pdf)
11. Has the applicant submitted a benefit-risk analysis for the product?	x			Module 2, (2.5 Clinical Overview; Section 7(tmc278-20100702-clo.pdf)
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	x			Module 5: (tmc278-c204-crri-w48.pdf); (tmc278-c204-crri-w96.pdf)

designed dose-ranging studies)? ***Study Number**: Phase 2b study: TMC278 C204* ***Sample size**: 368 (279 active; 89 control)* ***Arms**: 25mg (n=93); 75mg (n=95); 150mg (n=91); control (n=89)*				
EFFICACY				
14. Do there appear to be the requisite number of adequate and well controlled studies in the application? ***Pivotal Studies**: C209 and C215* ***Indication:** treatment of HIV infection*	x			
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			Multinational trial with numerous sites in U.S.
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			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed? ***Studies:** TMC278-TiDP6-131 (75mg, 300mg), TMC278-TiDP6-152 (25mg)*	x			tmc278-20100700-cls-saf.pdf Positive QT results (at 75 mg and above); information will be included in label
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			Coding dictionary found in the TS datasets per study: \\Cdsesub1\evsprod\NDA202022\0000\m5\datasets\tmc278-c904\analysis\define.xml
24. Has the applicant adequately evaluated the	x			

safety issues that are known to occur with the drugs in 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		The applicant discussed the pediatric development plan. However, the deferral request has not been submitted. Request for deferral has been issued (to be submitted prior to filing date)
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	Multiple U.S. sites were used in addition to the non-U.S. sites.
DATASETS				
31. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Global Submit
32. Has the applicant submitted datasets in the format agreed to previously by the Division?		x		Format of the laboratory toxicity dataset did not follow the format requested by the Division. Request for revised format for the laboratory toxicity dataset has been requested for submission prior to filing due date
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	x			

Financial Disclosure information?				
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.

None identified at this time.

Yodit Belew	August 31, 2011
Reviewing Medical Officer	Date
Kimberly Struble	August 31, 2011
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YODIT BELEW
04/01/2011

KIMBERLY A STRUBLE
04/01/2011
Due to technical difficulties with DAARTS this document is being checked in again

CLINICAL REVIEW

Application Type	NDA
Submission Number	202-022 (SDN 000)
Submission Code	Type 1 (NME)
Letter Date	July 23, 2010
Stamp Date	July 23, 2010
PDUFA Goal Date	May 23, 2010
Reviewer Name	Yodit Belew
Review Completion Date	March 28, 2010
Established Name	Rilpivirine (TMC278)
(Proposed) Trade Name	
Therapeutic Class	NNRTI
Applicant	Tibotec
Priority Designation	S
Formulation	25 mg tablet
Dosing Regimen	25 mg, once daily
Indication	Treatment of HIV-1 infection
Intended Population	HIV-1 infected, treatment naïve adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of rilpivirine (TMC278) is recommended for treatment of HIV-1 infection in treatment naïve adults. This recommendation is based on the data contained in NDA 202-022. Rilpivirine in combination with other ARVs, was demonstrated to be non-inferior to efavirenz (EFV) in suppressing HIV-1 RNA in one Phase 2b and two Phase 3 trials.

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 safety and 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. Both trials were stratified by baseline viral load (</> 100,000 and </> 500,000). 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.

The Applicant demonstrated an acceptable safety profile for rilpivirine. The principal treatment-related, grade 2 and above adverse events identified during the Phase 3 trials include psychiatric disorders (depression, insomnia, abnormal dreams) and rash. With exception of depression, these adverse events occurred with either similar or lower incidence in the rilpivirine group compared to EFV group: insomnia (3% vs. 3%), abnormal dreams (2% vs. 4%), and rash (2% vs. 9%). The incidence of depression was 3% and 2% in the rilpivirine and EFV groups, respectively. None of these adverse events were found to have an exposure-response correlation.

The clinical laboratory results demonstrated an increase in serum creatinine over time, an observation only seen in the rilpivirine group. A small mean increase in serum creatinine was observed in the rilpivirine treated subjects (mean change of 0.19 mg/dL at Week 24 compared to baseline; maximum mean change <1 mg/dL). Most of the increase occurred during the first 2 to 4 weeks of treatment and appears to be reversible. Although the mechanism by which the increase in serum creatinine is thought to be by inhibition of renal tubular secretion of serum creatinine, the mechanism has not been established with certainty. Another significant laboratory finding included asymptomatic hyperbilirubinemia. Most cases were mild (grade 1) and were due to an increase in indirect bilirubin. No

Hy's law case was identified. An exposure-response relationship was not demonstrated for either the increase in serum creatinine or the hyperbilirubinemia.

Adrenal suppression was identified early in the pre-clinical developmental stage. During the Phase 3 clinical trials, no adverse report of adrenal insufficiency was reported. However, a small (-13.1nmol/L) mean decrease in basal cortisol levels and an attenuated cortisol response to ACTH stimulation was observed in 3% of subjects treated with rilpivirine. These changes are small and of questionable clinical significance.

Finally, based on a thorough QT study, rilpivirine has been shown to prolong the QT interval at a supratherapeutic doses (75 mg qd, 300 mg qd). A supportive QT study at the recommended dose of 25 mg qd did not demonstrate a substantial effect on the QT interval; the upper bound of the 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction (QTcF) was below 10 ms, the threshold for regulatory concern.

1.2 Risk Benefit Assessment

Many treatment naïve, HIV-infected patients choose an NNRTI based regimen for their initial treatment. Rilpivirine, an NNRTI, would provide an additional treatment option from which an NNRTI based regimen could be constructed.

The effectiveness of rilpivirine in suppressing HIV-1 RNA to undetectable levels (<50 copies/mL) was demonstrated in two Phase 3 trials and a supportive Phase 2b trial. The durability of the efficacy data extends for 48 weeks in the Phase 3 trials and 192 weeks in the Phase 2b trial.

Additional benefits demonstrated for rilpivirine include less discontinuations due to adverse events compared to EFV. Overall, fewer subjects treated with rilpivirine discontinued due to adverse events (2% vs. 7%).

The nonclinical data for rilpivirine demonstrated that rilpivirine does not have reproductive toxicity.

Treatment with HAART, in particular with PI based regimens, is known to cause hyperlipidemia. The effect of rilpivirine on lipids was evaluated in the Phase 3 trials. Although the clinical significance was not demonstrated, the mean increase from baseline in total cholesterol, LDL and triglycerides was less for the rilpivirine group compared to the EFV group.

Among the limitations of rilpivirine is that its effectiveness may vary by baseline HIV-1 RNA. In the Phase 3 trials, virologic response rates for rilpivirine ranged from 89% (for subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL) to 79% (for subjects with baseline HIV-1 RNA >100,000 copies/mL); the virologic failure rate (HIV-1 >50 copies/mL at Week 48) was 5% and 22%, respectively for those with baseline HIV-1 RNA ≤ 100,000 and >100,000 copies/mL. Furthermore, exposure appears to be a factor in achieving suppression, particularly for subjects with baseline HIV-1 RNA >100,000 copies/mL. An exposure-response analysis demonstrated that for subjects with baseline HIV-1 RNA >100,000 copies/mL, an increase in exposure would result in a greater proportion of subjects achieving virologic success. This is in contrast to subjects with baseline HIV-1 RNA <100,000 copies/mL. However, dose adjustment or therapeutic drug monitoring is not recommended because this strategy was not evaluated and there may be concern about the effect on the QT interval if doses other than 25 mg of rilpivirine are given. Additionally, cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine-containing regimen.

Rilpivirine was shown to prolong the QT interval at supratheraputic doses. Increase in serum creatinine over time (compared to baseline) was noted only in rilpivirine-treated subjects. Finally, although no adverse events of adrenal insufficiency were reported in the Phase 3 trials, a small decrease in basal cortisol and attenuation of cortisol response to ACTH was observed.

Despite these limitations, rilpivirine would offer a valid treatment alternative from which to construct an NNRTI based regimen. It has been demonstrated to be effective and appears to be better tolerated than its comparator as there were less discontinuations due to adverse events. The lower rate of success for those with high pre-treatment viral load is communicated in the Indications and Usage and Clinical Studies sections of the Package Insert. 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 avoided during treatment with rilpivirine. In the Contraindications and Warnings and Precautions Sections, information has been included to communicate the risk of drug-drug interactions leading to lower exposure of rilpivirine. With regards to the effect of rilpivirine on cardiac conduction, the recommended dose (25 mg qd) did not have a substantial effect on the QT interval. In addition, in the Warnings and Precautions Section, a risk mitigation step has been taken to reduce the risk of QT prolongation with the 25 mg qd dose, if co-administered with drugs with a known risk of Torsade de Pointes. Although an increase in mean serum creatinine was observed, the change was small and of questionable clinical significance. An exposure-response analysis showed no trend in maximum change in eGFR from baseline (based on creatinine). When eGFR was calculated based on cystatin C levels, no trend between rilpivirine exposure and GFR is observed. Because a mild effect of rilpivirine on renal function cannot be excluded with certainty, the Package Insert includes the laboratory data for all graded serum creatinine elevations as well as the mean change of serum creatinine from baseline. Although no clinical case of adrenal insufficiency was reported, because HIV-1 infected patients are at risk population for adrenal insufficiency (independent of exposure to rilpivirine), the Package Insert for rilpivirine includes information with regards to effect of rilpivirine on adrenal function.

Finally, 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.

In conclusion, in addition to the overall effectiveness, safety and tolerability of rilpivirine, and given the convenient once daily dosing regimen, rilpivirine, in combination with other ARVs, is valid therapeutic option for treatment of HIV-1 infection in treatment-naïve adult patients.

1.3 Recommendations for Postmarketing Risk Management Activities

A risk management plan was not submitted with NDA 202-022. The Applicant states that risk assessments based on available data indicate routine monitoring of the safety profile in ongoing and planned clinical trials and routine pharmacovigilence activities provide sufficient tools to identify potential risks for rilpivirine. The clinical data from the Phase 3 trials supports the proposed plan to conduct routine pharmacovigilence monitoring. The Division agrees no additional risk management activities are required at this time.

1.4 Recommendations for other Post Marketing Study 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 has 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 the Applicant is planned for the study completion and final report submission due dates.

2 Introduction and Regulatory Background

2.1 Product Information

Generic (trade) name	Rilpivirine (trade name under review)
Chemical class	New molecular entity
Pharmacological class	Nonnucleoside reverse transcriptase inhibitor (NNRTI)
Proposed indication	Rilpivirine in combination of other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment naïve adults

Dosage form and regimen 25 mg tablet; 25 mg once daily

Age group Adults

Rilpivirine (rilpivirine hydrochloride, RPV), is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1(HIV-1). Rilpivirine binds directly to reverse transcriptase (RT) and blocks the DNA polymerase activities by causing a disruption of the enzyme's catalytic site. There are currently 4 NNRTIs available on market. Rilpivirine, a new molecular entity, would be the fifth addition to the class.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 25 drugs approved for the treatment of HIV-1 infection (excluding fixed dose combinations or different formulations). Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the approved anti-retroviral drugs.

Table 1 Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz	Sustiva®
	Etravirine	Intelence®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir	Reyataz®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Tipranavir	Aptivus®
	Darunavir	Prezista®

Table 1 Approved Antiretroviral Drugs (Continued)

Drug Class	Generic Name	Trade Name
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is not marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently four NNRTIs available commercially, including efavirenz, nevirapine, etravirine and delavirdine. Adverse events from NNRTIs tend to occur early during treatment, usually in the first few weeks, and 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.

Although NNRTIs have demonstrated a robust impact on immunologic and virologic parameters and offer convenient dosing, their use is limited by the emergence of single viral mutation that can lead to loss of activity not only to the drug in use but also often leads to cross resistance with other drugs in this class.

Efavirenz is recommended as first-line regimen in antiretroviral-naive patients by the U.S. DHHS HIV treatment guideline. Efavirenz is also available as part of a fixed-dose combination drug product, offering a one pill, once daily regimen for naïve patients. Adverse reactions associated with efavirenz include neuropsychiatric disorders such as depression and dizziness, rash, as well as hepatic toxicity. Nevirapine is recommended as a first-line regimen in antiretroviral-naive patients by the WHO for resource poor countries. Serious and fatal hepatic events have been observed with nevirapine, often in association with a skin rash with or without fever or flu-like symptoms. Serious and life-threatening skin reactions including Stevens-Johnson syndrome have been reported with nevirapine. In addition, gender and pre-treatment CD4 T- cell count are considered prior to prescription of nevirapine. Women with higher CD4 T cell counts appear to be at highest risk.

Etravirine is the latest NNRTI to become available commercially. It is approved for use only in treatment experienced patients with evidence of viral replication and HIV-1 strains resistant to NNRTI and other ARVs. Known adverse events associated with use of etravirine include severe life threatening and fatal skin reactions, including Stevens-Johnson syndrome, hypersensitivity reaction, toxic epidermal necrolysis and erythema multiforme.

Delavirdine, although commercially available, is not recommended by DHHS guidelines due to weaker efficacy compared to other available antiretroviral drugs, unfavorable effects on lipid profile, and high pill burden.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Investigational New Drug application (IND 67,699) for rilpivirine was submitted on October 29, 2004. The notable events throughout drug development are summarized below.

Proof of Concept Study (R278474-C201): This phase 2a, 7-day functional monotherapy study in HIV-1 infected, treatment naive subjects was initiated on October 8, 2003 and ended on June 30, 2004. Thirty six (36) treatment-naïve subjects were enrolled and administered 25 mg, 50 mg, 100 mg or 150 mg. The median $\log_{10}$ plasma viral load reduction from baseline to Day 8 was 1.2 $\log_{10}$ HIV-1 RNA copies/mL (range 1.86-0.66).

Proof of Concept Study (R278474-C202): This phase 2a, 7-day functional monotherapy study in HIV-1 infected subjects was initiated on June 15, 2004 and completed on December 9, 2004. Thirty six (36) treatment-experienced subjects, 24 of whom were NNRTI experienced were enrolled and administered 25 mg, 50 mg, or 150 mg.

The overall reduction in $\log_{10}$ plasma viral load from baseline through Day 7 was 0.84 $\log_{10}$ HIV-1 RNA copies/mL with no statistically significant differences between the dose groups. The baseline fold change for rilpivirine was predictive of the virologic response to rilpivirine on Day 8 which also explained the difference in virologic response on Day 8 in subjects failing a PI-containing regimen (-1.19 $\log_{10}$ HIV-1 RNA copies/mL) compared to subjects failing a NNRTI-containing regimen (-0.71 $\log_{10}$ HIV-1 RNA copies/mL). Subjects with history of NNRTI-containing failing regimen had a higher baseline FC (3.57) than those with history of PI-containing failing regimen (1.71).

Based on the data from R278474-C202, the development of rilpivirine was geared towards HIV-1 infected, treatment naïve patients. Of note, Etravirine was in development by the Applicant for treatment of HIV-infected, treatment experienced patients.

End of Phase 2 meeting (EOP2): This meeting occurred on July 18, 2007. Topline results of the Phase 2b study (TMC278-C204) were submitted in support of initiation of the Phase 3 programs. TMC278-C204 is a Phase 2b, dose selection study comparing 25 mg qd, 75 mg qd, 150 mg qd and efavirenz 600 mg qd. Based on the topline results and the dose selection rationale, the Division agreed that the 75 mg qd dose was appropriate for the proposed Phase 3 programs (TMC278-C209 and TMC278-C215). The rationale included:

- There was a trend for a lower response rate with the 25mg qd dose in subjects with high baseline viral load (e.g.>500,000 copies/mL)
- Exploratory analyses of PK/PD relationships suggest that no additional efficacy benefit was likely from doses greater than 75 mg qd.
- There were more adverse events and more discontinuations due to adverse events in the 150 mg qd dosing group.
- Overall, the 75 mg qd dosing gave the maximum therapeutic window, allowing for variability in pharmacokinetics (e.g. drug-drug-interaction, suboptimal adherence) without negative effects on safety or efficacy.

Prior to initiation of the Phase 3 trials, results from the thorough QT study became available. In summary, TMC278-C131 evaluated the effect of the proposed therapeutic (75mg) dose and supra-therapeutic (300mg) dose of rilpivirine on cardiac conduction. After 11 days of treatment, a mean increase from baseline in QTcF was observed at all time points. The QTcF values (90% CI) at these

timepoints in the rilpivirine 75 mg qd and 300 mg qd dose group were 10.4 ms (7.7; 13.1) and 23.8 ms (19.3; 28.2), respectively. Higher plasma concentrations were associated with larger changes in QTcF.

Due to the positive thorough QT study findings, the dose selection for the Phase 3 program was reassessed. The Applicant proposed 25 mg qd as an alternative dose. Although the Division agreed that the 25 mg dose was shown to be effective during the Phase 2b trial, the Applicant was encouraged to include a 50 mg qd treatment dose group into the Phase 3 trial design. The Applicant declined and initiated the Phase 3 program with 25 mg qd as the selected therapeutic dose.

During the pre-clinical studies, rilpivirine was identified to have a potential effect on adrenal function; rilpivirine appears to suppress cortisol production. Although no clinical cases of adrenal insufficiency or crises were identified from the topline results of the phase 2b study, there was laboratory evidence suggesting potential adrenal suppression. Consultation with the Division of Metabolic and Endocrinology Products (DMEP) was obtained to assist with recommendations for the Phase 3 trial protocols, including exclusion of a specific at-risk patient population and monitoring plans for adrenal suppression. DMEP also provided their expertise during the analysis of the current NDA data. Summary of their findings and recommendations are included in this NDA review. Refer to review by Dr. Ali Mohamadi, Clinical Reviewer from DMEP, for full details.

Pre-NDA meeting: The meeting was held on June 3, 2010. Among the negotiations during the Pre-NDA meeting was the submission of the cystatin C data in the original NDA. The topline summary results of the Phase 3 trials were noted for increased serum creatinine in the rilpivirine group when compared to the efavirenz group. The increase was mild, primarily grade 1 and appeared to plateau. This safety finding was also observed in the Phase 2b trial. In order to further evaluate any possible effect of rilpivirine on GFR, cystatin C was added to the safety biochemistry laboratory assessments of trial C215. The Division stressed that it considered the cystatin C data to be an important component of the Division's renal evaluation and therefore should be included with the submission of the NDA. The data has been submitted and included in the current review. To assist with in-depth analysis of renal safety in studies TMC278C-209 and TMC278-C215, the Division of Renal and Cardiovascular Drug Products was consulted. This NDA review contains summary of their findings and recommendations. Refer to review by Dr. Melanie Blank, Clinical Reviewer from the Division of Renal and Cardiovascular Drug Products, for further details.

2.6 Other Relevant Background Information

Tibotec submitted a justification for waiver of an Advisory committee meeting. Reference is made to the *Draft Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings, August 2008* outlining the factors and scenarios that the FDA considers when deciding to refer a matter to an Advisory Committee:

> "In those instances in which FDA is not legally compelled to refer a matter to an advisory committee, it may nevertheless choose to do so voluntarily. When considering whether to convene such a meeting, FDA should consider the following three factors:
>
> > (a) Is the matter at issue of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?

(b) Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?

(c) Is there a special type of expertise that an advisory committee could provide that is needed for the agency to fully consider a matter?

In summary, Tibotec believed that an Advisory Committee meeting was not warranted for NDA 202-022 because there were several previously approved agents in the non-nucleoside class of drugs, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the results from the safety and efficacy trials did not pose particular concerns.

The Division agreed, that based on the NDA's topline results, an Advisory Committee was not warranted. In addition, although rilpivirine is a new molecular entity, it is not a first-in class drug as there are 4 previously approved NNRTIs currently on market. An internal meeting was held between the clinical review team and OAP to discuss if an Advisory Committee was essential for NDA 202-022. After the presentation of the topline data, it was agreed that Advisory Committee may be waived for this application. Had an unexpected safety or efficacy concerns arisen during the review of NDA 202-022, the Division planned to convene a Regulatory Briefing to present and discuss the issues.

No safety or efficacy concerns warranting a discussion before a Regulatory Briefing Panel were identified.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A routine consultation was issued to the Division of Scientific Investigation (DSI) at the filing of the NDA. Please refer to Dr. Antoine El-Hage'd review for further details. One domestic and three international sites were inspected. The data from these sites were deemed acceptable in support of Tibotec's NDA application for rilpivirine.

3.2 Compliance with Good Clinical Practices

The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). The IEC or IRB approvals are contained in the NDA application. Written consents were obtained from all subjects prior to any trial-related procedure. The clinical trials were conducted in accordance with the Declaration of Helsinki and with ICH Good Clinical Practice guidelines. Furthermore, inspections of the clinical sites by DSI found the data to be acceptable. Refer to section 3.1 for further detail.

3.3 Financial Disclosures

With exception of 2 investigators, no investigator who participated in the Phase 3 trials, Phase 2b trial or the thorough QT studies entered into financial arrangement with the Applicant.

One investigator received $ 45,819.00 as honoraria from the Applicant. This investigator enrolled 3 subjects out of a total of 680 subjects in TMC278-C215 trial. The second investigator received $74,430.00 in honoraria from the Applicant. The investigator enrolled 6 subjects out of a total of 680 subjects in TMC2780-C215 trial.

All case reports forms and data were analyzed by the Applicant to minimize any potential bias on the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Rilpivirine, in the form of rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range. The 25 mg rilpivirine tablet is white to off-white, film-coated, round, biconvex, and measuring 6.4 mm.

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6$. HCl and its molecular weight is 402.88.

Please refer to FDA CMC Review by Dr. Celia Cruz for further details.

4.2 Clinical Microbiology

Please refer to FDA Virology Review by Dr. Lisa Naeger for details.

Antiviral Activity in Cell Culture

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of 5220 nM (range 2510 to 10830 nM) (920 to 3970 ng/mL).

Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and was less active against group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

Resistance in Cell Culture

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I, K101E and P, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C and M230I and L.

Resistance in Treatment-Naïve Subjects

In the pooled resistance analysis from the Phase 3 trials, the emergence of resistance was greater in the rilpivirine group compared to the EFV group. In an as-treated analysis of the combined studies, 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. Moreover, phenotypic resistance to a background 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.

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Emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and the tenofovir resistance-associated substitutions K65R or N emerged more frequently in rilpivirine virologic failures compared to EFV virologic failures.

Cross-Resistance

Site-Directed NNRTI Mutant Virus

The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. Combinations of 2 or 3 NNRTI resistance-associated substitutions showed decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutants, respectively.

Treatment-naïve HIV-1-infected subjects

Considering all of the available cell culture and clinical data, the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179I/L, Y181C, Y181I, Y181V, H221Y, F227C and M230I or L.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine-containing regimen. In the pooled analyses of the Phase 3 trials, 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.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology Review by Dr. Mark Seaton for details.

Carcinogenesis and Mutagenesis

The carcinogenic potential of rilpivirine has been assessed in 2-year carcinogenicity studies in rats and in mice. In rats, rilpivirine was negative for statistically significant drug related neoplasms. In mice, hepatocellular adenomas alone and hepatocellular adenomas-carcinomas were observed. The

findings are considered to be treatment related; however, the increased incidence of liver tumors is thought to result from a rodent-specific mechanism related to induction of hepatic enzymes, such that the tumors may not be relevant to humans.

A series of in *vitro* and *in vivo* genotoxicity tests have shown rilpivirine to be free of genotoxic potential. Rilpivirine did not show a potential for phototoxicity, skin irritation, or allergic or delayed sensitization reactions. Rilpivirine was a moderate eye irritant in an *in vitro* test.

General Toxicology Studies

No adverse effects of rilpivirine on the cardiovascular, respiratory, or central nervous systems were noted during initial safety pharmacology studies. Subsequently, a Phase 1 clinical trial demonstrated a QT interval-prolonging effect of rilpivirine at supratherapeutic doses. In follow-up safety pharmacology studies, rilpivirine demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization. Refer to Section 7.4.4 ECG for additional details.

The primary toxicity findings in nonclinical studies were adrenal effects observed in rats, dogs, Cynomolgus monkeys, and possibly mice. These effects are thought to be associated with an inhibition of the steroidogenesis at the level of 21-hydroxylase and 17-hydroxylase (the latter observed in Cynomolgus monkeys only). The Phase 3 clinical data indicated that 21-hydroxylase is not affected by treatment with rilpivirine. However, there is a small mean decrease in basal cortisol levels and the cortisol response to ACTH stimulation is attenuated. See Section 7.3.5 for further details.

Effects on the ovaries of dogs were characterized by premature activation and overstimulation. The premature ovulation noted in immature dogs treated for 4 weeks was not found in immature Cynomolgus monkeys, although the lack of an early puberty effect in the monkeys may be related to the young age of the monkeys and the fact that the monkeys were still pre-pubertal at the end of the study. Growth and development will be carefully monitored during the pediatric clinical trials.

Renal effects were observed in mice and dogs. In mice, findings in the kidney were limited to minimal to moderate nephropathy that was noted in half of the female mice treated with the high dose, 320 mg/kg/day. Findings of kidney toxicity in the dog were only noted at exposures more than 25-fold the exposure in humans at the recommended clinical dose. Effects were limited to acute interstitial nephritis in two males and minimal to slight corticomedullary mineralization in all females sacrificed at the end of the study. Renal effect of rilpivirine was also noted in humans - a small increase in serum creatinine over time. See section 7.4.5.

Reproductive Toxicology Studies

The reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity, on parturition, or maternal behavior. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, minimal effects on bone ossification and other developmental endpoints 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. See Section 7.5.7

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Rilpivirine (rilpivirine hydrochloride, RPV), is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1(HIV-1). Rilpivirine binds directly to reverse transcriptase (RT) and blocks the DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

4.4.2 Pharmacodynamics

In summary, exposure-response analysis was conducted for efficacy (by baseline viral load- </> 100,000 copies/mL) and safety [psychiatric, skin (rash), dizziness, hepatobiliary adverse events and GFR]. No exposure-response relationship was established for the safety variables evaluated. Overall, subjects with higher exposure were more likely to achieve virologic suppression. More specifically, the exposure-response analysis suggests that higher exposure is needed in subjects with baseline HIV-1 RNA >100,000 copies/mL to attain similar virologic suppression when compared to subjects with baseline HIV-1 RNA $\leq$ 100,000. See section 6.0 for further details. However, dose adjustment or therapeutic drug monitoring is not recommended because this strategy was not evaluated and there is concern about the effect on the QT interval if additional doses of rilpivirine are given. Please also refer to FDA's Pharmacometrics Review by Dr. Jeff Florian for additional details.

4.4.3 Pharmacokinetics

A brief summary of the pharmacokinetics of rilpivirine is presented in this section. Please refer to FDA's Clinical Pharmacology Review of NDA 202-022 by Dr. Stanley Au for details.

Absorption
The solubility of rilpivirine drug substance is low and pH dependent. Therefore, the oral bioavailability of rilpivirine can vary based on concomitant food intake and presence of drugs that increase gastric pH.

Distribution
Rilpivirine is highly protein-bound. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

Metabolism
A major metabolic pathway of rilpivirine is oxidation.

Elimination
Rilpivirine is excreted in feces. Excretion in urine was limited to a mean of 6.1%, with <1% of the unchanged rilpivirine being detected in urine.

Food Effect
It is recommended that rilpivirine be administered with a meal to ensure optimal absorption and exposure. In the Phase 2b trial and the Phase 3 trials, subjects were instructed to take the rilpivirine with a meal.

Special Populations
The effects of HIV status, hepatic function, gender, and race on rilpivirine pharmacokinetics were assessed. No dose adjustment is required for mild and moderate hepatic impairment; the effect of severe hepatic impairment was not evaluated. Since rilpivirine is primarily eliminated hepatically, a renal impairment study was not conducted. There was no effect noted for either gender or race on rilpivirine pharmacokinetics; there were too few geriatric subjects enrolled to make any definitive conclusions about effect of age. The pharmacokinetics of rilpivirine in the pediatric population is currently under investigation.

5 Sources of Clinical Data

The two pivotal phase 3 trials, C209 and C215 provided the primary data for characterization of the tolerability, safety and effectiveness of rilpivirine in HIV-infected, treatment naive subjects. Both trials were multi-centered, international, randomized, double-blind, double-dummy studies comparing the safety and efficacy of rilpivirine (TMC278) 25mg qd to efavirenz (EFV) 600 mg qd. The two trials were identical in design with exception of the background regimen. Study C209 only allowed tenofovir (TDF)/emtricitabine (FTC) (either as a FDC or as individual drugs) to construct a background regimen. Three options were available to construct the background regimen for study C215: TDF/FTC, zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC (either as FDC or as individual drugs). Most (60%) had TDF/FTC as their background regimen. Some (30%) and few (10%) received AZT/3TC or ABC/3TC, respectively in combination with rilpivirine 25 mg qd or EFV 600 mg qd.

The 192 Week data from C204, a phase 2b trial, also provided supportive data for evaluation of the safety and efficacy of rilpivirine. In addition, Cystatin C data from trial C215 provided additional information for characterization of the effect of rilpivirine on renal function.

5.1 Tables of Clinical Studies

The two pivotal Phase 3 studies and the supportive phase 2b study, all conducted in HIV-1 infected, treatment naïve subjects are summarized in Table 2. In addition, a number of phase 1 clinical pharmacology studies, including 3 QTc studies have been submitted by the Applicant. Please refer to Dr. Stanley Au's Clinical Pharmacology Review, for further details.

Table 2 Summary of Phase 3 and Phase 2b studies

Trial Name	Study Design	Rilpivirine dose	Comparator dose	Background regimen	# randomized/ treated	Primary efficacy endpoint
C204	Randomized, partially blinded dose finding study	25mg qd 75mg qd 150mg qd	EFV 600 mg qd	TDF/FTC AZT/3TC	373/368	Plasma HIV-1 RNA <50 copies/mL at Week 48
C209	Randomized, double-blinded, double-dummy, active-control	25 mg qd	EFV 600 mg qd	TDF/FTC	694/690	Plasma HIV-1 RNA <50 copies/mL at Week 48
C215	Randomized, double-blinded, double-dummy, active-control	25 mg qd	EFV 600 mg qd	TDF/FTC AZT/3TC ABC/3TC	680/678	Plasma HIV-1 RNA <50 copies/mL at Week 48

5.2 Review Strategy

The clinical review for this NDA was primarily based on the data from the two Phase 3 trials, C209 and C215. The safety analysis was conducted by integrating safety data from the two trials. In addition, results from the Phase 2b trial were reviewed for key safety analysis. The Safety Update Report (SUR) containing safety data up to the cut-off dates of 07 August 2009 for C204, 01 February 2010 for C209, and 28 January 2010 for C215, was also reviewed. Review of efficacy was conducted in collaboration with the Dr. Lei Nie, statistical reviewer from the Division of Biometrics.

5.3 Discussion of Individual Studies

TMC278-C209 (C209, ECHO): An ongoing, randomized, double-blind, double-dummy, active-controlled, international trial to assess the long-term efficacy, safety, and tolerability of rilpivirine compared to EFV, each in combination with a fixed background regimen containing TDF and FTC, in HIV-1 infected, treatment-naïve subjects.

The primary objective was to demonstrate non-inferiority of treatment with rilpivirine when administered as 25 mg q.d. compared to the control (EFV) group in regards to the proportion of virologic responders (plasma viral load < 50 copies/mL), at 48 weeks, with a maximum allowable difference of 12%.

The primary efficacy endpoint, plasma HIV-1 RNA <50 copies/mL at Week 48 was analyzed using FDA's Snap-shot algorithm. HIV viral load is an established endpoint for assessment of treatment effect, as cited in the FDA Guidance, "Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval".

The randomization was stratified by screening plasma viral load (≤ 100,000; > 100,000 - ≤ 500,000; and > 500,000 copies/mL).

Inclusion criteria included plasma HIV-1 viral load at screening ≥ 5000 copies/mL, confirmed sensitivity to TDF/FTC and, no NNRTI resistance-associated mutations (RAMs).

Evaluations for subject safety (history, physical exam, laboratory test, ECG) and efficacy (HIV viral load, CD4 count, HIV-1 resistance testing) were performed at scheduled visits: Week 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. An independent DSMB was established to monitor the safety of the subjects and evaluate the efficacy of the study drug. Key stopping criteria includes lack or virologic response.

A total of 690 subjects were enrolled and treated: 346 were randomized to rilpivirine 25 mg qd and 344 were randomized to efavirenz. The duration of the trial is for a minimum of 96 weeks.

TMC278-C215 (C215, THRIVE): An ongoing, randomized, double-blind, double-dummy, active-controlled, international trial to assess the long-term efficacy, safety, and tolerability of rilpivirine compared to EFV each in combination with a background regimen containing 2 NRTIs in HIV-1 infected, treatment-naïve subjects. The investigator-selected NRTIs were ABC/3TC, AZT/3TC, or TDF/FTC.

TMC278-C215 is identical to TMC278-C209 with the exception of the allowed background regimen and stratification. Inclusion criteria included plasma HIV-1 viral load at screening ≥ 5000 copies/mL, confirmed sensitivity to ABC/3TC, AZT/3TC and/or TDF/FTC, no NNRTI resistance-associated

mutations (RAMs) and negative HLA-B*5701 results if ABC/3TC was to be used as the background regimen. The randomization was stratified by screening plasma viral load (≤ 100,000; > 100,000 to ≤ 500,000; and > 500,000 copies/mL) and the selected background regimen.

A total of 678 subjects were enrolled and treated: 340 randomized to rilpivirine 25 mg qd and 338 randomized to EFV. Refer to discussion under TMC278-C209 for further details on the study design.

TMC278-C204 (C204): An ongoing, randomized, partially blinded, active-controlled, dose-finding trial in HIV-1 infected, treatment-naïve subjects to evaluate antiviral activity, safety and tolerability of rilpivirine as part of an ARV therapy with a background regimen containing 2 investigator selected NRTIs, either AZT/3TC or TDF/FTC. Subjects were randomized to the control group (EFV) or to 1 of the 3 rilpivirine dose regimens. All subjects could enter an optional trial extension up to 240 weeks. After 240 weeks, subjects on rilpivirine will have the option to enter another trial extension. A total of 368 subjects were enrolled and treated: 93 subjects in rilpivirine 25 mg qd arm, 95 subjects in rilpivirine 75 mg qd arm, 91 subjects in rilpivirine 150 mg arm, and 89 subjects in EFV 600 mg qd arm. The primary efficacy endpoint is plasma HIV-1 RNA <50 copies/mL at Week 48.

All rilpivirine-treated subjects who consented to continue were switched to rilpivirine 75 mg q.d. + background regimen after Week 96 for the first optional open-label trial extension up to 144 weeks. EFV-treated subjects who re-consented also continued. All rilpivirine-treated subjects who consented to continue were switched to rilpivirine 25 mg q.d. + background regimen at approximately Week 144 for the second optional open-label trial extension up to 240 weeks. Please refer to Section 2.5 for discussion of the reason for switching to 25 mg. Only subjects on rilpivirine treatment who completed the 240 weeks of treatment, and consented to continue, could enter a third optional open-label trial extension until rilpivirine is commercially available, reimbursed or available through another program.

6 Review of Efficacy

Efficacy Summary

Efficacy of rilpivirine in HIV- infected, treatment naïve subjects was demonstrated in the two Phase 3 trials. The efficacy conclusions were also supported by the Phase 2b trial in HIV- infected, treatment naïve subjects.

Both Phase 3 trials reached their primary endpoint (viral load <50 copies/mL) at Week 48. 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 subject 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 $\leq$ 100,000 copies/mL. The response rate was even lower in 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 any statistical conclusion.

The overall response rate (<50 copies/mL at Week 48) to treatment with rilpivirine was variable, depending on exposure (AUC_{24}), ranging from 78% in the lowest quartile to 96% in the highest quartile. For a given exposure (C_{0h}), subjects with baseline HIV-1 RNA ≤100,000 were more likely to have greater virologic suppression compared to subjects with baseline HIV-1 RNA >100,000. Although a exposure-response relationship was observed, therapeutic drug monitoring and dose adjustment is not recommended as rilpivirine has a narrow therapeutic window due to its known effect on QT interval at higher exposure (e.g. 75 mg qd). However, avoiding conditions that may result in decreased rilpivirine exposure (intake without food, co-administration with exposure-lowering drugs including drugs that lower gastric pH) is an important factor.

Subjects experiencing virologic failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on EFV.

In summary, rilpivirine is efficacious for treatment of HIV-1 infection in treatment naïve subjects. However, the efficacy results are influenced by baseline viral load and exposure to rilpivirine. These facts should be considered when treatment is initiated with rilpivirine. Therefore, the rilpivirine 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.

6.1 Indication

Rilpivirine in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment naïve adults.

6.1.1 Methods

The indication is based on the 48 week data from C209 and C215. Because the two Phase 3 trials are identical in design (with exception of the background regimen), a pooled efficacy analysis was conducted. Furthermore, the Phase 2b trial provided additional efficacy data (at Weeks 48, 96 and 192) supporting the indication.

6.1.2 Demographics

The intent to treat population (ITT) 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 (Table 3). 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 3 Demographics and Baseline Characteristics

	C209		C215		Pooled	
	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	Rilpivirine N=686	EFV N=682
Gender n (%)						
Male	268 (77)	275 (80)	250 (73)	244 (72)	518 (75)	519 (76)
Female	78 (23)	69 (20)	90 (27)	94 (28)	168 (25)	163 (24)
Race n (%)						
White	214 (62)	206 (60)	206 (61)	204 (60)	420 (61)	410 (60)
Black	89 (26)	80 (23)	76 (23)	76 (23)	165 (24)	156 (23)
Asian	33 (10)	48 (14)	45 (13)	49 (15)	78 (11)	97 (14)
Other	10 (2)	10 (2)	11 (3)	9(2)	21 (3)	19 (3)
Age (years)*						
Median (min, max)	36 (18-78)	36 (19-67)	36 (19-62)	36 (19-69)	36 (18-78)	36 (19-69)
Geographic Region n (%)						
N. America	116	104	89	84	205	188
S. America	60 (17)	69 (20)	90 (27)	85 (25)	150 (22)	154 (23)
Europe	86 (25)	82(24)	76(22)	69(20)	162(24)	151(22)
Russia Fed.	18(5)	13(4)	19(6)	14(4)	37(5)	27(4)
Australia	5(1)	7(2)	7(2)	1(<1)	12(2)	8(1)
Asia	29(8)	38(11)	40(12)	47(14)	69(10)	85(12)
Africa	32 (9)	31(9)	19(6)	38(11)	51(7)	69(10)
Plasma HIV- 1 RNA n (%)						
Median (min, max)	94950 (156-3300000)	105000 (1010-3360000)	83950 (836-20800000)	102500 (1140-4550000)	90450 (156-20800000)	104500 (1010-4550000)
<100,000	181(52)	163(47)	187(55)	167(49)	368(54)	330(48)
>100,000	131(38)	134(39)	118(35)	136(40)	249(36)	270(40)
>500,000	34(10)	47(12)	35(10)	35(11)	69(10)	85(12)
CD4+ Cell Count						
Median (min, max)	240 (1-888)	257 (1-757)	263 (2-744)	263 (1-1137)	249 (1-888)	260 (1-137)
Clinical stage of HIV infection at screening						
CDC Category A	249(72)	242(70)	237(70)	232(69)	486(71)	474(70)
CDC Category B	83(24)	79(23)	82(24)	90(27)	165(24)	169(25)
CDC Category C	14(4)	23(7)	21(6)	16(5)	35(5)	39(6)
Hepatitis active Co-Infection n (%)						
Positive	19(6)	30(9)	30(9)	33(10)	49(7)	63(10)
Background Regimen						
TDF/FTC	346(100)	344(100)	204(60)	202(59.7)	550(80.2)	546(90)
AZT/3TC	0	0	101(30)	103(30)	101(14.7)	103(15.1)
ABC/3TC	0	0	35(10)	33(9.7)	35(5.1)	33(4.8)

* 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

6.1.3 Patient Disposition

The number of subjects continuing treatment at the time of the 48 week analysis is similar between the two groups (Table 4). In the pooled analysis, the most common reason for discontinuation in the rilpivirine group was 'virologic endpoint reached' (5.2% vs. 2.1%); whereas, discontinuation due to

adverse events was the most common reason in the EFV group (7.8%) compared to 3.4% in the rilpivirine group. The proportion of subjects who discontinued due to non-compliance in the rilpivirine and EFV group were 1.2% and 0.6%, respectively. A greater proportion of subjects withdrew consent in the EFV group than in the rilpivirine group (2.6% vs. 0.9%, respectively).

Table 4 Disposition of the ITT Population

	C209		C215		Pooled	
Number of subjects n, (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Ongoing	296(86)	288(84)	296(83)	282(83)	592(86)	570(84)
Discontinued	50(14.5)	56(16.3)	44(12.9)	56(16.6)	94(13.7)	112(16.4)
Subject reached virologic endpoint	23(6.6)	6(1.7)	13(3.8)	8(2.4)	36(5.2)	14(2.1)
Adverse event	8(2.3)	28(8.1)	15(4.4)	25(7.4)	23(3.4)	53(7.8)
Lost to follow-up	5(1.4)	9(2.6)	10(2.9)	6(1.8)	15(2.2)	15(2.2)
Non-compliant	6(1.7)	2(0.6)	2(0.6)	2(0.6)	8(1.2)	4(0.6)
Withdrew consent	4(1.2)	7(2)	2(0.6)	11(3.3)	6(0.9)	18(2.6)
Other	1(0.3)	1(0.3)	1(0.3)	3(0.9)	2(0.3)	4(0.6)
Sponsor's Decision	2(0.6)	1(0.3)	0	0	2(0.3)	1(0.1)
Ineligible to continue trial	1(0.3)	2(0.6)	1(0.3)	0	2(0.3)	2(0.3)
Did not fulfill inclusion/exclusion Criteria	0	0	0	1(0.3)	0	1(0.1)

Source: Dataset DSAD for pooled trials

6.1.4 Analysis of Primary Endpoint(s)

In the pooled ITT population, the proportions of subjects with viral load <50 copies/mL at Week 48 for rilpivirine and EFV groups were 83% and 80%, respectively (Table 5). The difference in virologic response between the groups was 2.0 [95% CI: -2.0; 6.0]. The lower limit of the 95% CI of the difference between the treatment groups was above -12% and -10%, hence establishing the non-inferiority of rilpivirine to EFV at the pre-specified non-inferiority margins.

In the Phase 3 pooled analysis, the proportions of subjects categorized under 'virologic failure' were 13% in the rilpivirine group and 9% the EFV group. Among these, a greater proportion of subjects discontinued due to 'discontinued due to virologic failure' in the rilpivirine group than in the EFV group (5% vs. 2%, respectively). For the other sub-categories of 'virologic failure', the outcomes were comparable between the two treatment groups. The proportion of subjects with 'no data at Week 48' was lower in the rilpivirine than in the EFV group (5% vs. 11%, respectively). 'Discontinuation due to AE or death' was the most common reason for 'no data at Week 48' (2% for rilpivirine and 7% for EFV group). Table 5 summarizes virologic outcome at Week 48.

Table 5 Virologic outcome at Week 48

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
HIV-1 RNA < 50 copies/mL	285 (82.4)	280 (81.4)	281 (82.6)	267 (79)	566 (82.5)	547 (80.2)
Virologic failure	47(13.6)	24(7)	41(12.1)	37(10)	88(12.8)	61(9.1)
Ongoing and viral load >50 copies/mL	17(4.9)	13(3.8)	17(5)	14(4.1)	34(5)	27(4)
Discontinued due to virolgoic failure	20(5.8)	4(1.2)	12(3.5)	8(2.4)	32(4.7)	12(1.8)
Discontinued due other reasons and viral load >50 copies/mL at time of the discontinuation	10(2.9)	7(2)	8(2.4)	9(2.7)	18(2.6)	16(2.3)
Switch in background regimen not allowed by protocol	0	0	4(1.2)	6(1.8)	4(0.6)	6(0.9)
No virologic data at Week 48 window	14(4)	40(11.6)	18(5.3)	38(11.2)	32(4.7)	78(11.4)
Discontinued due to adverse event or death	6(1.7)	25(7.3)	9(2.6)	24(7.1)	15(2.2)	49(7.2)
Discontinued for other reasons and last available HIV-1 RNA < 50 copies/mL (or missing)	5(1.4)	12(3.5)	8(2.4)	11(3.3)	13(1.9)	23(3.4)
Missing data during window but on study	3(0.9)	3(0.9)	1(0.3)	3(0.9)	4(0.3)	6(0.9)

Source: Dataset VLAD from pooled studies

6.1.5 Analysis of Secondary Endpoint

Immunology

Overall, the mean change in CD4 cell count from baseline was 219 cells/mm^3 in the rilpivirine group and 206 cells/ mm^3 in EFV group (Table 6).

Table 6 Mean Change in CD4+ Cell Count from Baseline

	C209		C215		Pooled	
CD4+, Week 48	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
CD4+ count, mean (cell/mm^3)	489	479	483	471	486	475
Change from baseline at Week 48	224	211	212	200	219	206

Source: FDA Statistical Reviewer's Analysis

6.1.6 Subpopulations

Proportion of patients with HIV RNA < 50 copies/mL (Virologic Success) by Baseline HIV-1 RNA

Table 7a summarizes the virologic success rate based on baseline HIV-1 RNA.

Intra-group comparisons: Subjects with viral load ≤ 100,000 vs. >100,000 copies/mL at baseline and who received rilpivirine had a response rate of 89% and 75%, respectively. The mean difference of the response rate is 14% with a 95% confidence interval of (0.09, 0.20) (p=0.000001).
Similar findings (83% vs.77%) were observed for the EFV group. However, the difference, was less pronounced, but remained statistically significant (p = 0.044).

Inter-group comparisons: For subjects with baseline plasma viral load ≤ 100,000 copies/mL, the proportion of subjects who achieved virologic suppression was 6% higher in the rilpivirine group when compared to EFV group. Conversely, the rilpivirine group responded 2% worse in subjects with baseline plasma viral load >100,000 copies/mL.

Table 7a Virologic Success Rate at Week 48 by Baseline Viral Load

Virological Response (< 50 HIV-1 RNA copies/ml) at 48 Weeks by Baseline Viral Load (Pooled Data from the TMC278-C209 and TMC278-C215 Trials)				
	Rilpivirine N=686		EFV 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	368	89%(328/368)	330	83%(275/330)
> 100,000	318	75%(238/318)	352	77%(271/352)
≤100,000	368	89%(328/368)	330	83%(275/330)
>100,000 - ≤ 500,000	249	78%(193/249)	270	78%(211/270)
> 500,000	69	65%(45/69)	82	73%(60/82)

Source: FDA Statistical Reviewer's Analysis

Virologic Failure by Baseline HIV-1 RNA

Virologic failure is defined as 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 but with viral value of ≥ 50 copies/mL at the time of discontinuation, and subjects who had a switch in background regimen that was not permitted by the protocol. Table 7b summarizes the virologic failure rate based on baseline HIV-1 RNA. Unlike the virologic success rates, there appears to be greater difference in virologic failure rate between the two treatment groups among subjects with baseline HIV-1 >100,000 copies/mL; the failure rate is almost twice as high in the rilpivirine group, 22% vs. 13%. Due to this observed difference, the Usage and Indications Section will include the following information:

- More rilpivirine treated subjects with HIV RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to patients with HIV RNA less than 100,000 copies/mL at the start of therapy.

In addition, the efficacy table under Clinical Studies Section will reflect virologic success and failure rates by the three baseline HIV-1 RNA strata.

Table 7b Virologic Failure Rate at Week 48 by Baseline Viral Load

	Rilpivirine N=686		**EFV 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)[(a)]	368	5.2% (19/368)	330	5.5% (18/330)
> 100,000 (p=.002)	318	21.7% (69/318)	352	12.5% (44/352)
≤ 100,000 (p=.86)	368	5.2% (19/368)	330	5.5% (18/330)
> 100,000 and ≤ 500,000 (p=0.007)	249	19.7% (49/249)	270	11.1% (30/270)
> 500,000 (p=0.08)	69	29.0% (20/69)	82	17.1%(14/82)

[(a)]p is the statistical significance level (p-value) showing the difference between TMC and EFV in each subgroup. The p-value is calculated using chi-square test.

Source: FDA Statistical Reviewer's Analysis

Of note, similar efficacy analyses were performed on the Phase 2b data (see Section 6.1.7). The results support the findings from the Phase 3 trials.

Virologic Outcome by Background Regimen

Virologic outcomes were similar between the two groups, regardless of the background regimen selected (Table 8). Furthermore, no difference was noted among the 3 options available for constructing the background regimens.

Table 8 Virologic Outcome (HIV-1 RNA <50 copies/mL) at Week 48 by Background Regimen

	C209		C215		Pooled	
Background Regimen	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	Rilpivirine N=686	EFV N=682
TDF/FTC	82.4%	81.4%	82.4%	78.7%	82.6%	80.4%
AZT/3TC	-	-	81.2%	73.8%	81.2%	73.8%
ABC/3TC	-	-	82.9%	84.9%	82.9%	84.9%

Source: FDA Statistical Review's Analysis

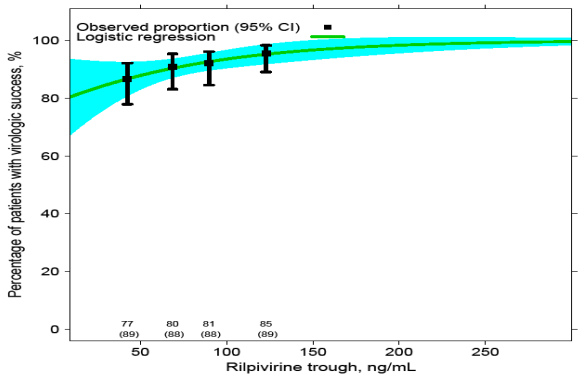
Exposure-response

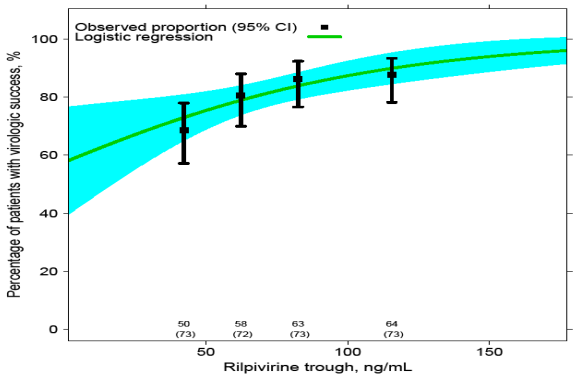
According to the Applicant, in the Phase 3 trials, virologic response rates ranged from 78.3% (lowest AUC_{24} quartile) to 95.7% (highest AUC_{24} quartile); the median exposure (AUC_{24}) was lower for subjects who did not achieve a plasma viral load of < 50 copies/mL. Exposure-response analysis was 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. Refer to Dr. Jeff Florian's Pharmacometrics Review for details.

In summary, 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.

As mentioned previously, increasing exposure by increasing rilpivirine dose is not a valid option. 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 has been included in the Contraindications Section of the label.

Figure 1: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus Rilpivirine C_{0h} for Patients with Baseline Viral Load <100,000 (left) and ≥100,000 Copies/mL (right) from C209 and C215.





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Source: Pharmacometrics Reviewer's Analysis

Emergence of Resistance and Cross-Resistance

In the pooled resistance analysis from the Phase 3 trials, the emergence of resistance was greater in the rilpivirine group compared to the EFV group. In the pooled analysis, 41% (38/92) of the virologic failures in the rilpivirine arms developed rilpivirine phenotypic and genotypic resistance compared to 25% (15/60) of the virologic failures in the EFV group who developed efavirenz resistance. Additionally, resistance to a background drug occurred in 48% (44/92) of the virologic failures in the rilpivirine group compared to 15% (9/60) in the efavirenz group (Table 9). Of the rilpivirine subjects who were virologic failures, 89% (34/38) were resistant to etravirine and efavirenz, and 63% (24/38) were resistant to nevirapine. Subjects experiencing virologic failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on EFV. Refer to Section 4.2 Clinical Microbiology for details. The Usage and Indications Section will therefore include the following information:

- Rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz.

Table 9 Frequent Emergent RT Substitutions in Virologic Failures

	TMC278 N=686	**EFV Control N=682**
As-Treated Virologic Failures	92/652 (14%)	60/604 (10%)
Emergent NNRTI Substitutions in Virologic Failures		
V90I	11% (10/92)	2% (1/60)
K101E/P/T	15% (14/92)	2% (1/60)
K103N	0	20% (12/60)
E138K/G	30% (28/92)	0
V179I/L/D	11% (10/92)	7% (4/60)
Y181C/I	8% (7/92)	0
V189I	7% (6/92)	2% (1/60)
H221Y	7% (6/92)	0
E138K M184I	22% (20/92)	0
Emergent NRTI Substitutions in Virologic Failures		
M184I or V	43% (40/92)	13% (8/60)
K65R/N	8% (7/92)	3% (2/60)

Source: Virology Reviewer's Analysis

Effect of Gender and Race

No statistically significant difference was noted in the overall efficacy of rilpivirine when analyzed by gender or race (Caucasians vs. non-Caucasians). In addition the overall response rate (HIV-1 RNA <50 copies/mL at Week 48) was similar between the two treatment groups among the respective genders and race subpopulations. See Statistical Review by Dr. Nie for additional details.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendation

Once the in-vitro activity and pre-clinical safety of rilpivirine were ascertained, dose ranges and a once daily dosing regimen was established with healthy volunteer studies. Subsequent to single dose and multiple ascending dose trials in healthy volunteers, Phase 2a studies were conducted to establish the antiviral activity of rilpivirine. Based on the pharmacokinetic data from the healthy volunteer data and the short term antiviral activity data from the Phase 2a studies, a long term, dose finding (25 mg qd, 75

mg qd, 150 mg qd), Phase 2b study (C204) was initiated. Refer to section 5.3 for additional details on phase 2a and 2b study designs and results.

The dose of rilpivirine 75mg qd was initially selected for the Phase 3 trials based on the assessments of the 48 week efficacy, safety, pharmacokinetic and pharmacodynamic data from the dose-finding Phase 2b trial. The results did not demonstrate a statistically significant difference in virologic response (<50 copies/mL at Week 48) among the 3 doses [81%, 80%, 77% in the 25 mg, 75 mg and 150 mg qd groups, respectively]. The 75 mg dose was selected as the optimal dose for further development for the following reasons: per Applicant, for the subgroup of subjects with baseline viral load >300,000 copies/mL, 68% of subjects from the 25 mg qd group met the primary endpoint compared to 71% in the 150 mg group and 77% in the 75 mg group; in addition, more (11%) discontinuations due to adverse events were noted in the highest (150 mg qd) dose group-compared to 8% in the 75mg group and 6% in the 25 mg group. Prior to initiation of the Phase 3 trails, the thorough QT (TQT) study results demonstrated a dose and concentration dependent QT prolongation with the 75 mg qd dose. A reassessment of the risks and benefits of the 75 mg was conducted and the 25 mg qd dose was selected for the Phase 3 trials.

Long term (Weeks 96) efficacy data from the phase 2b trial demonstrated durable efficacy for all 3 rilpivirine doses (25 mg qd, 75 mg qd, 150 mg qd): virologic response rate (confirmed viral load < 50 copies/mL) was 76.3%, 71.6% and 71.4%, respectively. The response rate for the control group (EFV) was 70.8%. .

Therefore, although the optimal dose for further development was revised to a lower, 25 mg qd dose, the durability and comparability of the 25 mg to EFV has been demonstrated with a 96 Week data.

6.1.8 Discussion of Persistence of Efficacy

The FDA Guidance, “Antiretroviral Drugs Using Plasma HIV RNA Measurements- Clinical Considerations for Accelerated and Traditional Approval” states that a 48-Week data can be used for traditional approval. The Division considers a 48-Week efficacy data sufficient for demonstration of persistence of efficacy in HIV-1 infected, treatment naïve subjects. See Sections 6.1.4 for results of the 48 Week data. The Phase 3 trials are designed to continue for a minimum of 96-Weeks. Additional efficacy and safety data will be submitted once the 96 week data are available.

The Phase 2b trial provides a longer duration (96 Week) efficacy data. Below is the overall efficacy outcome from TMC278-C204.

Table 10 Phase 2b Virologic Outcome at Week 96

	Rilpivirine 25 mg N=93	EFV N=89
Virologic success HIV-1 RNA < 50 copies/mL	71(76.3)	63(70.8)
Non-responders	22(23.7)	26(29.2)
Virologic failure†	13(14)	14(15.7)
Death	0	0
Discontinuation due to AE	8(8.6)	7(7.9)
Discontinuation for other reasons	1(1)	5(5.6)

† Includes subjects who had ≥ 50 copies/mL in the Week 96 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
Source: Dataset VLAD phase 2b trial

The Applicant has also submitted a Week 144 and Week 192 efficacy data (Table 11). Note, between Week 96 and Week 144, subjects were switched to 75 mg qd as 75 mg qd was originally selected for further development. Per Tibotec, among the suppressed subjects who were enrolled in the 150 mg, none lost their virologic suppression when switched to the 75 mg qd. At Week 144, the proportions of subjects with HIV-1 RNA <50 copies/mL for the rilpivirine group and the EFV group were 68.8% and 61.8%, respectively. The difference (8%) in the success rate is higher in the Phase 2b trial when compared to the pooled Phase 3 trials; this may be due to the roll-over of subjects who had been receiving higher doses of rilpivirine. In addition, unlike the Phase 3 pooled results, the proportion of virologic failures in the rilpivirine group was smaller compared to EFV group (16.1% vs. 19.1%, respectively). Again, this may be due to the higher doses used in the Phase 2b trial between weeks 96 and 144.

At Week 144 (or no later than Week 157), all subjects were switched to the revised Phase 3 dose of 25 mg qd. By Week 196, the proportion of rilpivirine treated subjects who were virologically suppressed was 63.4% compared to 60.7% in the EFV treated group. Similar to the Phase 3 findings, more subjects had virologic failure in the rilpivirine group (20.4% vs. 18%), although the difference is smaller in the Phase 2b result. In the Phase 3 trials, as discussed before, the proportions of subjects with virologic failure were 12.8% in the rilpivirine group and 9.1% in the EFV group.

Table 11 Phase 2b Virologic Outcome at Week 144, Week 196

n(%)	Rilpivirine 25 mg N=93	EFV N=89
Week 144		
Viral load <50 copies/mL	63(68.8)	55(61.8)
Non-responders	27(29)	34(38.2)
Virologic failure†	15(16.1)	17 (19.1))
Deaths	1(1)	0
Discontinuation due to AE	10(10.8)	9(10.1)
Discontinuations for other reasons	4(4.3)	8(9)
Week 196		
Viral load <50 copies/mL	59(63.4)	54(60.7)
Non-responders	(36.6)	35(39.3)
Virologic failure†	19(20.4)	16(18)
Deaths	1(1)	0
Discontinuation due to AE	10(10.8)	11(12.4)
Discontinuation for other reasons	4(4.3)	8(9)

† Includes subjects who had ≥ 50 copies/mL in the Week 144,192 windows, 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
Source: Datasets VLAD Phase 2b trial

Virologic Failure by Baseline HIV-1 RNA

At the time of EOP2 and preNDA meetings, the summary data provided by the Applicant showed comparability of the three doses of rilpivirine to EFV in meeting the primary efficacy endpoint (proportion of subjects with HIV-1 RNA < 50 at Week 48). However, after establishing the Phase 3 virologic failure rate by baseline HIV-1 RNA, the Phase 2b data were re-examined (Table 7c), which showed a higher virologic failure rate in rilpivirine treated subjects with HIV-1 RNA >100,000 copies/mL at baseline compared to subjects treated with EFV at the 48 week and later timepoints. The overall efficacy outcomes for the Phase 2b trial are presented under Section 6.1.8.

The results for the 25 mg rilpivirine dose from the Phase 2b analysis (by baseline HIV-1 RNA) at Week 48 and 96 are displayed in Table 7c. Overall, the data supports the Phase 3 trials finding. The results for Weeks 144 and 192 should be interpreted with caution as these were from open-label, optional extension phase. Overall, 5 subjects did not enter the extension phase- 2 in the EFV group and 3 in the rilpivirine group, all of whom were suppressed at Week 96.

Table 7c Virologic Failure Rate at Weeks 48, 96, 144, 192 by Baseline Viral Load

	Rilpivirine 25 mg		EFV	
	N=93	Proportion of Subjects with HIV-1 RNA < 50 copies/ml, (%) n; [≥ 50 copies/ml, (%) n]*	N=89	Proportion of Subjects with HIV-1 RNA < 50 copies/ml, (%) n; [≥ 50 copies/ml, (%) n]*
Baseline Plasma Viral Load (copies/ml), Snapshot algorithm				
Week 48				
≤ 100,000	61	51/61(83.6); [6/61 (9.8)]	56	46/56(82.1); [7/56 (12.5)]
> 100,000	32	23/32(71.9); [7/32 (21.9)]	33	26/33(78.8); [4/33 (12.1)]
Week 96				
≤ 100,000	61	48/61(78.7); [4/61 (6.6)]	56	39/56(69.6); [10/56 (17.9)]
> 100,000	32	23/32(71.9); [7/32 (21.9)]	33	24/33(72.7); [3/33 (9.1)]
OPTIONAL EXTENSION PHASE				
Week 144				
≤ 100,000	61	42/61(68.9); [5/61(8.2)]	56	34/56(64.2); [8/56 (14.3)]
> 100,000	32	21/32(65.6); [9/32 (28.1)]	33	21/33(63.6); [5/33 (15.2)]
W192				
≤ 100,000	61	40/61(65.6); [9/61(14.8)]	56	34/56(60.7); [7/56 (12.5)]
> 100,000	32	19/32(59.4); [10/32 (31.3)]	33	20/33(60.6); [5/33 (15.2)]

*Virologic failure is defined as subjects who had ≥ 50 copies/mL in the defined window (Week 48, 96, 144 or 192), 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 but with viral value of ≥ 50 copies/mL at the time of discontinuation
Source: Datasets VLAD Phase 2b trial

7 Review of Safety

Safety Summary

The principal treatment-related adverse events identified during the Phase 3 trials include psychiatric disorders (depression, insomnia, abnormal dreams) and rash. With exception of depression, these adverse events (at least grade ≥ 2 in severity) occurred with lower or similar incidence in the rilpivirine group compared to EFV group: insomnia (3% vs. 3%), abnormal dreams (2% vs. 4%), and rash (3% vs. 11%). The incidence of depression was 3% in the rilpivirine group and 2% in the EFV group. None of these adverse events were found to have an exposure-response correlation.

The clinical laboratory results demonstrated an increase in serum creatinine over time, an observation only seen in the rilpivirine group. Most of the increase occurred in the first 2 weeks then plateaued. Although an increase in mean serum creatinine was noted, the maximum mean change at Week 24 compared to baseline was less than 1 mg/dL. Furthermore, the event appears to reverse after cessation of treatment, although the reversal was not complete. This increase is hypothesized to be due to an effect on the renal tubules whereby rilpivirine is thought to interfere with tubular secretion, similar to cimetidine. Although there is strong evidence in support of the hypothesis, it was not established. Most of the graded renal adverse events were mild to moderate and the incidence of renal failure was comparable between the two treatment groups.

Other significant laboratory findings include asymptomatic hyperbilirubinemia. Most cases were mild (grade 1) and were due to an increase in indirect bilirubin. No Hy's Law cases of drug-induced hepatotoxicity were identified. An exposure-response relationship was not demonstrated for either the increase in serum creatinine or the hyperbilirubinemia.

Adrenal suppression was identified early in the pre-clinical developmental stage. The clinical data from the Phase 3 trials were significant for an overall small mean change from baseline in basal cortisol -a decrease of -13.1 nmol/L in the rilpivirine group, compared to an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+16.5 ±6.14 nmol/L) than in the efavirenz group (+58.1 ±6.66 nmol/L). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Finally, based on a thorough QT study, rilpivirine has been shown to prolong the QT interval at supratherapeutic doses (75 mg qd, 300 mg qd). A supportive QT study at the recommended dose of 25 mg qd did not have a substantial effect on the QT interval.

7.1 Methods

As discussed previously, the Phase 3 trials, TMC278-C209 and TMC278-C215 are double-blind, double-dummy, active-controlled with a 1:1 randomization scheme. The two trials are identical with the exception of the background regimen used. Pooled AE data was reviewed from 1368 subjects who received at least 1 dose of treatment to identify clinical adverse effects and laboratory toxicities associated with rilpivirine use. In addition, selected safety data from the Phase 2b trial (TMC278-C204) was reviewed. The Applicant identified specific adverse events based on the cumulative safety data from Phase 1 through Phase 3 trials, as well as the safety profile already described for the NNRTI class. The cumulative data was used to create a specific safety analysis section- ' Submission Specific Primary Safety Concerns' which is also referred to as 'adverse events of special interest' in this review.

Review of this original NDA includes safety data from trials with cut-off dates of 28 January 2010 for C209 and 01 February 2010 for C215. Line listings and safety reports for SAEs that occurred after the respective database cut-off dates up until 05 July 2010 were also included in the NDA submission and reviewed. This review also incorporates data submitted in the Safety Update Report (SUR) with clinical cutoff dates of 07 August 2009 for C204, 01 February 2010 for C209, and 28 January 2010 for C215.

Overall the pooled Phase 3 safety data analyses performed replicated the Applicant's findings with few exceptions. The exceptions did not lead to a difference of beyond 1-2% and were due to methods used for identifying treatment windows, pooling preferred terms or attribution of treatment-relatedness.

7.1.1 Clinical Studies Used to Evaluate Safety

The Applicant's analysis for summary of clinical safety, in support of rilpivirine for the treatment of HIV-1 infection in treatment-naïve adult patients, relied on safety data from 35 trials: 30 Phase 1 trials, 2 Phase 2a trials, 1 Phase 2b trial, and 2 Phase 3 trials.

This NDA review focuses on safety data from the two Phase 3 trials with additional supporting data from the Phase 2b trial. As mentioned above, safety data from the Phase 1, 2a, and 2b were considered for identification of specific adverse events (adverse events of special interest).

7.1.2 Adequacy of Data

The FDA Guidance, "Antiretroviral Drugs Using Plasma HIV RNA Measurements- Clinical Considerations for Accelerated and Traditional Approval" considers safety data from a minimum of 500 patients who have received a drug for approximately 48 weeks as a minimum requirement for traditional approval. In addition, safety data from earlier study enrollees who have been followed for periods longer than 48 weeks are expected. Controlled comparison is an important aspect for safety analysis as it is helpful in characterizing and defining drug associated adverse events. The Applicant has submitted safety data from controlled Phase 3 and Phase 2b studies in 1736 subjects (1368 from Phase 3 + 268 from Phase 2b). Of these, 965 received rilpivirine (686 from Phase 3 and 279 from Phase 2b). The duration of the studies at the time of the safety data submission is 48 weeks for the Phase 3 data and 192 weeks for the Phase 2b data.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The Phase 3 trials are identical in design with the exception of the background regimen used. Therefore, the safety data were pooled for estimating and comparing safety incidence.

7.2 Adequacy of Safety Assessments

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

The dose selected for marketing is 25 mg qd. During the Phase 3 trials, 25 mg qd was used throughout the treatment period. In addition, during the Phase 2b trial, the doses used were either 25 mg qd or higher (i.e. 75 mg qd, 150 mg qd). Therefore inclusion of all Phase 2b subjects for safety assessment is appropriate. As stated previously, 965 subjects from the Phase 3 and 2b trials received rilpivirine. Of these, 611 (89%) from the Phase 3 trials and 183 (66%) from the Phase 2b trial have been dosed for a minimum of either 48 weeks (Phase 3) or 192 weeks (Phase 2b) and were continuing on treatment at the time of the cut-off. Please refer to Section 6.1.2 for demographic information.

7.2.2 Explorations for Dose Response

Dose response relationship has been evaluated by the Applicant and the FDA. Psychiatric events, hepatobiliary events, rash and dizziness were assessed for dose response correlation. In addition, exploration to evaluate the relationship between laboratory toxicities – hyperbilirubinemia and elevation in serum creatinine- and rilpivirine exposure was conducted. Refer to Dr. Jeff Florian's Pharmacometrics Review for further details.

7.2.3 Special Animal and/or In Vitro Testing

The preclinical program for rilpivirine was consistent with acceptable scientific practices and international guidelines. The pivotal studies were conducted according to good laboratory practices (GLP) standards as per Organization for Economic Cooperation and Development (OECD) Principles of GLP, which concur with FDA GLP regulations.

Rilpivirine demonstrated in vitro activity against wild-type HIV-1 virus. Nonclinical safety, pharmacology and toxicology studies demonstrated its safety for use in clinical testing. Rilpivirine did not show a potential for genotoxicity, teratogenicity and phototoxicity in animals. Fertility, early embryonic development, pre- and postnatal development, and the immune system were not affected by rilpivirine in animals. Refer to reviews by Drs. Lisa Naeger, Virology reviewer, and Mark Seaton, Pharmacology/Toxicology reviewer for further details.

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety included medical history taking for assessment of symptoms of adverse events, vital sign measurements and physical examinations for assessment of signs of adverse events, laboratory evaluations and ECG for assessment of rilpivirine toxicities. Testing was scheduled to be conducted at baseline, Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, post Week 96. In addition, follow-up visits were scheduled for subjects with adverse events or who discontinued treatment prematurely.

7.2.5 Metabolic, Clearance, and Interaction Workup

A major metabolic pathway of rilpivirine is oxidation. Based on a mass-balance study in healthy volunteers, ^{14}C-rilpivirine has been showed to be excreted in feces. Excretion of the ^{14}C-rilpivirine in urine was limited to a mean of 6.1%, with <1% of the unchanged rilpivirine being detected in urine. Per Tibotec, during the clinical trials (Phase 2b and 3), the variability of the rilpivirine exposure is moderate for the 25mg dose, with an inter-individual variability for apparent oral clearance of 38% in the Phase 2b trial and 39% in the Phase 3 trials.

Numerous drug-drug interaction trials were conducted to evaluate the effects of co-administering rilpivirine with other drugs (e.g. ARVs, CYP3A substrates, CYP3A inducer or inhibitors, drugs that alter gastric pH). Overall, rilpivirine at the dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of co-administered drugs. Conversely, the exposure to rilpivirine can be affected by modulators of CYP3A enzyme activity and by drugs that increase the gastric pH. Refer to Dr. Stanley Au's Clinical Pharmacology Review.

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

Refer to Section 7.1 for discussion on this topic.

7.3 Major Safety Results

7.3.1 Deaths

In the pooled Phase 3 analysis, 5 subjects, 1 in the rilpivirine group and 4 in the EFV group, died during the 48 week treatment period. The adverse events leading to death are displayed in the table below.

Table 12 Adverse Events Leading to Death

	C209		C215		Pooled	
System Organ Class Preferred Term, n (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
All Deaths	0	1(0.3)	1(0.3)	3(0.9)	1(0.1)	4(0.6)
Infections and Infestations	0	0	1(0.3)	2(0.6)	1(0.1)	2(0.3)
Bronchopneumonia	0	0	1(0.3)	0	1(0.1)	0
Cerebral toxoplasmosis	0	0	0	1(0.3)		1(0.1)
Dysentery	0	0	0	1(0.3)		1(0.1)
Neoplasm benign, malignant and unspecified	0	1(0.3)	0	0		1(0.1)
Burkitt's lymphoma	0	1(0.3)	0	0		1(0.1)
Nervous system disorders	0	0	0	1(0.3)		1(0.1)
Cerebrovascular accident	0	0	0	1(0.3)		1(0.1)
Respiratory, thoracic and mediastinal disorders	0	0	0	1(0.3)		1(0.1)
Respiratory failure	0	0	0	1(0.3)		1(0.1)

Source: AEAD dataset for pooled trials

None of the adverse events leading to deaths were considered related to study drug.

The subject receiving rilpivirine was a 45 year old male with CDC category A at screening, baseline viral load 334,000 copies/mL and CD4+ count of 48 cells/mm^3. His background regimen was AZT/3TC which was switched to TDF/FTC after approximately 7 weeks of treatment due to anemia. The subject was diagnosed with grade 2 bronchopneumonia and thrombocytopenia approximately 52 days after start of treatment. Rilpivirine was continued and treatment with an antibiotic (clindamycin) was initiated for the pneumonia. No treatment was initiated for the thrombocytopenia which persisted and worsened to grade 3. After 23 days, the subject was hospitalized for grade 3 bronchopneumonia and thrombocytopenia and study medication was discontinued. Treatment was revised for the pneumonia, which included TB and Pneumocystis therapy. The subject died after 19 days of hospitalization (18 days after discontinuation of treatment). The investigator assessed the relationship between the AE and the study medication or the background regimen as not related. In reviewing the adverse events data, laboratory data (including the low baseline CD4+ count) and case narrative, the death does not appear to be drug related. The low CD4+ count likely contributed to the respiratory infection which led to death. At the time of death, the subject had been off treatment for 18 days.

An additional 4 subjects died during the Phase 2b trial, none are related to study drug.

- A 42 year old male from Russia with baseline viral load and CD4+ of 431,000 and 326 cells/mm^3, who had been on rilpivirine for 104 Weeks died of road traffic accident. His last recorded viral load and CD4+ count were <49 copies/mL and 683 cells/mm^{3}at Week 96.
- Subject was a 49 year old male from South Africa with screening CDC class B, baseline viral load 49,100 copies/mL and CD4+ 103 cells/mm^3. After 116 weeks of treatment with rilpivirine, he complained of headache for 5 days prior to his death. Two days prior to his death, he became

unresponsive and was taken to the emergency department. He was pronounced dead on arrival. The cause of death was “natural causes” and no autopsy was performed. His last recorded viral load and CD4+ cell count was 49 copies/mL and 130 cells/mm^3at Week 108.

- A 39 year old female from Brazil with CDC class A, viral load of 368,000 copies/mL and CD4+ of 66 cells/mm^3 at baseline. She had been on rilpivirine and AZT/3TC for 34 weeks prior to her death. Subject had a history of anemia prior to enrollment. She was admitted to a hospital for evaluation of anemia and dehydration. While hospitalized, she developed lung infection and metabolic acidosis leading to multi-organ failure and death. The last recorded CD4+ and viral load were 11 cells/$mm^3$and <49 copies/mL at Week 32.
- A 55 years old male from the U.S. with concurrent history of hepatitis C, depression, substance abuse and malaise, with baseline CDC classification B, had received 144 weeks of rilpivirine prior to his death. The subject suffered from grade 4 drug toxicity and intestinal infarction and died. An autopsy was performed and reported that the subject had suffered from an acute infarction of the intestines due to vasospastic and cardiovascular effect of methamphetamine combined with pre-existing compromised mesenteric arteries due to aortic arthrosclerosis. His last recorded viral load and CD4+ count were <49 copies/mL and 980 cells/mm^3at Week 132.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

A total of 100 subjects had SAE (regardless of causality). The most common SAE was ‘Infection and Infestations’ (3% in each group). No other SAE (by System Organ Class) occurred with > 1% incidence for either group. With exception of ‘hepatobiliary disorders’, all other SAE occurred with similar incidence between the two groups. The 6 subjects in the rilpivirine arm who experienced hepatobiliary disorder did not discontinue study drug and the events were not considered related to treatment drug. The events were: cholecystitis acute (n=3), cholelithiasis (n=2), hyperbilirubinemia (n=1). The subject with hyperbilirubinemia was also co-infected with hepatitis C. Table 13 summarizes all SAE that occurred during treatment in the 48 Week Phase 3 trials. Subjects with psychiatric disorders, skin disorders, hepatobiliary disorders and renal disorders are further discussed in their respective sections under Submission Specific Primary Safety Concerns (Section 7.3.5).

Table 13 Serious Adverse Events in the Phase 3 Trials

	C209		C215		Pooled	
System Organ Class n (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Number of subjects with any SAEs	23(6.6)	31(9)	22(6.5)	24(7.1)	45(6.6)	55(8.1)
Infections and Infestations	10(2.9)	8(2.3)	8(2.4)	9(2.7)	18(2.6)	17(2.5)
Hepatobiliary Disorders	2(0.6)	1(0.3)	4(1.2)	0	6(0.9)	1(0.1)
Gastrointestinal Disorders	2(0.6)	3(0.9)	3(0.9)	2(0.6)	5(0.7)	5(0.7)
Psychiatric Disorders	3(0.9)	4(1.2)	2(0.6)	3(9.9)	5(0.7)	7(1)
Neoplasms Benign, Malignant and unspecified (including Cysts and Polyps)	4(1.2)	3(0.9)	0	1(0.3)	4(0.6)	4(0.6)
Nervous System Disorders	1(0.3)	4(1.2)	3(0.9)	3(0.9)	4(0.6)	7(1)

Table 13 Serious Adverse Events in the Phase 3 Trials (Continued)

	C209		C215		Pooled	
System Organ Class n (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
General Disorders and Administration Site Conditions	1(0.3)	3(0.9)	2(0.60	1(0.3)	3(0.4)	4(0.6)
Injury, Poisoning and Procedural Complications	1(0.3)	190.30	2(0.6)	3(0.9)	3(0.4)	4(0.6)
Renal and Urinary Disorders	2(0.6)	0	1(0.3)	1(0.3)	3(0.4)	1(0.1)
Respiratory, Thoracic and Mediastinal Disorders	1(0.3)	3(0.9)	1(0.3)	2(0.6)	2(0.3)	5(0.7)
Immune System Disorders	0	0	2(0.6)	1(0.3)	2(0.3)	1(0.1)
Musculoskeletal and Connective Tissue Disorders	2(0.6)	1(0.3)	0	0	2(0.3)	1(0.1)
Skin and Subcutaneous Disorders	1(0.3)	1(0.3)	1(0.3)	2(0.6)	2(0.3)	3(0.4)
Investigations	0	3(0.9)	1(0.3)	1(0.3)	1(0.1)	4(0.6)
Blood and Lymphatic System Disorders	0	1(0.3)	1(0.3)	2(0.6)	1(0.1)	3(0.4)
Metabolism and Nutrition Disorders	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)
Pregnancy, Puerperium and Perinatal Conditions	0	0	1(0.3)	0	1(0.1)	0
Reproductive System and Breast Disorders	1(0.3)	0	0	0	1(0.1)	0
Surgical and Medical Procedures	0	2	0	0	0	2(0.3)
Cardiac Disorders	0	1(0.3)	0	0	0	1(0.1)
Congenital, Familial and Genetic Disorders	0	1(0.3)	0	0	0	1(0.1)

Source: AEAD Dataset for the pooled trials

Serious Adverse Events at Least Related to Rilpivirine or EFV Group

Overall, the incidence of SAE at least related to study drug was similar between the two groups- 1% vs. 0.9% for rilpivirine and EFV groups, respectively. Table 14 summarizes SAE considered at least related to rilpivirine or EFV. See Section 7.3.5 Submission Specific Primary Safety Concerns for further details.

Table 14 Serious Adverse Events at Least Related to Rilpivirine or Efavirenz

	C209		C215		Pooled	
System Organ Class Preferred terms n (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any treatment-related SAEs	3(0.9)	6(0.7)	4(1.2)	0	7(1.0)	6(0.9)
Psychiatric Disorders	1(0.3)	2(0.6)	2(0.6)	0	3(0.4)	2(0.3)
Suicide attempt	1(0.3)	0	1(0.3)	0	2(0.3)	0
Depression	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)
Sleep disorder	0	0	1(0.3)	0	1(0.1)	0
Homicidal ideation	0	1(0.3)	0	0		1(0.1)
Nervous system disorders	1(0.3)	1(0.3)	0	0	1(0.1)	1(0.1)
Miller Fisher syndrome	1(0.3)	0	0	0	1(0.1)	0
Headache	0	1(0.3)	0	0	0	1(0.3)
Skin and subcutaneous tissue disorders	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)

Table 14 Serious Adverse Events at Least Related to Rilpivirine or Efavirenz (Continued)

System Organ Class Preferred terms n (%)	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Pruritis generalized	0	0	1(0.3)	0	1(0.1)	0
Rash generalized	0	1(0.3)	0	0	0	1(0.1)
Renal and urinary disorders	1(0.3)	0	0	0	1(0.1)	0
Glomerulonephritis membranous	1(0.3)	0	0	0	1(0.1)	0
Investigations	0	2(0.6)	1(0.3)	0	1(0.1)	2(0.3)
Brain scan abnormal	0	0	1(0.3)	0	1(0.1)	0
ALT increased	0	1(0.3)	0	0	0	1(0.1)
Transaminases increased	0	1(0.3)	0	0	0	1(0.1)
General disorders and administration site conditions	0	0	1(0.3)	0	1(0.1)	0
Asthenia	0	0	1(0.3)	0	1(0.1)	0

Source: AEAD Dataset for the pooled trials

7.3.3 Dropouts and/or Discontinuations

Overall, 23 subjects (3.4%) in the rilpivirine group and 52 subjects (7.6%) in the EFV group had at least 1 AE leading to discontinuation. The most common AEs (by System Organ Class) leading to discontinuation were 'psychiatric disorders', 1.5% in the rilpivirine group and 2.2% in EFV group. The incidence of 'skin disorders' leading to discontinuation was higher in the EFV group, (0.3% on rilpivirine vs. 1.8% on EFV group), mostly driven by the preferred term 'rash'. Table 15 summarizes AEs occurring in more than 1 subject leading to discontinuation. In summary, based on discontinuation rate from the pooled Phase 3 trials, rilpivirine appears to be better tolerated than EFV, particularly for rash. The rate of discontinuation due to rash is almost twice as high in the EFV group compared to rilpivirine.

Table 15 Adverse Events Occurring in More Than 1 Subject Leading to Discontinuation

	C209		C215		Pooled	
System Organ Class Preferred term, n (%)	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any discontinuation due to adverse events	8(2.3)	27(7.8)	15(4.4)	25(7.4)	23(3.4)	52(7.6)
Psychiatric Disorders	4(1.2)	9(2.6)	6(1.8)	6(1.8)	10(1.5)	15(2.2)
Abnormal dreams	1(0.3)	2(0.6)	1(0.3)	1(0.3)	2(0.3)	3(0.4)
Depressed mood	0	0	2(0.6)	0	2(0.3)	0
Depression	0	3(0.9)	2(0.6)	1(0.3)	2(0.3)	4(0.6)
Insomnia	1(0.3)	3(0.9)	0	0	1(0.1)	3(0.4)
Suicide attempt	1(0.3)	0	1(0.3)	0	2(0.3)	0
Suicide ideation	0	1(0.3)	1(0.3)	1(0.3)	1(0.1)	2(0.3)
Investigations	1(0.3)	3(0.9)	3(0.9)	3(0.9)	4(0.6)	6(0.9)
AST increased	1(0.3)	1(0.3)	2(0.6)	1(0.3)	3(0.4)	2(0.3)
ALT increased	0	2(0.6)	2(0.6)	1(0.3)	2(0.3)	3(0.4)
Pregnancy, puerperium and perinatal condition	0	3(0.9)	3(0.9)	0	3(0.4)	3(0.4)
Pregnancy	0	3(0.9)	3(0.9)	0	3(0.4)	3(0.4)

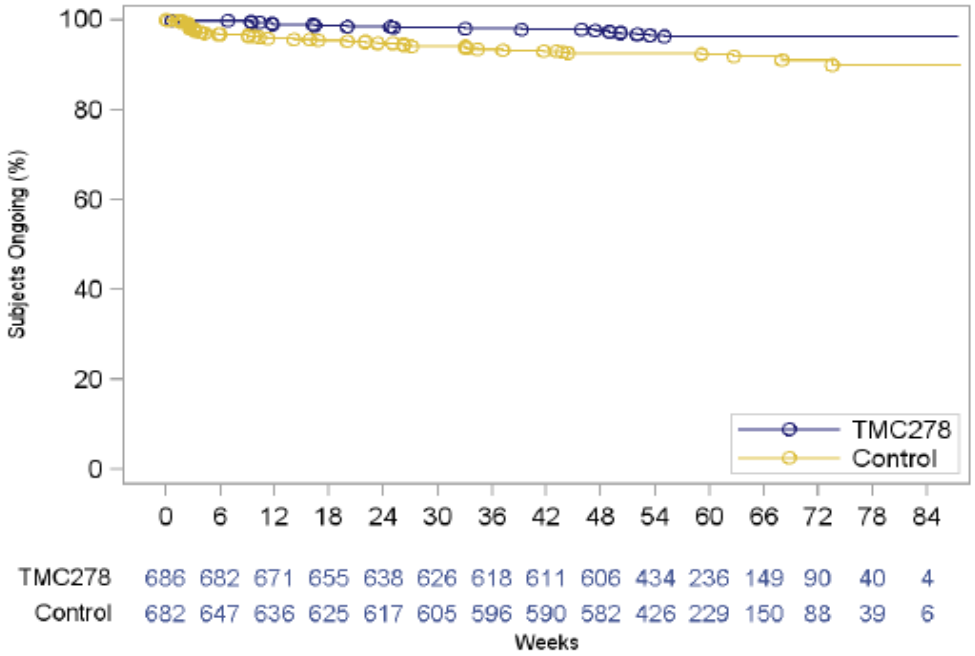
Table 15 Adverse Events Occurring in More Than 1 Subject Leading to Discontinuation (Continued)

System Organ Class Preferred term, n (%)	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Skin and subcutaneous tissue disorders	1(0.3)	5(1.5)	1(0.3)	7(2.1)	2(0.3)	12(1.8)
Rash	1(0.3)	3(0.9)	0	5(1.5)	1(0.1)	8(1.2)
Rash maculo-papular	0	1(0.3)	0	1(0.3)	0	2(0.3)
Infections and infestations	0	3(0.9)	2(0.6)	6(1.8)	2(0.3)	9(1.3)
Pulmonary tuberculosis	0	1(0.3)	1(0.3)	1(0.3)	1(0.1)	2(0.3)
Hepatitis C	0	1(0.3)	0	2(0.6)	0	3(0.4)
General disorders and administration site condition	0	4(1.2)	2(0.6)	1(0.3)	2(0.3)	5(0.7)
Fatigue	0	2(0.6)	1(0.3)	0	1(0.1)	2(0.3)
Nervous system disorders	2(0.6)	3(0.9)	0	2(0.6)	2(0.3)	5(0.7)
Somnolence	0	2(0.6)	0	0	0	2(0.3)
Hepatobiliary disorders	0	1(0.3)	0	2(0.6)	0	3(0.4)
Neoplasms benign, malignant and unspecified (inc. cysts and polyps)	0	2(0.6)	0	0	0	2(0.3)
Burkitt'slymphoma	0	2(0.6)	0	0	0	2(0.3)

Source: AEAD Datasets for the pooled trials

The Applicant provided a Kaplan-Meier plot of time to discontinuation due to AE (Figure 2). The analysis showed that more subjects in the EFV group discontinued and generally sooner than subjects in the rilpivirine group; the difference was sustained throughout the treatment period.

Figure 2 Kaplan-Meier Plot of Time to Discontinuation Due to Adverse Events



Source: Summary of Clinical Safety, Figure 4

7.3.4 Significant Adverse Events

Treatment related adverse events

Table 16 summarizes treatment-related adverse events (all grades) that occurred during the treatment period in at least 2% of subjects in either rilpivirine or EFV arm. Treatment-related is defined as adverse events at least possibly, probably, or very likely related to the drug. Overall the incidence of treatment related adverse events was higher in EFV arm (46% vs. 64%). The greatest difference was observed in nervous system disorder (primarily driven by incidence of dizziness) and skin and subcutaneous disorders (grouped term rash). For the rash analyses, the following terms were pooled: macoulo-, papulo-erythematous-, pruritic- rash; drug rash, urticaria, facial swelling, pruritis, and prurigo.

Table 16 Treatment-related Adverse Events that Occurred During Treatment Period in at Least 2% of Subjects

System Organ Class, Preferred Term, n(%)	C209		C215		Pooled	
	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	Rilpivirine N=686	Efavirenz N=682
Any treatment-related AE	147(42.5)	214(62.2)	171(50.3)	223(66)	318(46.4)	437(64.1)
Gastrointestinal disorders	56(16.2)	46(13.4)	76(22.4)	75(22.2)	132(19.2)	121(17.7)
Nausea	30(8.7)	24(7)	39(11.5)	53(15.7)	69(10.1)	77(11.3)
Diarrhea	13(3.8)	20(5.8)	15(4.4)	11(3.3)	28(4.1)	31(4.5)
Vomiting	7(2)	9(2.6)	6(1.8)	15(4.4)	13(1.9)	24(3.5)
Nervous system disorders	52(15)	117(34)	66(19.4)	133(39.3)	118(17.2)	250(36.7)
Dizziness	22(6.4)	85(24.7)	33(9.7)	94(27.8)	55(8)	179(26.2)
Headache	22(6.4)	15(4.4)	20(5.9)	27(8)	42(6.1)	42(6.2)
Somnolence	12(3.5)	21(6.1)	13(3.8)	28(8.3)	25(3.6)	49(7.2)
Disturbance in attention	2(0.6)	10(2.9)	3(0.9)	7(2.1)	5(0.7)	17(2.5)
Psychiatric disorders	50(14.5)	86(25)	52(15.3)	69(20.4)	102(14.9)	155(22.7)
Abnormal dreams	26(7.5)	39(11.3)	17(5)	25(7.4)	43(6.3)	64(9.4)
Insomnia	14(4)	23(6.7)	20(5.9)	16(4.7)	34(5)	39(5.7)
Nightmare	7(2)	10(2.9)	8(2.4)	15(4.4)	15(2.2)	25(3.7)
Depression	6(1.7)	9(2.6)	6(1.8)	6(1.8)	12(1.7)	15(2.2)
Sleep disorder	2(0.6)	11(3.2)	7(2.1)	9(2.7)	9(1.3)	20(2.9)
Anxiety	2(0.6)	8(2.3)	2(0.6)	6(1.8)	4(0.6)	14(2.1)
Skin and subcutaneous tissue disorders	21(6.1)	61(17.7)	27(7.9)	49(14.5)	48(7)	110(16.1)
Rash †	13(3.7)	57(16.5)	17(5)	45(13.3)	30(4.4)	102(15)
General disorders and administration site conditions	23(6.6)	42(12.2)	20(5.9)	30(8.9)	43(6.3)	72(10.6)
Fatigue	10(2.9)	13(3.8)	9(2.6)	13(3.8)	19(2.8)	26(3.8)
Asthenia	4(1.2)	7(2)	2(0.6)	7(2.1)	6(0.9)	14(2.1)
Investigations	20(5.8)	19(5.5)	21(6.2)	20(5.9)	41(6)	39(5.7)
Metabolism and Nutrition Disorders	10(2.9)	22(6.4)	6(1.8)	23(6.8)	16(2.3)	45(6.6)
Cardiac disorders	5(1.4)	9(2.6)	4(1.2)	9(2.7)	9(1.3)	18(2.6)
Ear and labyrinth disorders	2(0.6)	16(4.7)	1(0.3)	4(1.2)	3(0.4)	20(2.9)
Vertigo	2(0.6)	13(3.8)	0	3(0.9)	2(0.3)	16(2.3)

† Includes: macoulo-, papulo-, erythematous-, pruritic- rash; drug rash, urticaria, facial swelling, pruritis, prurigo
Source: AEAD Dataset for pooled trials

Treatment-related Adverse Events of at Least Moderate Severity

Overall the incidence of treatment-related AE with a severity grade of 2 or higher was lower in the rilpivirine group than in the EFV group (16% vs. 31%). Again, the greatest differences observed between the two groups were for rash and dizziness. Rash was reported in 1.6% of rilpivirine treated subjects and in almost 9% of subjects treated with EFV. See Section 7.3.5 for additional discussion on rash. Dizziness occurred in <1% of rilpivirine treated subjects and in 6% of EFV treated subjects.

Table 17 Treatment-Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) Reported in at Least 2% of Subjects

System Organ Class, Preferred Term, n (%)	C209		C215		Pooled	
	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	Rilpivirine N=686	EFV N=682
Any grade ≥2, treatment related AE	55(15.9)	108(31.4)	54(15.9)	104(30.8)	109(15.9)	212(31.1)
Psychiatric Disorders	15(4.3)	32(9.3)	21(6.2)	25(7.4)	36(5.2)	57(8.4)
Insomnia	5(1.4)	10(2.9)	7(2.1)	6(1.8)	12(1.9)	16(2.2)
Depression	4(1.2)	6(1.8)	5(1.5)	8(2.4)	9(1.3)	14(2.2)
Abnormal dreams	3(0.9)	12(3.5)	4(1.2)	4(1.2)	7(1)	16(2.3)
Gastrointestinal Disorders	7(2)	15(4.4)	13(3.8)	17(5)	20(2.9)	32(4.7)
Nausea	2(0.9)	8(2.3)	2(0.9)	9(2.7)	4(0.7)	17(2.5)
Investigation	8(2.3)	10(2.9)	11(3.2)	8(2.4)	19(2.8)	18(2.6)
General disorders and administration site condition	4(1.2)	21(6.1)	8(2.4)	4(1.2)	12(1.7)	25(3.7)
Nervous System Disorders	14(4)	35(10.2)	7(2.1)	33(9.8)	21(3.1)	68(10)
Headache	6(1.8)	6(1.8)	5(1.5)	9(2.7)	11(1.6)	15(2.2)
Dizziness	4(1.2)	23(6.7)	0	20(5.9)	4(0.6)	43(6.3)
Skin and Subcutaneous Tissue Disorders						
Rash †	7(2)	27(7.8)	4(1.2)	32(4.7)	11(1.6)	59(8.7)
Metabolism and Nutrition Disorders	5(1.4)	8(2.3)	4(1.2)	9(2.7)	9(1.3)	17(2.5)

† Includes: macoulo-, papulo-, erythematous-, pruritic- rash; drug rash, urticaria, facial swelling, pruritis, prurigo)
Source: AEAD Dataset for pooled trials

The adverse drug reaction (ADR) table included in the Package Insert for rilpivirine is based on adverse reactions considered to be at least related to study drug and occurring in ≥ 2% of subjects in either group. The incidence calculated by the Applicant for the Package Insert table is based on the table above (Table 17). However, the Applicant also utilized an additional tool to reassess treatment-relatedness of adverse reactions. Their methodology did not solely rely on investigator-assessment to consider an event to be treatment-related. Some events not considered treatment-related were revised by the Applicant to be treatment-related. Therefore, some ADRs reported in the table of the Package Insert have higher incidence than what is reflected in Table 17.

To briefly describe the Applicant's algorithm, ADRs were identified from the overall safety database of reported AEs in the (pooled) Phase 1, Phase 2a, Phase 2b and pooled Phase 3 clinical trials. The AE

data were reviewed and ADRs were identified, using the following approach: once a list of terms was identified from Phase 1, 2a, 2b and Phase 3 trials, MedDRA preferred terms were grouped to a single common preferred term. Then the (grouped) terms were selected as potential ADRs when they fulfilled at least 1 of the following criteria: had incidence of at least 1.0%; irrespective of their incidence, led to discontinuation (in at least 1 instance), were considered at least possibly related to rilpivirine by the investigator (in at least 1 instance), were reported (in at least 1 instance) as a SAE, were of special interest, or were considered typically drug-related. This 'Draft 1 potential ADR list' was reviewed by 'qualified MDs' and the terms were identified as ADRs or not ADRs. In the final ADR adjudication step, list of potential ADRs was reviewed and discussed in a broader medical and safety group and the ADR adjudication was based on the combined assessment of incidence patterns, biological and clinical plausibility, the investigator's causality assessment and, as necessary, individual patient profile review.

When differences occurred in the rates between Table 17 and the Package Insert, the differences were by no more than 1% for most of the preferred terms. In addition, the increased incidences generally affected both treatment groups equally and thus did not lead to a different interpretation of the overall results. Depression and rash are further discussed under 'Submission Specific Primary Safety Concerns'.

Note, 'investigations' and 'metabolic and nutrition disorders' were not included in the ADR section of the Package Insert because they are discussed in the laboratory section of the Package Insert, if appropriate.

Package Insert for Treatment-related Adverse Events

Table 2: 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	
	TRADE NAME™ + 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

AIDS-defining Illness

The incidence of AIDS-defining illness in the pooled Phase 3 trials was comparable between the treatment groups (0.9% and 1.0% in the rilpivirine and EFV groups, respectively). The AIDS-defining illnesses reported in the 6 subjects from the rilpivirine group include mouth ulceration, bronchopneumonia, infectious diarrhea, mycobacteria (MAC), cervical carcinoma and Kaposi's sarcoma. In the EFV group, cerebral toxoplasmosis, pulmonary tuberculosis, tuberculosis, and Burkitt's lymphoma were reported among the 7 subjects with AIDS-defining illness. Three of the events in each group were grade 3, with no grade 4 event in the rilpivirine group and two grade 4 events in the EFV group. Three subjects discontinued treatment due to AIDS-defining illness, 1 subject from the rilpivirine group (bronchopneumonia) and 2 subjects from the EFV group (both with Burkitt's lymphoma).

7.3.5 Submission Specific Primary Safety Concerns

Safety data from pre-clinical studies, adverse event data from the clinical trials as well as the known safety profile for the NNRTI class were used to identify specific safety concerns. The following section discusses adverse events of special interest.

Psychiatric Disorders

All the preferred terms (regardless of causality, severity) within the psychiatric disorders were grouped into sub-category of related disorders. The incidences were then compared for the two groups. Overall, there were numerically fewer psychiatric disorders reported with rilpivirine group compared to EFV group (25% vs. 29%). The greatest differences were in the abnormal dreams (9% vs. 14%) and anxiety disorders (4 % vs. 7%).

Table 18 Psychiatric Adverse Events of Interest

Grouped term, Preferred term n (%)	Risk Difference	Rilpivirine N=686	EFV N=682
Any psychiatric disorder		170(24.5)	199(29.2)
Mood Disorders		61(8.9)	54(7.9)
Depression	7.5	41(6)	33(4.8)
Depressed mood	1.6	7(1)	5(0.7)
Major depression	0.2	2(0.3)	2(0.3)
Suicide attempt	1.2	2(0.3)	0
Suicidal ideation	-0.3	2(0.3)	3(0.4)
Dysphoria	0.1	1(0.1)	1(0.1)
Negative thoughts	0.6	1(0.1)	0
Mania	0.6	1(0.1)	0
Euphoric mood	0.6	1(0.1)	0
Affect lability	0.6	1(0.1)	0
Mood swings	0.1	1(0.1)	1(0.1)
Mood altered	-0.9	1(0.1)	3(0.4)
Depressive symptom	-1.0	0	2(0.3)
Adjustment disorder with depressed mood	-0.5	0	1(0.1)
Seasonal affective disorder	-0.5	0	1(0.1)
Dysthymic disorder	-0.5	0	1(0.1)
Bipolar disorder	-0.5	0	1(0.1)

Table 18 Psychiatric Adverse Events of Interest (Continued)

Grouped term, Preferred term n (%)	Risk Difference	Rilpivirine N=686	EFV N=682
Sleep Disorders		71(10)	80(11.7)
Insomnia	6.8	56(8.1)	52(7.6)
Sleep disorder	-5.6	11(1.6)	24(3.5)
Initial insomnia	1.2	2(0.3)	0
Middle insomnia	0.6	1(0.1)	0
Early morning awakening	0.6	1(0.1)	0
Dyssomnia	-2.0	0	4(0.6)
Abnormal Dreams		63 (9.2)	92(13.5)
Abnormal dreams	-5.5	47(6.9)	66(9.7)
Nightmare	-3.7	16(2.3)	26(3.8)
Psychotic Disorders		5(0.7)	8(1)
Hallucination	-0.3	2(0.3)	3(0.4)
Hallucination, visual	0.6	1(0.1)	0
Hallucinations, mixed	0.6	1(0.1)	0
Hallucination, auditory	0.1	1(0.1)	1(0.1)
Acute psychosis	-0.5	0	1(0.1)
Paranoia	-0.5	0	1(0.1)
Psychotic disorder due to a general medical condition	-0.5	0	1(0.1)
Homicidal ideation	-0.5	0	1(0.1)
Anxiety Disorders		25(3.6)	48(7)
Anxiety	-7.0	18(2.6)	35(5.1)
Anxiety disorder	1.2	2(0.3)	0
Nervousness	-0.4	1(0.1)	2(0.3)
Agoraphobia	0.1	1(0.1)	1(0.1)
Panic attack	-1.5	0	3(0.4)
Agitation	-2.0	0	4(0.6)
Post-traumatic stress disorder	-0.5	0	1(0.1)
Stress	0.8	3(0.4)	2(0.3)
Sexual Dysfunction Disorders		7(1)	9(0.4)
Libido decreased	-0.7	4(0.6)	6(0.9)
Loss of libido	0.6	1(0.1)	0
Libido increased	0.6	1(0.1)	0
Psychogenic erectile dysfunction	0.6	1(0.1)	0
Mental status changes	-0.5	0	1(0.1)
Orgasm abnormal	-0.5	0	1(0.1)
Male orgasmic disorder	-0.5	0	1(0.1)

Source AEAD Dataset for the pooled trials

Unlike abnormal dreams and anxiety disorders, the incidence of depressive disorders (regardless of causality, severity) was similar between the two groups (8% in the rilpivirine group vs. 7% in the EFV group) (Table 19).

According to DSM-IV-TR, depressive disorders includes:

Major Depressive Disorder,

The essential features include: a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities, PLUS at least four additional symptoms from the following list: changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts.

Depressive Disorder Not Otherwise Specified

This category includes for coding disorders with depressive features that do not meet criteria for Major Depressive Disorder, Dysthymic Disorder, Adjustment Disorder With Depressed Mood, or Adjustment Disorder With Mixed Anxiety and Depressed Mood

Examples include:

- Minor depressive disorder: episodes of at least 2 weeks of depressive symptoms but with fewer than the five items required for Major Depressive Disorder
- Situations in which the clinician has concluded that a depressive disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance induced.

Suicide is among the associated descriptive features and mental disorders for Depressive Disorders (e.g. Major Depression). Therefore, for the FDA analysis, depressive disorders contained the following 'grouped terms':

- 'Depression'- which includes preferred terms 'depression', 'major depression'
- 'Depressed mood'- includes preferred terms 'depressed mood', 'dysphoria', 'mood altered' 'negative thoughts'
- Suicidal thoughts
- Suicidal ideations

Table 19 Depressive Disorders Regardless of Causality, Severity

Grouped term, Preferred term, n (%)	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any subject with Depressive Disorders	27(7.8)	24(7)	25(7.4)	20(5.9)	52(7.8)	44(6.5)
Any subject with depression	24(6.9)	17(4.9)	18(5.3)	17(5)	42(6.1)	34(5)
Depression	22(6.4)	17(4.9)	18(5.4)	15(4.4)	40(6)	32(4.8)
Major depression	2(0.6)	0	0	2(0.6)	2(0.3)	2(0.3)
Any subject with depressed mood	3(0.9)	7(2)	7(2.1)	2(0.6)	10(1.6)	9(1.3)
Depressed mood	3(0.9)	4(1.2)	4(1.2)	1(0.3)	7(1)	5(0.7)
Dysphoria	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)
Negative thoughts	0	0	1(0.3)	0	1(0.1)	0
Mood altered	0	2(0.6)	1(0.3)	1(0.3)	1(0.1)	3(0.4)
Suicide attempt	1(0.3)	0	1(0.3)	0	2(0.3)	0
Suicidal ideation	0	2(0.6)	1(0.3)	1(0.3)	1(0.1)	3(0.4)

Source AEAD Dataset for the pooled trials

The incidence of grade 3 or 4 depressive disorders (regardless of causality) was similar between the two groups: 5 (0.7%) in rilpivirine group and 6 (0.9%) in the EFV group. Three subjects had grade 3 adverse events in the rilpivirine group: 'depression' (n=1), 'suicide attempt' (n=1) and 'suicide ideation' (n=1). All except for the 'depression' were thought to be treatment related. The subject with 'depression' had history of depression and the current episode of was related to "relationship and

financial difficulties". Two of the subjects discontinued rilpivirine due to the adverse events. The grade 3 adverse events in the 5 subjects in the EFV group were 'depression', 'major depression' and 'suicidal ideation'. All except for one subject who had 'worsening of depression' were thought to be treatment-related. With the exception of this subjects, all discontinued treatment.

Two subjects in rilpivirine group had grade 4, life threatening event. 'Major depression', thought to be worsening of depression and not treatment-related occurred in 1 subject. This subject did not discontinue treatment. The second subject attempted suicide. This event was considered treatment related and led to discontinuation of rilpivirine.

Serious psychiatric events were similar between the two groups, 1% in each. However, more significant events such as major depression and suicide attempt occurred with greater incidence in the rilpivirine group.

Important to note is that 2 subjects attempted suicide in the rilpivirine group, both thought to be treatment-related and leading to discontinuation. These subjects had no previously reported history of suicidal ideation or attempt. However, one of the subjects had a history of depression.

Discontinuation of treatment due to depressive disorders was similar between the two groups. In the rilpivirine group, 6 subjects discontinued treatment due to depressive disorders. All events were considered possibly or probably related to rilpivirine. One subject experienced 'depression' and 'suicidal ideation' (both grade 3), one subjects had 'depression' (grade 2), two subjects experienced 'depressed mood' (grade 1 or 2), and two subjects attempted suicide (grade 3 in one subject and grade 4 or life-threatening in the second subject).

In the EFV group, one subject had 'depression' and 'suicidal ideation', two subjects had 'depression', and one subject had 'suicidal ideation' (grade 2). All events were considered possibly, probably or very likely related to treatment drug. With the exception of the grade 2 'suicidal ideation' as noted above, all events were grade 3 and no grade 4 event was recorded.

The exposure-response analysis for psychiatric events and rilpivirine did not demonstrate a correlation between exposure and adverse events. Refer to Section 7.5.1

In summary, based on the Phase 3 trials analysis, depressive disorder events occurred at similar rates between the two groups. The control arm, EFV, is known to have psychiatric adverse events including depressive disorders. The Package Insert for EFV includes language about depressive disorders in the Warnings and Precautions Section. Therefore, the Package Insert for rilpivirine should also include similar language in the Warnings and Precautions Section.

The following text has been recommended to be included in the Package Insert, Warnings and Precautions Section:

> **Depressive Disorders**
> Adverse reactions, including depression, major depression, suicidal ideation and suicidal attempt have been reported with rilpivirine. During the Phase 3 trials (N= 1368), the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (n=686) or Efavirenz (n=682) were 8% and 7%, respectively. Among the subjects who experienced depressive disorders, most were mild-to-moderate. The incidence of treatment-related depressive disorders (regardless of severity) reported among rilpivirine or efavirenz was 3% and 4%, respectively. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for each rilpivirine and Efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or Efavirenz was 1% in

each arm. Suicide attempt was reported in 2 subjects in the rilpivirine arm while suicide ideation was reported in 1 subject in TRADE NAME™ arm and in 3 subjects in Efavirenz arm. Both subjects with suicide attempt discontinued treatment. Subjects with suicidal ideation also discontinued treatment, except for 1 subject in the Efavirenz arm. Patients with serious psychiatric adverse reactions should seek immediate medical evaluation to assess the possibility the symptoms are related to rilpivirine, and if so, to determine whether the risks of continued therapy outweigh the benefits.

In addition, the ADR table in the Adverse Events Section of the Package Insert displays ADRs with Grade 2 and above in intensity and at least possibly related to treatment. The incidence of 'depressive disorders' in the ADR is based on Table 20. The Applicant also identified additional cases which were not considered treatment-related by investigators. Therefore the incidence of 'Depressive disorders' for rilpivirine in the (b) (4) Package Insert is higher than what is reported in Table 20 (4% vs. 2%).

Table 20 Treatment Related Depression Disorders of at least moderate intensity (≥ Grade 2) reported in at least 2% of subjects

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any subject with ≥ Grade 2 Depressive Disorders	5(1.4)	5(1.5)	5(1.5)	8(2.4)	10(1.5)	13(1.9)
Depression	4(1.2)	5(1.5)	4(1.2)	7(2.1)	8(1.2)	12(1.8)
Depression	4(1.2)	5(1.5)	4(1.2)	5(1.5)	8(1.2)	10(1.5)
Major Depression	0	0	0	2(0.6)	0	2(0.3)
Depressed mood	0	0	1(1.1)	0	1(0.1)	0
Depressed mood	0	0	1(1.1)	0	1(0.1)	0
Suicidal ideation	0	1(1.1)	1(1.1)	1(0.3)	1(0.1)	2(0.3)
Suicide attempt	1(1.1)	0	1(1.1)	0	2(0.3)	0

Source AEAD Dataset for the pooled trials

Hepato-biliary Adverse Events

Hepatobiliary events were selected as adverse events of special interest because of known hepatotoxicity with use of NNRTI such as nevirapine. In order to allow for a thorough evaluation of hepatic related adverse events the following preferred terms were used to identify hepatic events of interest: 'hepatic pain', 'hepatic steatosis', 'cytolytic hepatitis', 'hepatitis', 'hepatitis acute', 'hepatitis B', 'hepatitis C', 'hepatitis alcoholic', 'hepatomegaly', 'biliary colic', 'bile duct obstruction', 'cholecystitis', 'cholecystitis acute', 'cholelithiasis', 'hepatic function abnormal', 'hyperbilirubinemia', 'hypertransaminasemia'. Of note, the preclinical data for rilpivirine did not suggest rilpivirine is associated with hepatotoxicity. See Section 4.3.

Table 21 summarizes the hepatobiliary disorders (regardless of causality, severity) for the pooled Phase 3 trials. Overall, the incidence of hepatic events of interest was 5.5% in the rilpivirine group and 6.6% in the EFV. Among these, 2.2% of the rilpivirine treated subjects and 2.1% of the EFV treated subjects were considered to be treatment-related by the investigator. Most hepatic events were grade 1 and 2 in both treatment groups.

Apparent imbalance in biliary events was observed between the two groups, with greater incidence occurring in the rilpivirine group. In total, 8 (1.2%) subjects in the rilpivirine group experienced 'cholecystitis' (n=3), 'cholelithiasis' (n=4) or 'biliary colic' (n=2), compared to 2 (0.3%) subjects in the EFV group (1 subject with 'bile duct obstruction' and 1 subject with 'cholecystitis'). Of note, asymptomatic hyperbilirubinemia (primarily total/ indirect bilirubin) was also noted in greater incidence in the rilpivirine group. See laboratory section for details. Establishing a causal relationship between cholelithiasis and rilpivirine is very difficult; no analysis of the stones has been provided. In addition, no exposure-response between hepatobiliary events and rilpivirine exposure has been established. Nonetheless, due to the imbalance in the rate of cholelithiasis between the two treatment groups, it is recommended that cholelithiasis be included in the Package Insert under 'Less Common Adverse Drug Reactions'.

Table 21 Hepatobiliary Adverse Events of Interest

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Hepatobiliary disorders n(%)						
Cholelithiasis	3(0.9)	1(0.3)	1(0.3)	0	4(0.6)	1(0.1)
Cholecystitis acute	1(0.3)	0	2(0.6)	0	3(0.4)	0
Biliary colic	0	0	2(0.6)	0	2(0.3)	0
Hepatomegaly	1(0.3)	3(0.9)	1(0.3)	1(0.3)	2(0.3)	4(0.6)
Hepatic pain	1(0.3)	1(0.3)	1(0.3)	0	2(0.3)	1(0.1)
Hepatitis C	2(0.6)	2(0.6)	0	2(0.6)	2(0.3)	4(0.6)
Hepatitis B	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)
Hepatitis	0	0	1(0.3)	1(0.3)	1(0.1)	1(0.1)
Hepatic steatosis	0	2(0.6)	0	0	0	2(0.3)
Cytolytic hepatitis	0	1(0.3)	0	0	0	1(0.1)
Hepatitis acute	0	1(0.3)	0	0	0	1(0.1)
Hepatitis alcoholic	0	1(0.3)	0	0	0	1(0.1)
Cholecystitis	0	1(0.3)	0	0	0	1(0.1)
Bile duct obstruction	0	1	0	0	0	1(0.1)

Source: AEAD Datasets for the pooled trials

Grade 3 and 4 hepatic events of interest (excluding laboratory) were reported in <1% of either group, 0.4% and 0.1% in rilpivirine and EFV group, respectively (Table 22).
Less than 1% of subjects in either treatment group had grade 4 hepatic events of interest – 3 subjects in the rilpivirine group and 6 subjects in the EFV group:

- Subject 209-0128 (rilpivirine group) with hepatitis B/C co-infection at baseline developed active hepatitis C disease during the trial. This event was reported to be not related to study medication by the investigator.

- Subject 215-0007 (rilpivirine group) with known hepatitis B/C co-infection had a grade 4 ALT increased during treatment; event was considered possibly related to rilpivirine by the investigator and led to permanent discontinuation.

- Subject 215-0921 (rilpivirine group) with known hepatitis B/C co-infection had a grade 4 ALT and AST increased on, considered probably related to rilpivirine by the investigator and led to permanent discontinuation.

The above events were also reported as SAEs. In addition to these cases, 3 more hepatic events (2 in rilpivirine group) were reported as SAEs.

- Subjects 209-0933 and 215-0192 in the rilpivirine group had grade 1 or 2 cholelithiasis, considered either doubtfully or not related to rilpivirine by the investigator.

Grade 3 and 4 laboratory toxicities reported in laboratory datasets are also summarized in Table 22. Overall, the incidences of grade 3 and 4 laboratory toxicities are low and similar between the two arms. All other laboratory related findings, whether reported under 'investigations' or in the laboratory dataset are presented in the laboratory section.

Table 22 Grade 3 or 4 Hepatobiliary Adverse Events and Laboratory Toxicities

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Hepatobiliary disorders Grade 3, n(%)						
Cholecystitis acute	1(0.3)	0	1(0.3)	0	2(0.2)	0
Cholecystitis	0	0	0	1(0.3)	0	1(0.1)
Hepatobiliary disorders Grade 4, n(%)	1	0	0	0	1(0.1)	0
Hepatitis C	1(0.3)	0	0	0	1(0.1)	0
Grade 3 (worst grade toxicity), n(%)						
Increased AST	7(2)	10(2.9)	4(1.2)	3(0.9)	11(1.6)	13(1.9)
Increased ALT	1(0.3)	8(2.4)	4(1.2)	6(1.8)	5(0.7)	14(2)
Increased Bilirubin total	0	1(0.3)	4(1.2)	0	4(0.6)	1(0.1)
Grade 4 (worst grade toxicity), n(%)						
Increased ALT	3(0.9)	4(1.2)	2(0.6)	5(1.5)	5(0.7)	9(1.3)
Increased AST	1(0.3)	2(0.6)	2(0.6)	4(1.2)	3(0.4)	6(0.9)

Source: AEAD and LBAD for the pooled trials

The number of subjects who discontinued due to hepatic events of interest was 0.4% and 1.3%, in the rilpivirine and EFV groups, respectively.

Hy's Law

Hy's Law refers to the observation made by Dr. Zimmerman that drug induced hepatocellular injury accompanied by jaundice had a poor prognosis. Hepatocellular injury sufficient to impair bilirubin excretion has been used at the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as indicator of clinical concern for drug-induced liver injury includes: > 3x ULN ALT or AST, total bilirubin > 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, other drug).

To help identify hepatic adverse events which may be treatment related, the criteria above were applied to both the Phase 3 and the Phase 2b trials. In summary, no unconfounded case meeting the definition of Hy's Law (e.g. FDA's definition of drug induced liver injury) was identified.

From the rilpivirine treated group, 2 subjects met the laboratory criteria for Hy's Law. However, the events were cofounded with abnormal baseline laboratory and/or co-infection with hepatitis C. The subjects had active hepatitis C infection. One subject had baseline grade 3 total bilirubin (TB). At week 48, the subject had grade 2 TB, grade 2 AST and grade 3 ALT. The subject continues on treatment and had completed Week 60 visit at the time of the cut-off period for the 48 Week analysis. The second HCV co-infected subject had baseline grade 2 ALT and AST and normal TB. At Week 8, ALT/AST remained grade 2 with higher absolute numbers (i.e. 3 x ULN) and new onset of grade 2 TB. The total bilirubin value normalized by Week 12 and remained within normal limit (except grade 1 at Week 40). ALT and AST continued be grade 2 throughout the treatment period. The subject continued on study and last recorded visit is Week 60.

In summary, most of the hepatobiliary adverse events were mild or moderate. When the events were severe (grade 3) or life threatening (grade 4), the events were confounded by other ongoing medical events such as cholecystitis and hepatitis C. The incidence of grade 3 and 4 elevation in ALT or AST was low and generally similar between the rilpivirine and the EFV groups. No Hy's Law case was identified. An exposure-response analysis for hepatobiliary events (including laboratory hyperbilirubinemia) did not identify a relationship between exposure and adverse events. See Section 7.5.1. Based on the totality of the data, including the laboratory results, a warning, precaution or special monitoring for hepatotoxicity or hepatobiliary disorders is not warranted. (b) (4) a display of the graded laboratory changes through Week 48 as described in the laboratory section below.

Skin

In order to gain a comprehensive overview of all reported skin events of interest, grouped terms were created and used for the analysis. The grouped terms for skin event of interest included 'rash', 'contact dermatitis', 'skin appendages', 'skin discoloration', and 'other'. 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, prurigo. The grouped term for contact dermatitis included 'eczema', 'dermatitis contact'. Table 23 summarizes skin events of interest by grouped terms, regardless of severity and causality.

Overall, grouped term 'rash' had a lower incidence in the rilpivirine group (17%) compared to the EFV group (31%). The greatest difference was in the preferred term 'rash', 6% vs. 14% for rilpivirine and EFV groups, respectively.

Table 23 Skin Adverse Events of Interest

Grouped Adverse Events Preferred terms, n(%)	Risk Difference	Rilpivirine N=686	EFV N=682
Grouped term 'rash'		114(16.6)	210 (30.8)
Rash	-18.5	42(6)	96(14)
Pruritus	0.6	21(3)	26(4)
Dermatitis	2.6	9(1.3)	6(0.9)
Skin exfoliation	4.1	7(1)	0
Erythema	-0.5	6(0.9)	9(1.3)

Table 23 Skin Adverse Events of Interest (Continued)

Grouped Adverse Events Preferred terms, n(%)	Risk Difference*	Rilpivirine N=686	EFV N=682
Rash papular	-2.5	5(0.7)	12(1.7)
Rash pruritic	-1.3	4(0.6)	8(1.2)
Prurigo	2.4	4(0.6)	0
Rash macular	-1.4	3(0.4)	7(1)
Urticaria	-1.4	3(0.4)	7(1)
Dermatitis allergic	-1.9	2(0.3)	7(1)
Rash maculo-papular	-5.6	2(0.3)	15(2.2)
Pruritus generalized	0.7	2(0.3)	1(0.1)
Blister	0.7	2(0.3)	1(0.1)
Rash erythematous	-1.2	1(0.1)	4(0.6)
Rash generalized	-2.6	1(0.1)	7(1)
Drug eruption	-2.6	0	5(0.7)
Exfoliative rash	-0.5	0	1(0.1)
Palmar-plantar erythrodysaesthesia syndrome	-0.5	0	1(0.1)
Rash morbilliform	-0.5	0	1(0.1)
Swelling face	-1.4	0	3(0.4)
Grouped term contact dermatitis		46(6.7)	37(5.4)
Seborrheic dermatitis	4.6	14(2)	8(1.2)
Eczema	3.9	12(1.7)	7(1)
Dry skin	1.5	11(1.6)	11(1.6)
Dandruff	-0.2	2(0.3)	3(0.4)
Dermatitis contact	-1.9	2(0.3)	7(1)
Seborrhea	0.7	2(0.3)	1(0.1)
Neurodermatitis	0.6	1(0.1)	0
Dermatitis atopic	0.6	1(0.1)	0
Xeroderma	0.6	1(0.1)	0
Grouped term skin appendages		12(1.7)	8(1)
Alopecia	3.4	8(1.2)	3(0.4)
Nail discoloration	0.3	2(0.3)	2(0.3)
Hair growth abnormal	0.6	1(0.1)	0
Ingrowing nail	0.6	1(0.1)	0
Alopecia areata	-0.5	0	1(0.1)
Nail pigmentation	-0.5	0	1(0.1)
Grouped term skin discoloration		4(0.6)	7(1)
Skin discoloration	1.3	3(0.4)	1(0.1)
Skin hypopigmentation	-0.3	1(0.1)	2(0.3)
Pityriasis alba	-0.5	0	1(0.1)
Pigmentation disorder	-0.5	0	1(0.1)
Skin hyperpigmentation	-0.5	0	1(0.1)
Leukoplakia	-0.5	0	1(0.1)
Other			
Petechiae	-0.5	0	1(0.1)
Ecchymosis	-0.5	0	1(0.1)

*Risk difference is difference in the relative risk for a given adverse event between the two treatment groups
Source: AEAD for the pooled trials

The group term 'rash' was further analyzed by causality, severity, exposure-response correlation and time of onset and discontinuation.

The majority of the rash events (grouped term) were grade 1 or 2 in severity. In the rilpivirine group, three subjects had grade 3 rash and no subject had a grade 4 rash. The preferred terms for the grade 3 events were 'rash' in 1 subject, which was serious and considered very likely related to rilpivirine and led to treatment discontinuation. The second subject had 'generalized pruritis' and was considered not treatment related by the investigator and led to temporary discontinuation of rilpivirine. The third subject had 'rash pruritis' and was considered not treatment related by the investigator. In addition to these grade 3 rashes, 1 additional subject in the rilpivirine arm had a SAE (preferred term localized erythema). This subject also had pruritic blisters. The event was not considered treatment related and the subject continued on treatment.

In the EFV group, 6 subjects had grade 3 rash (grouped term) and no grade 4 rash was reported. In addition, 3 subjects had rash reported as SAE (grade 3 generalized rash considered treatment related, grade 2 rash considered not treatment related, and grade 2 plantar erythrodysesthesia syndrome, not treatment related).

The incidence of rash (grouped term), regardless of severity and causality, was highest in the first 4 weeks of treatment for both arms. Per Tibotec, the median duration of rash was 18 days for rilpivirine group and 10 days for EFV group.

No exposure-response correlation was identified between rash and rilpivirine exposure (see Section 7.5.1). Treatment-related, grouped term rash was observed with higher incidence in the EFV group compared to rilpivirine group (3.1% vs. 13.6%, respectively).

In summary, the incidence of rash in the rilpivirine group is significantly lower than what was observed in the EFV group. No grade 4 rash was reported for rilpivirine. The discontinuation rate due to rash is also significantly lower in the rilpivirine group when compared to EFV group. Most subjects were treated through the rash (grouped term) without discontinuation. In total 13 subjects from the EFV group (11 of whom had treatment related rash) and 1 subject from the rilpivirine group (considered treatment-related) discontinued treatment due to rash.

(b) (4)

Note, additional treatment-related rash events were identified by the Applicant and included in the ADR table; the incidence for rash in the ADR as calculated by the Applicant is slightly different: 3% for the rilpivirine group and 11% in the EFV group. However, the overall difference in incidence of rash between the two treatment groups remains generally the same.

Endocrine

As previously discussed, during the pre-clinical studies, rilpivirine was identified to have a potential effect on adrenal function. Consultation with the Division of Metabolic and Endocrinology Products

(DMEP) was obtained and the consulting Division has reviewed the endocrine data in this NDA data. Conclusions and final recommendations have been provided. Refer to review by Dr. Ali Mohamadi, clinical reviewer from DMEP, for full 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) will include information with regards to potential effect of rilpivirine on adrenal function:

> *Adrenal Function*
> In the pooled Phase 3 trials, at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the rilpivirine group, and an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+16.5 ±6.14 nmol/L) than in the efavirenz group (+58.1 ±6.66 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Renal Adverse Events

Renal effects were observed in mice and dogs at high doses (see Section 4.3). In dogs, effects were limited to acute interstitial nephritis in two males and minimal to slight corticomedullary mineralization in all females sacrificed at the end of the study. In mice, findings in the kidney were limited to minimal to moderate nephropathy in half of the females.

Renal adverse event was included in the 'adverse events of special interest' section due to an observed increase in serum creatinine over time. Therefore, in addition to adverse events listings and analysis, serum creatinine trend overtime is presented. For in-depth analysis of the Phase 3 trials, including the cystatin C data, please refer to analysis conducted by Dr. Melanie Blank, clinical reviewer from the Division of Cardiovascular and Renal Products (DCRP).

The AE analysis was performed by selecting all preferred AE terms in system organ class 'renal or urinary disorders' in Phase 3 trials. 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' AE (regardless of severity, causality) was higher in the rilpivirine group, 50 (7.2%) compared to the EFV group 38 (5.6%). Similarly, the incidence of 'renal' AEs (Table 24) such as renal colic and glomerulonephritis was higher in the rilpivirine group. However, similar incidence was noted for 'renal failure' (0.4% in each group). The incidences of proteinuria and hematuria (coded under adverse events –'investigations') were also similar between the two groups. With the exception of glomerulonephritis, all cases of renal AEs in the rilpivirine group have resolved.

Table 24 Selected Renal and Urinary Adverse Events Regardless of Causality, Severity

	C209		C215		Pooled	
Adverse events, n(%)	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Glomerulonephritis	2(0.6)	0	0	0	2(0.3)	0
Glomerulonephritis membranous	1(0.1)	0	0	0	1(0.1)	0
Glomerulonephritis mesangioproliferative	1(0.1)	0	0	0	1(0.1)	0
Renal failure	2(0.6)	1(0.3)	1(0.3)	2(0.6)	3(0.4)	3(0.4)
Renal failure	1(0.3)	0	0	0	1(0.1)	0
Renal failure acute	0	1(0.3)	1(0.3)	2(0.6)	1(0.1)	3(0.4)
Renal failure chronic	1(0.3)	0	0	0	1(0.1)	0
Renal stone	5(1.4)	1(0.3)	3(0.9)	3(0.9)	8(1.2)	4(0.6)
Nephrolithiasis	2(0.6)	0	2(0.6)	2(0.6)	4(0.6)	2(0.3)
Renal colic	1(0.3)	0	1(0.3)	1(0.3)	2(0.3)	1(0.1)
Calculus ureteric	2(0.6)	1(0.3)	0	0	2(0.3)	1(0.1)
Proteinuria	4(1.1)	3(0.9)	7(2)	5(1.5)	11(1.6)	8(1.2)
Glycosuria	0	0	1(0.3)	0	1(0.1)	0
Hematuria	4(1.1)	5(1.4)	7(2)	5(1.5)	11(1.6)	10(1.5)
Chromaturia	0	0	0	1(0.3)	0	1(0.1)

Source AEAD Dataset from pooled Phase 3 trials

Most renal AEs were grade 1 or 2. There were five grade 3 'renal and urinary' AEs (2 nephrolithiasis, 1 pyuria, 1 mesangiocapillary glomerulonephritis, and 1 proteinuria) reported in 3 subjects from the rilpivirine group. All subjects with grade 3 'renal and urinary' AEs received tenofovir/emtricitabine as a background regimen. Therefore, the contribution of tenofovir to the reported adverse events cannot be ruled out. In the EFV treatment group, two grade 3 (acute renal failure, nephrolithiasis) and two grade 4 AEs (renal failure) were in 4 subjects. Only 1 subject received tenofovir/emtricitabine as background regimen.

Grade 3 'renal and urinary' AEs reported in the rilpivirine group:

- Subject 209-0142 is a 45 year old male with hypertension (on carvedilol) who experienced mesangioproliferative glomerulonephritis approximately 5 months into treatment. The subject had proteinuria (grade 3) approximately 12 days prior to the event. Right sided renal colic (grade 3) was also diagnosed ~2 months after the diagnosis of glomerulonephritis. None of the events were serious or considered to be related to rilpivirine by the investigator but proteinuria was considered to possibly be related to background regimen (TDF/FTC). The events did not lead to discontinuation of treatment.
  The cause of mesangioproliferative has not been identified. In review of the literature, mesangioproliferative glomerulonephritis is thought to be immune mediated. Although it is

plausible the event in this case could be treatment related, the event resolved and did not warrant discontinuation of rilpivirine.

- Subject 209-0297 had a ureteral calculus, a SAE but not considered to be treatment related by the investigator and did not lead to discontinuation. Nephrolithiasis cases are further discussed below.

- Subject 209-0555 had pyuria (leukocyturia), not considered treatment related by the investigator.

In addition to the above subject with a SAE of ureteral calculus, 2 more subjects, in the rilpivirine group, had SAEs. All received tenofovir as part of their background regimen therefore the contribution of tenofovir to the renal events cannot be ruled out:

- Subject 209-0387 is a 32 year old male without significant past medical history (PMH).The subject had grade 2 membranous glomerulonephritis, considered possibly related to rilpivirine by the investigator. The event occurred approximately 11 months into treatment and led to drug withdrawal. Associated renal AEs at the time of the event included proteinuria (grade 1, non serious and not related to study drug). His background regimen was constructed of TDF/FTC. Note, although the investigator considered glomerulonephritis to be possibly related, the Applicant does not believe the event is related to rilpivirine. However, despite the Applicant reclassification, the event was considered possibly treatment-related during the NDA analysis.

- Subject 215-0303 had acute renal failure (ARF). See below.

Of note, 1 subject in the EFV group had a renal SAE (acute renal failure).

Renal Failure
Three cases of renal failure (loss of kidney function) were identified in each treatment group. The cases from the rilpivirine group are further described below. Of note, none of the renal failure events in the rilpivirine group were grade 3 or 4 while grade 3 and 4 renal failure events occurred in the EFV group. In addition, all received tenofovir as part of their background regimen.

- Subject 215-0303 is a black male from Germany who had no significant PMH. On Day 351, the subject suffered acute renal failure (ARF), grade 2, considered not be treatment-related by the investigator. The event lasted for 11 days and recovered after additional medication was administered. On Day 371, subject had another ARF, grade 2, SAE, not related to study drug and recovered after 17 days. Note, at the time of the ARF, subject had recurrence of infection with isospora belli, dehydration, and urinary tract infection (UTI). Subject remains on study drug. The combination of the concurrent medical conditions- infection, dehydration and UTI could possibly have led to ARF. Therefore, the event of ARF is more likely related to these events, although attribution of rilpivirine or the background HAART regimen to the event cannot be excluded with certainty.

- Subject 209-0324 is a 41 year old male with PMH of chronic pericarditis. On Week 32, subject developed renal insufficiency/renal failure, grade 1, non-serious but considered possibly related to rilpivirine. The event lasted for approximately 2 months then resolved. No changes were made to his HIV medications (rilpivirine or TDF/FTC). Subject remains on study drug. Of note, serum creatinine was within normal limits at the time of the renal insufficiency diagnosis . The

diagnosis was based on estimations of renal function (GFR); the GFRcr at Week 32 was 79.8 (vs. 99.7 at screening). Based on the narrative provided, a causal relationship to rilpivirine cannot be excluded with certainty. However the event was considered mild (grade 1), non-serious by the investigator and the subject was able to continue study treatment without worsening of his renal function. The GFRcr at Week 60 was 85.7.

- Subject 209-0233 is a 33 year old male without pertinent PMH. On Day 238, subject had grade 1 increase in creatinine, which was believed not to be treatment related. On Day 288 (~Week 40), he was diagnosed with stage 2 chronic renal disease/renal failure. The event was classified as grade 2, non-serious and not related to study drug. The AEs (renal failure and increase in creatinine) resolved after 259 and 209 days, respectively. Screening creatinine and GFR were 1.1 and 80.6, respectively. At week 32 (Day 238), creatinine and GFR were 1.4 and 59.5 respectively. The subject was able to continue treatment with rilpivirine; at the last recorded visit (Week 60), the values were 1.3 and 68.2 for creatinine and GFR, respectively. The subject remains on study drug (rilpivirine + TDF/FTC).

In summary, renal failure occurred with similar incidence between the two arms. The events in the rilpivirine group were considered mild or moderate in severity and did not lead to treatment discontinuation. The contribution of tenofovir to the events cannot be ruled out.

Glomerulonephritis
The two cases of glomerulonephritis were identified in the rilpivirine group, one of which was considered treatment related by the investigators but both were considered possibly treatment-related during FDA analysis. Therefore, these cases have been included under the 'Less Common Adverse Events' section of the Package Insert.

Renal Colic (nephrolithiasis)
As noted previously, the incidence of renal AEs appears to be higher in the rilpivirine group. However, this imbalance is driven primarily by the renal colic adverse events. In total, there were 8 subjects with nephrolithiasis in the rilpivirine group compared to 4 subjects in the EFV group. It is unclear why twice as many subjects had renal stones in the rilpivirine group. As discussed in the pharmacokinetic section, <1% of rilpivirine is excreted renally. No data on the analysis of the renal stones are available.

In summary, renal failure-related adverse events were similar in the two treatment groups but the events were milder in the rilpivirine group. In addition, no subject from the rilpivirine group discontinued treatment due to renal failure. The one subject who discontinued treatment due to 'renal and urinary' adverse event was the subject with membranous glomerulonephritis. Both cases of glomerulonephritis occurred in the rilpivirine group. Finally, nephrolithiasis (renal colic) was reported more frequently in the rilpivirine group. The glomerulonephritis and nephrolithiasis cases were not always thought to be treatment related by the investigators. (b) (4)

Serum Creatinine

Serum creatinine can increase because of intrinsic renal injury, renal hemodynamic factors (reduction in intraglomerular pressure leading to decreased filtration), or interference with tubular secretion. Increase in serum creatinine during the treatment period was noted only in the rilpivirine group. Most increases were limited to grade 1 (Table 25 and Figure 3). Most of the increase occurred in the first two weeks of treatment and appeared to plateau after Week 2. In the rilpivirine group, the mean baseline

serum creatinine was 0.85 (range 0.4-1.4 mg/dL). At Week 24, the mean serum creatinine was 1.04 (0.53 -1.8 mg/dL). Although a mean change (0.19 mg/dL, maximum change 0.7mg/dL) was noted, the maximum change was < 1.0 mg/dL. A small trend of an increase in mean serum creatinine is noted again after Week 24. Of the subjects who were followed off treatment, subjects still had an elevated serum creatinine compared to baseline – a mean increase of 0.09 mg/dL at end of trial but decreased to 0.04 mg/dL in the follow-up period. Thus, the effect of rilpivirine on serum creatinine appears to be reversible after cessation of treatment, although the reversal was not complete. Of note, the follow-up period was only up to 4 weeks.

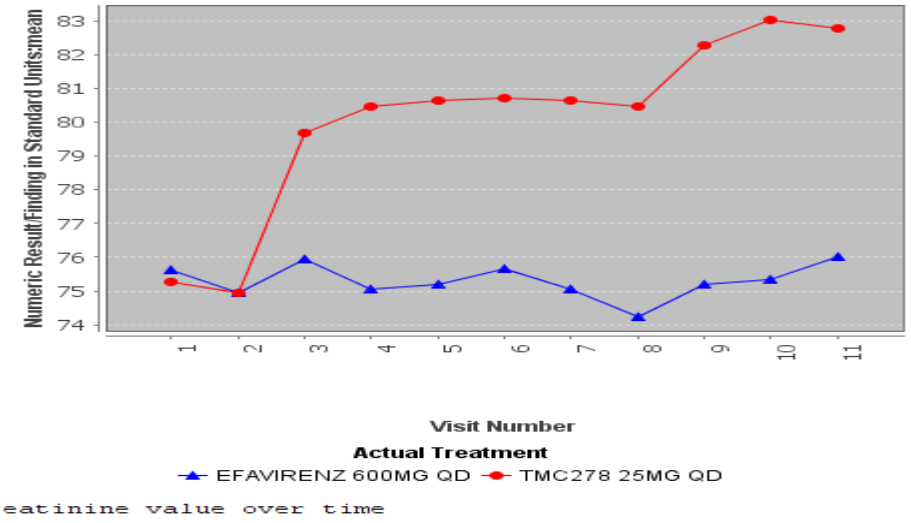
Change in serum creatinine was noted regardless of background regimen but the change was less pronounced in subjects who had received AZT/3TC as background regimen.

Table 25 Creatinine Laboratory Toxicity

	C209		C215		Pooled	
Creatinine worst grade toxicity, n(%)	Rilpivirine N=346	EFV N=344	Rilpivirine N=340	EFV N=338	Rilpivirine N=686	EFV N=682
Grade 1	15(4)	1(<1)	13(4)	2(1)	28(4)	3(<1)
Grade 2	1(<1)	1(<1)	1(<1)	4(1)	2(<1)	5(1)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	1(<1)	1(<1)	1(<1)

Source LBAD Dataset from pooled Phase 3 trials

Figure 3 Serum Creatinine Over Time



Note, conversion of the International Standard Units (ISU) (mmol/L) to mg/dl: multiply ISU by 0.088. The normal range for ISU is 40-110 ; normal range for mg/dl unit is 0.5-1.2

In order to further evaluate the cause for the observed increase in serum creatinine, additional analyses were conducted. Estimated GRF (eGFR) was calculated by both creatinine and cystatin to elicit whether there was an intrinsic injury vs. interference with tubular secretion. In addition, the effect on renal hemodynamic status was assessed by evaluating serum BUN. Please refer to Dr. Blank's review for further details. Based on Dr. Blank's review, no real difference between baseline levels and last visit levels were seen for both treatment groups. Therefore, rilpivirine likely has no effect on renal hemodynamics.

An exposure-response analysis was conducted for GFR and rilpivirine. No trend in maximum change in eGFR from baseline was observed with respect to rilpivirine exposure (Ctrough or AUC24). Please refer to Section 7.5.1 for additional details. However, using creatinine as marker for estimated GFR (eGFR), there was a mean decrease from baseline in eGFR which was noted only in the rilpivirine group. To assess possible effect of rilpivirine on the GFR, cystatin C was added to the safety biochemistry laboratory assessments of trial C215. A separate report (as an addendum to C215 study report), containing the findings from the cystatin C data analysis has been submitted in this NDA. According to the Applicant, there was an increase in eGFR (estimation of GFR by cystatin) at Week 2 and at Week 24 in both treatment groups, indicating that there is no rilpivirine-induced nephrotoxicity. The Applicant explains tubular secretion was the most likely explanation because the creatinine increased rapidly and plateaued in the first 2 weeks; and the majority of rilpivirine-treated subjects had an increase in serum creatinine, few with a large increase, and most recovered while on treatment. The likely effect on tubular secretion is also supported by the following points: a decrease in eGFRcystC was not seen; subjects with decrease in serum creatinine while on treatment were likely to recover after rilpivirine was discontinued; there was no greater incidence of marked increases in serum creatinine in the rilpivirine group compared to the EFV group; and there was no change in serum BUN over time.

Based on Dr. Blank's analysis, the estimated glomerular filtration rate for cystatin C (eGFRcystC) analysis was difficult to interpret due to the fact that the increase in eGFRcystC at Week 2 and 24 was larger in the EFV group than in the rilpivirine group. In the rilpivirine group, the eGFRcysC increased by +2.6 at Week 2 and +21.6 at Week 24, where as in the EFV group, the change from baseline at Week 2 and 24 was +5.3 and +31.3 respectively. In addition to the noted difference in eGFRcystC at Week 2 and 24 between the two treatment groups, the fact that there was a small trend of serum creatinine increase after Week 24 and an observed incomplete recovery of serum creatinine at 2-4 weeks of follow-up after discontinuation of treatment, raises the potential that rilpivirine may have an effect on renal function (GFR). Refer to Dr. Blank's review for further details.

In conclusion, there appears to be a small increase in serum creatinine in subjects treated with rilpivirine. Most of the increases occurred in the first 2 weeks then plateaued. Although an increase in mean serum creatinine was noted, the maximum mean change at Week 24 compared to baseline was less than 1 mg/dL. Additionally, there was a trend suggesting a small increase in serum creatinine after Week 24. Again, the increase in mean serum creatinine pre- or post- Week 24 remains small and of questionable clinical significance. Furthermore, the event appears to reverse after cessation of treatment, although the reversal was not complete. Most of the graded renal adverse events were mild to moderate and the incidence of renal failure was comparable between the two treatment groups. Although the mechanism by which the increase in serum creatinine is thought to be via inhibition of renal tubular secretion of serum creatinine, effects of rilpivirine on GFR cannot be ruled out. Based on the currently available data, including the points discussed above, the labeling recommendations for serum creatinine elevation are as follows:

- In the Adverse Reactions section, the laboratory table should include all graded (1-4) serum creatinine toxicities to reflect the difference between the two treatment groups.

- A statement should be added to reflect the mean change in serum creatinine at Week 24 vs. baseline:
  Renal Function
  Increases in serum creatinine (mean 0.19 mg/dL with a range of 0 – 0.7 mg/dL) commonly occurred during treatment with rilpivirine. The increases in serum creatinine occurred within the first two to four weeks of treatment then plateau.

Of note, in addition to the above recommendations, DCRP also suggested the following:

- Monitor serum creatinine levels closely for the first two months of treatment to ensure that serum creatinine levels have stabilized. If there is a marked or progressive rise in serum creatinine after the first two weeks of treatment with rilpivirine, a work up for other causes of renal toxicity should be considered.

Despite DCRP's recommendations, additional monitoring of serum creatinine beyond what is included in routine HIV management will not be recommended at this time because it is not warranted by the clinical data. Please refer to Dr. Florian's review for analysis supporting this decision.

In the Phase 3 clinical trials the observed increase in serum creatinine appears to plateau by Week 2 and as discussed above, the maximum mean increase in serum creatinine by Week 24 was <1mg/dL (see discussion above for details). There was no trend of marked and progressive increase in serum creatinine identified in the Phase 3 clinical trials. Close monitoring of serum creatinine in the first 2 months would not address the concern of GFR reduction [as suggested by: a small trend of serum creatinine increase after week 24; incomplete recovery of serum creatinine at 2-4 weeks of follow-up (note, mean creatinine increase was 0.04 mg/dL compared to baseline); and an unfavorable difference in eGFRcyst C between baseline and week 24 in the rilpivirine treatment group relative to the efavirenz group]. Therefore, the additional monitoring in the first 2 months beyond the routine monitoring may not be beneficial. Note, per the DHHS HIV-1 treatment guidelines, routine HIV care includes the following schedule for assessment of basic chemistry: at entry into care, follow-up before initiation of ART (every 3-6 months), at the time of ART initiation, 2-8 weeks post-ART initiation and every 3-6 months until clinically stable.

To further characterize the effect rilpivirine on eGFR, the following has been recommended by DCRP:

- Perform a study in healthy volunteers on no background nephrotoxic drugs to determine if pre-treatment/concurrent treatment with cimetidine prevents the rilpivirine induced rise in mean serum creatinine. If tubular secretion is the predominant mechanism for rilpivirine induced rises in mean serum creatinine there should be no increase in mean serum levels at 2 to 4 weeks from baseline mean serum measured after maximum cimetidine inhibition of tubular secretion is reached.

Please refer to Dr. Florian's review for further details.

Cardiac Events

No adverse effects of rilpivirine on the cardiovascular system were noted during initial safety pre-clinical pharmacology studies but subsequent safety pharmacology studies demonstrated that rilpivirine had the potential to inhibit some potassium channels involved in cardiac action potential repolarization (Section 4.4)

Cardiac events were considered adverse events of special interest due to the positive thorough QT study. As mentioned before, the 75 mg dose and the 300 mg supra-therapeutic dose prolonged QTc interval by 11 mm and 23 mm, respectively. An additional QTc study was conducted by the Applicant to assess if 25 mg qd had any effect on cardiac conduction. In summary, the 25 mg did not have an effect on QTc interval considered substantial (i.e. >10 ms). Refer to 7.4.4 for additional details on electrocardiogram findings during the Phase 3 trials.

Cardiac adverse events, including ECG-related adverse events were reviewed to assess the incidence cardiac events with use of rilpivirine. All the preferred terms within in the Cardiovascular Body System Organ Disorder were grouped based on the type of events (Table 26). The most commonly reported ECG-related AEs with rilpivirine compared to EFV were right bundle branch block (1.3% vs. 1.5%) and palpitations (1.7% vs. 1.0%) but these events occurred with similar incidence in the EFV group. One subject in the rilpivirine group discontinued treatment (per protocol) due to a grade 3 AE of QTc interval prolongation (QTcF interval at Week 48 was 457 ms, an increase by 77 ms from baseline). The subject is a 31 year old female from the U.S. who started treatment with rilpivirine and TDF/FTC on 12/23/08 and discontinued on 1/4/10; she experienced the event on (b) (4) The event appears to be at least probably related to rilpivirine. The subject did not have any clinical symptoms suggestive of cardiac adverse event recorded at the time of the QT prolongation. No concomitant medications were being given at the time of the QT prolongation. Refer to Section 7.4.4 for further discussion on ECG findings.

Table 26 Cardiac Related Adverse Events of Interest

	C209		C215		Pooled	
Grouped Term Preferred Term, n (%)	rilpivirine N= 346	EFV N = 344	rilpivirine N = 340	EFV N = 338	rilpivirine N = 686	EFV N = 682
Conduction disorders	9 (2.6)	7 (2.0)	14 (4.1)	20 (5.9)	23 (3.4)	27 (4.0)
Bundle branch block right	2 (0.6)	4 (1.2)	7 (2.1)	6 (1.8)	9 (1.3)	10 (1.5)
Conduction disorder	4 (1.2)	2 (0.6)	3 (0.9)	4 (1.2)	7 (1.0)	6 (0.9)
ECG T-wave abnormal	2 (0.6)	1 (0.3)	3 (0.9)	2 (0.6)	5 (0.7)	3 (0.4)
Bundle branch block	0	0	3 (0.9)	4 (1.2)	3 (0.4)	4 (0.6)
Atrioventricular block first degree	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.1)	2 (0.3)
ECG QT prolonged	0	0	1 (0.3)	4 (1.2)	1 (0.1)	4 (0.6)
ECG ST segment abnormal	0	0	0	1 (0.3)	0	1 (0.1)
Other	3 (0.9)	2 (0.6)	0	4 (1.2)	3 (0.4)	6 (0.9)
ECG abnormal	3 (0.9)	2(0.6)	0	3 (0.9)	3 (0.4)	5 (0.7)
Poor R-wave progression	0		0	1(0.3)	0	1(0.1)
Rate and rhythm disorders	11 (3.2)	20 (5.8)	12 (3.5)	8 (2.4)	23 (3.4)	28 (4.1)
Palpitations	7 (2.0)	5 (1.5)	5 (1.5)	2 (0.6)	12 (1.7)	7 (1.0)
Bradycardia	4 (1.2)	2 (0.6)	1 (0.3)	2 (0.6)	5 (0.7)	4 (0.6)
Sinus bradycardia	0	2 (0.6)	3 (0.9)	0	3 (0.4)	2 (0.3)
Supraventricular extrasystoles	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Tachycardia	0	7 (2.0)	1 (0.3)	2 (0.6)	1 (0.1)	9 (1.3)
Heart rate increased	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
Heart rate irregular	1 (0.3)	0	0	0	1 (0.1)	0
Sinus arrhythmia	0	0	1 (0.3)	0	1 (0.1)	0
Atrial flutter	0	1 (0.3)	0	0	0	1 (0.1)
Extrasystoles	0	1 (0.3)	0	0	0	1 (0.1)
Sinus tachycardia	0	1 (0.3)	0	0	0	1 (0.1)
Supraventricular tachyarrhythmia	0	1 (0.3)	0	0	0	1 (0.1)
Supraventricular tachycardia	0	0	0	1 (0.3)	0	1 (0.1)
Ventricular extrasystoles	0	1 (0.3)	0	0	0	1 (0.1)
Myocardial disorders	0	1(0.3)	1(0.3)	3(0.9)	2(0.3)	4(0.6)
Angina pectoralis			1(0.3)	3(0.9)	1(0.1)	3(0.4)
Myocardial ischemia	0	1(0.3)	0	0	0	1(0.1)
Functional blood flow disorder					1(0.1)	0

Source AEAD Dataset from the pooled Phase 3 trials

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events reported in at least 5% of subjects in either pooled treatment group are presented in Table 27. For the pooled analysis - by System Organ Class, the most common AEs in the rilpivirine group were 'infections and infestations' (58.6% in the rilpivirine group vs. 58.2% in the EFV group) and 'gastrointestinal disorders' (40.2% in the rilpivirine group vs. 37.0% in the EFV group).
The greatest differences between rilpivirine and EFV were in 'nervous system' (30.9% vs. 47.1%), 'skin and subcutaneous tissue disorders' (22.4% vs. 31.4%), 'general disorders and administration site conditions' (14.9% vs. 20.5%), and 'psychiatric disorders' (24.1% vs. 29.0%). The difference between the rilpivirine and EFV groups seen in 'nervous system disorders' was driven by the preferred term 'dizziness' (9.9% vs. 28.4%); the difference in 'skin and subcutaneous tissue' was mainly due to the preferred term 'rash' (5.2% vs. 13.2%).

Table 27 Common Adverse Events Reported in at least 5% of Subjects in Rilpivirine or Efavirenz Group

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	rilpivirine N = 346	EFV N = 344	rilpivirine N = 340	EFV N = 338	rilpivirine N = 686	EFV N = 682
Infections and Infestations	208(60.1)	212(61.6)	194(57.1)	185(54.7)	402(58.6)	397(58.2)
Nasopharyngitis	28(8.1)	42(12.2)	41(12.1)	33(9.8)	69(10.1)	75(11.0)
Upper respiratory tract infection	33(9.5)	36(10.5)	28(8.2)	31(9.2)	61(8.9)	67(9.8)
Influenza	26(7.5)	29(8.4)	21(6.2)	25(7.4)	47(6.9)	54(7.9)
Gastrointestinal disorders	135(39.0)	118(34.3)	141(41.5)	134(39.6)	276(40.2)	252(37.0)
Nausea	37(10.7)	33(9.6)	55(16.2)	64(18.9)	92(13.4)	97(14.2)
Diarrhea	36(10.4)	53(15.4)	42(12.4)	41(12.1)	78(11.4)	94(13.8)
Vomiting	13(3.8)	17(4.9)	20(5.9)	23(6.8)	33(4.8)	40(5.9)
Nervous system disorders	92(26.6)	148(43.0)	120(35.3)	173(51.2)	212(30.9)	321(47.1)
Headache	43(12.4)	38(11.0)	52(15.3)	54(16.0)	95(13.8)	92(13.5)
Dizziness	26(7.5)	88(25.6)	42(12.4)	106(31.4)	68(9.9)	194(28.4)
Somnolence	12(3.5)	23(6.7)	16(4.7)	28(8.3)	28(4.1)	51(7.5)
Psychiatric disorders	81(23.4)	112(32.6)	84(24.7)	86(25.4)	165(24.1)	198(29.0)
Insomnia	23(6.6)	32(9.3)	31(9.1)	20(5.9)	54(7.9)	52(7.6)
Abnormal dreams	28(8.1)	41(11.9)	18(5.3)	25(7.4)	46(6.7)	66(9.7)
Depression	22(6.4)	17(4.9)	18(5.3)	15(4.4)	40(5.8)	32(4.7)
Anxiety	4(1.2)	21(6.1)	12(3.5)	14(4.1)	16(2.3)	35(5.1)
Skin and subcutaneous tissue disorders	76(22.0)	107(31.1)	78(22.9)	107(31.7)	154(22.4)	214(31.4)
Rash	24(6.9)	41(11.9)	12(3.5)	49(14.5)	36(5.2)	90(13.2)
Musculoskeletal and connective tissue disorders	63(18.2)	58(16.9)	59(17.4)	59(17.5)	122(17.8)	117(17.2)
Back pain	16(4.6)	15(4.4)	14(4.1)	21(6.2)	30(4.4)	36(5.3)
Investigations	51(14.7)	51(14.8)	69(20.3)	60(17.8)	120(17.5)	111(16.3)
General disorders and administration site conditions	55(15.9)	79(23.0)	47(13.8)	61(18.0)	102(14.9)	140(20.5)
Fatigue	15(4.3)	26(7.6)	16(4.7)	27(8.0)	31(4.5)	53(7.8)

Table 27 Common Adverse Events Reported in at least 5% of Subjects in Rilpivirine or Efavirenz Group (Continued)

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	rilpivirine N = 346	EFV N = 344	rilpivirine N = 340	EFV N = 338	rilpivirine N = 686	EFV N = 682
Respiratory, thoracic and mediastinal disorders	38(11.0)	46(13.4)	63(18.5)	33(9.8)	101(14.7)	79(11.6)
Cough	14(4.0)	10(2.9)	26(7.6)	10(3.0)	40(5.8)	20(2.9)
Blood and lymphatic system disorders	24(6.9)	19(5.5)	35(10.3)	26(7.7)	59(8.6)	45(6.6)
Metabolism and nutrition disorders	24(6.9)	36(10.5)	27(7.9)	39(11.5)	51(7.4)	75(11.0)
Injury, poisoning and procedural complications	23(6.6)	30(8.7)	27(7.9)	23(6.8)	50(7.3)	53(7.8)
Renal and urinary disorders	25(7.2)	17(4.9)	25(7.4)	21(6.2)	50(7.3)	38(5.6)
Reproductive system and breast disorders	26(7.5)	18(5.2)	20(5.9)	25(7.4)	46(6.7)	43(6.3)
Cardiac disorders	18(5.2)	26(7.6)	22(6.5)	21(6.2)	40(5.8)	47(6.9)
Vascular disorders	16(4.6)	21(6.1)	23(6.8)	18(5.3)	39(5.7)	39(5.7)
Ear and labyrinth disorders	9(2.6)	27(7.8)	5(1.5)	11(3.3)	14(2.0)	38(5.6)

Source AEAD Dataset from pooled Phase 3 trials

7.4.2 Laboratory Findings

Hematology

Hematologic laboratory toxicities are summarized in Table 28 below. In general, few grade 3 and 4 toxicities were observed in the rilpivirine group. The greatest incidence of laboratory toxicities were observed for WBC, specifically, grade 3 decrease in WBC. These events occurred almost exclusively in trial C215 where zidovudine was among the NRTIs used to construct a background regimen.

Table 28 Hematology Laboratory Findings

	C209		C215		Pooled	
n(%)	TMC278 N=346	EFV N=344	TMC278 N=340	EFV N=338	TMC278 N=686	EFV N=682
Hemoglobin, worst grade toxicity						
Grade 3	1(0.3)	0	0	1(0.3)	1(0.1)	1(0.1)
Grade 4	0	1(0.3)	0	0	0	1(0.1)
WBC, worst grade toxicity						
Grade 3	0	1(0.3)	7(2.1)	5(1.5)	7(1)	6(0.9)
Grade 4	0	0	0	0	0	0
Platelet, worst grade toxicity						
G3	0	1(0.3)	1(0.3)	1(0.3)	1(0.1)	2(0.3)
G4	0	0	0	0	0	0

Source LBAD Datasets for pooled Phase 3 trials

Hepatic

In the pooled analysis, the incidence of laboratory toxicities for ALT and AST was higher in the EFV group (Table 29). However, hyperbilirubinemia was observed with greater incidence in the rilpivirine group. This is particularly true for grade 1 elevation in total bilirubin, where the incidence was 5% in the rilpivirine group vs. <1% for the EFV group. The hyperbilirubinemia appears to be a result of elevation in indirect (unconjugated) bilirubin.

An exposure-response analysis was performed to evaluate if hyperbilirubinemia was due to drug exposure. The analysis suggested no exposure-response relationship between hyperbilirubinemia and degree of rilpivirine exposure. Refer to review by Dr. Jeff Florian, Pharmacometrics Reviewer for full analysis of exposure-response. The mechanism by which TMC278 may cause an increase in bilirubin (indirect bilirubin) has not been investigated.

Because the difference in the incidence of hyperbilirubinemia was highest for the grade 1 events, the Package Insert laboratory table (Table 3) has been revised to include laboratory toxicities ≥ grade 1 in order to reflect the differences between the two treatment groups.

Table 29 Hepatobiliary Laboratory Toxicities

	C209		C215		Pooled	
n(%)	Rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
AST worst grade toxicity						
G1	53(15.3)	60(1.7)	51(15)	63(18.6)	104(15.2)	123(18)
G2	8(2.3)	25(7.2)	11(3.2)	18(5.3)	19(2.8)	43(6.3)
G3	6(1.7)	11(3.2)	4(1.2)	4(1.2)	10(1.5)	15(2.2)
G4	1(0.3)	2(0.6)	2(0.6)	3(0.9)	3(0.4)	5(0.7)
ALT worst grade toxicity						
G1	54(16)	62(18)	48(14)	55(16)	102(15)	117(17)
G2	12(3.5)	26(7.6)	15(4.4)	22(6.5)	27(3.9)	48(7)
G3	1(0.3)	9(2.6)	4(1.2)	6(1.8)	5(0.7)	15(2.2)
G4	3(0.9)	5(1.5)	2(0.6)	5(1.8)	5(0.7)	9(1.3)
TB worst grade toxicity						
G1	14(4)	1(0.3)	21(6.2)	2 (0.6)	35(5.1)	3(0.4)
G2	7(2)	1(0.3)	11(3.2)	0	18(2.6)	1(0.1)
G3	0	1(0.3)	4(1.2)	0	4(0.6)	1(0.1)
DB above ULN	2(0.6)	3(0.9)	5(1.5)	2(0.6)	7(1)	5(0.7)
IB above ULN	11(3.2)	2(0.6)	26(7.6)	1(0.3)	37(5.4)	3(0.4)

Source LBAD Dataset from pooled Phase 3 trials

Comparison of laboratory toxicities between non co-infected and co-infected subjects were conducted (Table 30). In general, co-infected subjects had higher incidence of toxicities for ALT and AST. In addition, grade 3 and 4 elevation in ALT and AST were generally similar between co-infected subjects in rilpivirine and EFV treatment groups.

Table 30 Laboratory Toxicities in Non-Co-infected and Co-infected Subjects

	Rilpivirine		EFV	
LFT worst grade toxicity, n(%)	Non Co-infected N=632	Co-infected N=54	Non Co-infected N=616	Co-infected N=66
AST				
Grade 1	72(11.4)	11(20.4)	98(15.9)	12(18.2)
Grade 2	15(2.4)	4(7.4)	34(5.5)	7(10.6)
Grade 3	7(1.1)	4(7.4)	11(1.8)	2(3)
Grade 4	0	3(5.6)	3(0.5)	4(4.5)
ALT				
Grade 1	97(15)	9(16.7)	114(18.5)	9(23.6)
Grade 2	16(2.5)	9(16.7)	35(5.7)	8(12.1)
Grade 3	1(0.2)	4(7.4)	9(1.5)	5(7.6)
Grade 4	0	5(9.3)	3(0.5)	6(9.1)
Total bilirubin				
Grade 1	33(5.2)	3(5.6)	2(0.3)	0
Grade 2	13(2.1)	4(7.4)	1(0.2)	1(1.5)
Grade 3	4(0.6)	0	1(0.2)	0

Source LBAD and DMAD Datasets from pooled Phase 3 trials

Pancreatic Amylase and Lipase

Laboratory findings for pancreatic amylase and lipase are summarized in Table 31. No clinical case of pancreatitis in the rilpivirine group whereas 2 cases in the EFV group were reported. In the Phase 2b trial, one case of pancreatitis (due to cholecysitis) was reported in the 150 mg qd rilpivirine group.

Table 31 Laboratory Findings for Pancreatic Amylase and Lipase

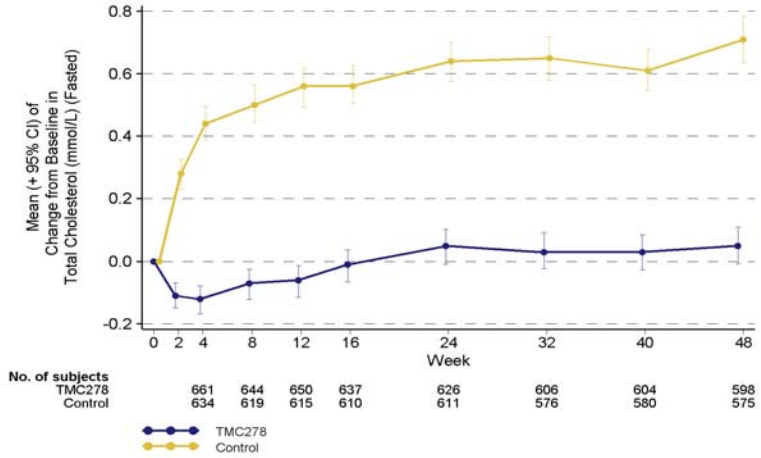
	C209		C215		Pooled	
n(%)	TMC278 N=346	EFV N=344	TMC278 N=340	EFV N=338	TMC278 N=686	EFV N=682
Pancreatic amylase, worst grade toxicity						
G1	20(5.8)	22(3.4)	28(8.2)	27(8)	48(7)	49(7)
G2	15(4.3)	17(4.9)	7(2.1)	16(4.7)	22(3.2)	33(4.8)
G3	11(3.2)	16(4.7)	7(2.1)	9(2.7)	18(2.6)	25(3.7)
G4	0	0	2(0.6)	2(0.6)	2(0.3)	2(0.3)
Lipase, worst grade toxicity						
G1	8(2.3)	9(2.6)	6(1.8)	7(2.1)	14(2)	16(2.3)
G2	8(2.3)	11(3.2)	5(1.5)	7(2.1)	13(1.9)	18(2.6)
G3	0	3(0.9)	1(0.3)	2(0.6)	1(0.1)	5(0.7)
G4	1(0.3)	1(0.3)	1(0.3)	3(0.9)	2(0.3)	4(0.6)

Source LBAD Datasets from pooled Phase 3 trials

Lipids

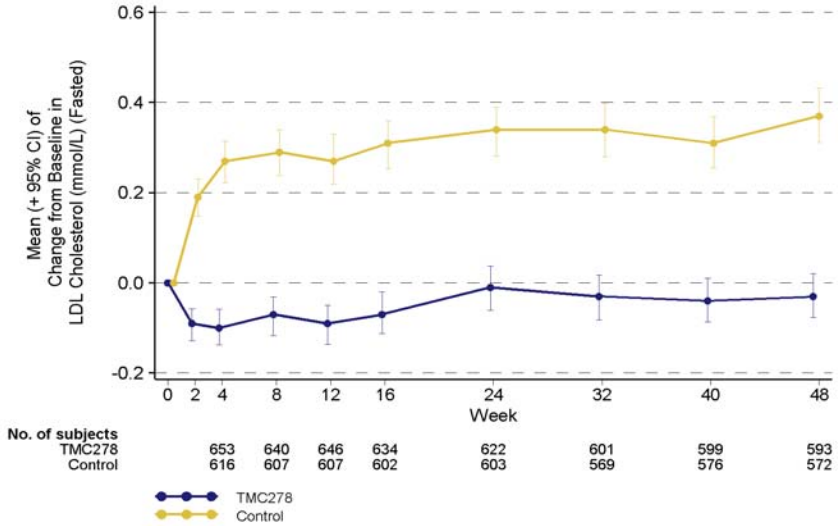
The Applicant evaluated the mean changes from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (Figures 4-6). Compared to the EFV group, in the rilpivirine group, small mean decreases from baseline were seen in total cholesterol and LDL up to Week 16 and 24, respectively, after which small mean increases to just above baseline levels were observed. In the EFV group, total cholesterol and LDL increased from baseline over the whole treatment period. Mean decreases from baseline were observed for triglycerides over time in the rilpivirine group, compared with mean increases from baseline in the control group. Lipid lowering drugs were used by 2% and 4% of subjects in the rilpivirine and EFV groups, respectively. The clinical significance of these results has not been assessed.

Figure 4 Mean Change in Total Cholesterol Over Time



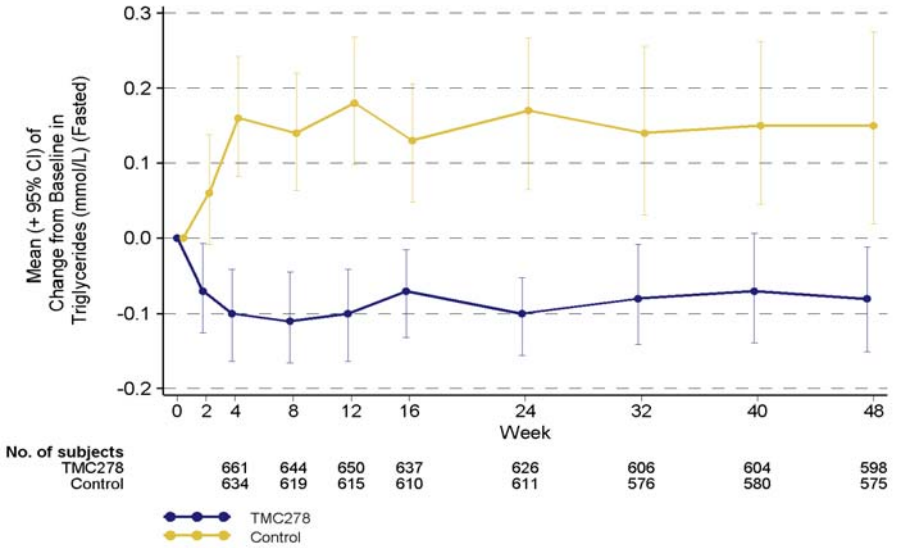
Source Integrated Summary of Safety

Figure 5 Mean Change in LDL Over Time



Source Integrated Summary of Safety

Figure 6 Mean Change in Triglycerides Over Time



Source Integrated Summary of Safety

Package Insert

Laboratory parameters for hematology are not included in the package insert as the incidence grade 3 and 4 toxicities were very low and appeared to be associated with use of specific background regimens. Similarly, pancreatic enzyme abnormalities are not included in the package insert because few grade 4 toxicities were reported and no clinical case of pancreatitis (drug induced) was reported in the Phase 2b and 3 trials.

Package Insert for Laboratory Findings

(b) (4)

(b) (4)

7.4.3 Vital Signs

Vital signs including pulse and blood pressure (BP) were obtained at screening and at each visit. Systolic and diastolic BP was recorded in sitting position and after 5 minutes of rest. There were no consistent or clinically relevant changes over time in vital sign parameters observed in the Phase 3 trials.

7.4.4 Electrocardiograms (ECGs)

No adverse effects of rilpivirine on the cardiovascular system were noted during initial safety pharmacology studies but subsequent safety pharmacology studies demonstrated that rilpivirine had the potential to inhibit potassium channels involved in cardiac action potential repolarization. See Section 4.4.

During the development period of rilpivirine, the Applicant conducted three QT trials:

> C131: Randomized, double-blind, double-dummy, placebo- and active-controlled, 3-way crossover trial to evaluate the effect of rilpivirine (75mg qd, 300 mg qd) after a single dose and at steady-state on the QT/QTc interval.

C151: An exploratory, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel trial to explore the effect of rilpivirine (25 mg qd) at steady-state on the QT/QTc interval.

C152: double-dummy, placebo- and active-controlled, crossover trial to evaluate the effect of rilpivirine (25 mg qd) at steady-state and the effect of EFV (600 mg qd) at steady-state on the QT/QTc interval, in two randomized panels.

The results of study C131 were as follows: at steady-state (Day 11), both rilpivirine 75 mg and 300 mg treatments were associated with a prolongation of the QTcF interval. The largest mean increase from baseline for both rilpivirine 75 mg q.d. (+10.4 ms; 90% CI [7.7, 13.1]) and 300 mg q.d. (+23.8 ms; [19.8, 27.8]) was observed at 5 hours post-dose. The results of the exploratory C151 trial showed that the highest upper limit of the 90% CI of the time-matched change from baseline in QTcF during rilpivirine 25 mg q.d. dosing did not cross the 10 ms threshold. The maximum mean time-matched change from baseline in QTcF was < 5 ms, suggesting that there is no clinically relevant effect on the QTc interval. Similar findings were seen in trial C152. Refer to TQT team's review for additional details.

Due to the known effect of a supratherapeutic rilpivirine dose on QT interval, an independent cardiologist was consulted by the Applicant to assess data from nonclinical and clinical trials in establishing the potential effect of rilpivirine on the QTc interval. The report of the cardiologist has been submitted as part of the NDA: for the Phase 3 trials, there was an increase over time in the mean QTcF interval in both treatment groups; the increase was gradual and numerically higher in the EFV group. The mean maximum change from baseline in QTcF interval was +17.9 ms in the rilpivirine group and +19.2 ms in the EFV group. Refer to TQT team's review for additional details.

Package Insert
The findings from trials C151, C152 and the Phase 3 trials demonstrated that 25 mg qd does not exceed the QTc threshold as defined by ICH E14, indicating that the rilpivirine 25 mg q.d. dose is not associated with a clinically relevant effect on QTcF interval. Nonetheless, rilpivirine does prolong QTc at higher doses (e.g. 75 mg qd). It is therefore important to include this information in the label, specifically in the Warnings and Precautions section and clinical pharmacology section.

> In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram [*see Drug Interactions (7)* and *Clinical Pharmacology (12.2)*]. TRADE NAME™ should be used with caution when co-administered with a drug known risk of Torsade de Pointes.

7.4.5 Special Safety Studies

Cystatin C (TMC278-C215)

In order to further evaluate whether the effect of rilpivirine on serum creatinine was due to an interaction with the tubular secretion of creatinine or due to a true effect on glomeruli function, cystatin C was measured in subjects in the C215 trial at baseline, Week 2 and Week 24, and eGFRcyst was calculated. Cystatin C is believed to be a better marker for estimating GFR because it is freely filtered by the glomeruli without secretion in the proximal tubular.

The results of the calculated eGFRcyst along with serum creatinine and eGFRcreat data from Phase 3 trials were evaluated by Dr. Melanie Blank, clinical reviewer from the Division of Cardiovascular and Renal Products (DCRP). Please refer to Section 7.3.5 and to Dr. Blank's review for further details.

Hepatic Impairment Study

Hepatic impairment study has been conducted in mild and moderately impaired non-HIV infected subjects. Based on the study results, no dose adjustment is recommended for HIV-1 infected patients with mild to moderate hepatic impairment. See Dr. Stanley Au's review for further details.

7.4.6 Immunogenicity

As rilpivirine is not a peptide, immunogenicity effects were not evaluated during the clinical trials. Rilpivirine, a small molecule, is highly unlikely to have a potential for immunogenicity. Please refer to Pharmacology and Toxicology Review by Dr. Mark Seaton for details on the findings from the pre-clinical studies.

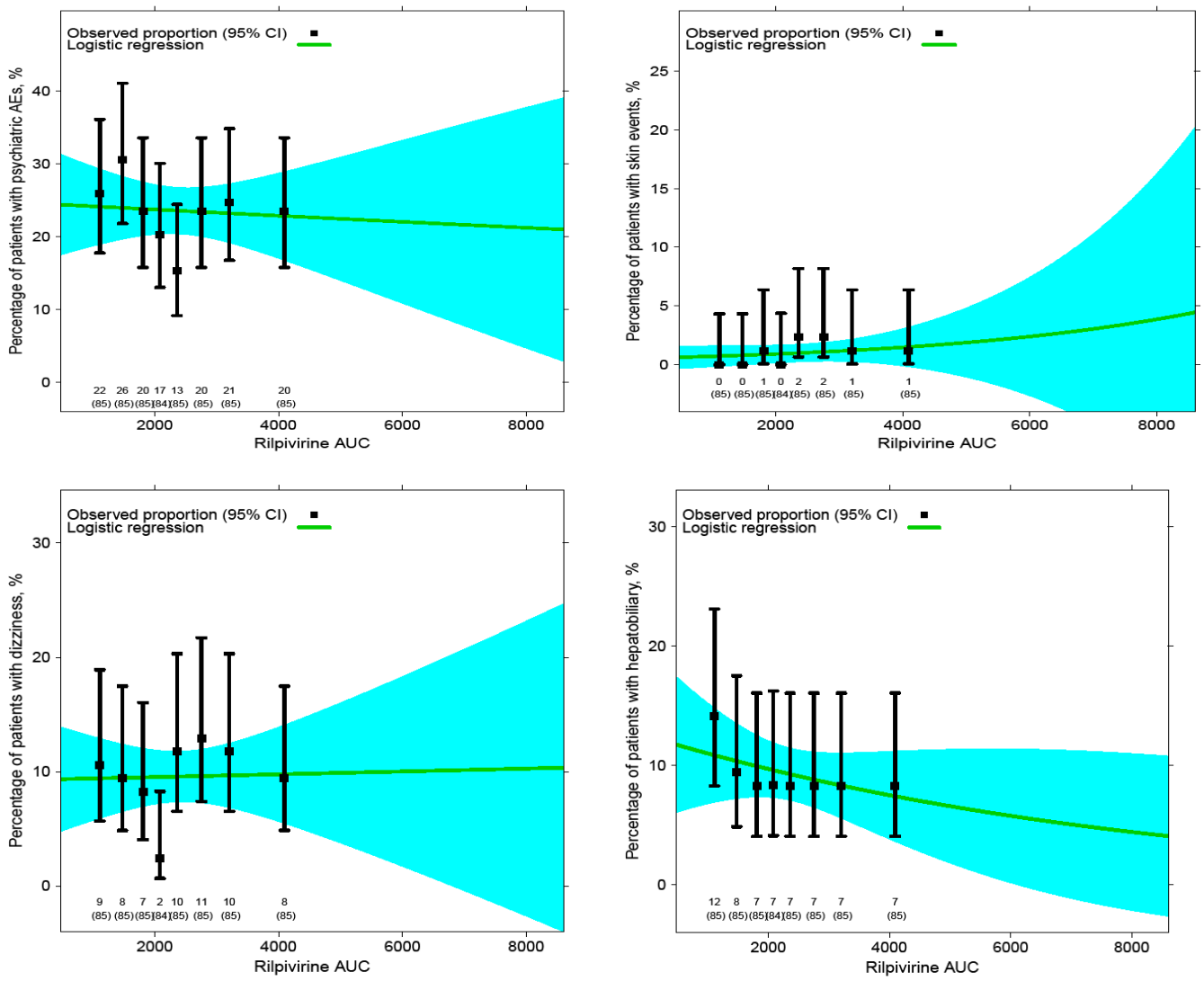
7.5 Other Safety Explorations

At the time of the cut-off date of the Phase 3 Week 48 analysis, the clinical safety database consisted of 1736 subjects participating in the Phase 3 trials and the Phase 2b trial, 965 of whom received rilpivirine. The subject-years of exposure was 740.1 years for the rilpivirine group and 714.4 years for the EFV group. The median treatment duration was 55.7 weeks and 55.6 weeks for rilpivirine and EFV groups, respectively.

7.5.1 Dose Dependency for Adverse Events

Pharmacokinetic and pharmacodynamic relationships for safety were evaluated. No apparent clear relationship was observed between rilpivirine pharmacokinetics and psychiatric, skin (rash), dizziness or hepatobiliary events (Figure 7). Refer to Pharmacometrics review by Dr. Jeff Florian for details.

Figure 7: Percentage of Patients with Psychiatric (top left), Skin (top right), Dizziness (bottom left), and Hepatobilliary (bottom right) Adverse Events Versus TMC278 AUC_{τ} for All Treatment Naïve Patients Administered TMC278 25 mg Q.D.

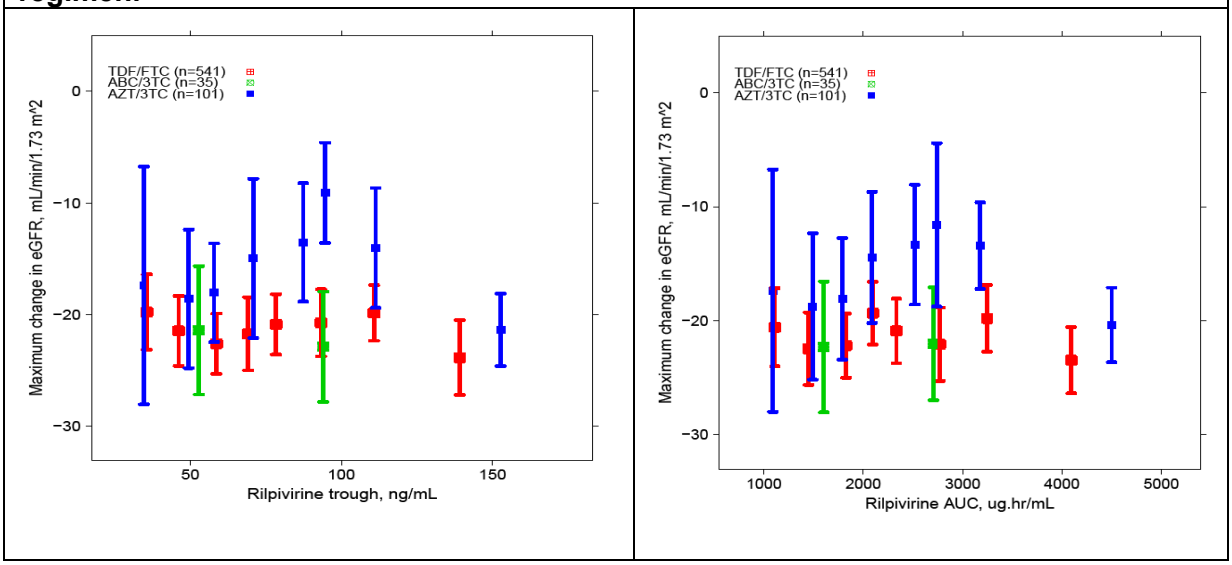


Source: Pharmacometrics Review

No trend in maximum change in eGFR from baseline was observed with respect to rilpivirine exposure (Ctrough or AUC24) for any of the three background regimens. On average across all background regimens, a net decrease in eGFR of -20 mL/min/1.73 m^2 was observed for patients on rilpivirine with a slightly lower decrease for patients on TDF/FTC (-21 mL/min/1.73 m^2) (Figure 8). When GFR is calculated instead based on cystatin C levels, no trend between rilpivirine exposure and GFR is

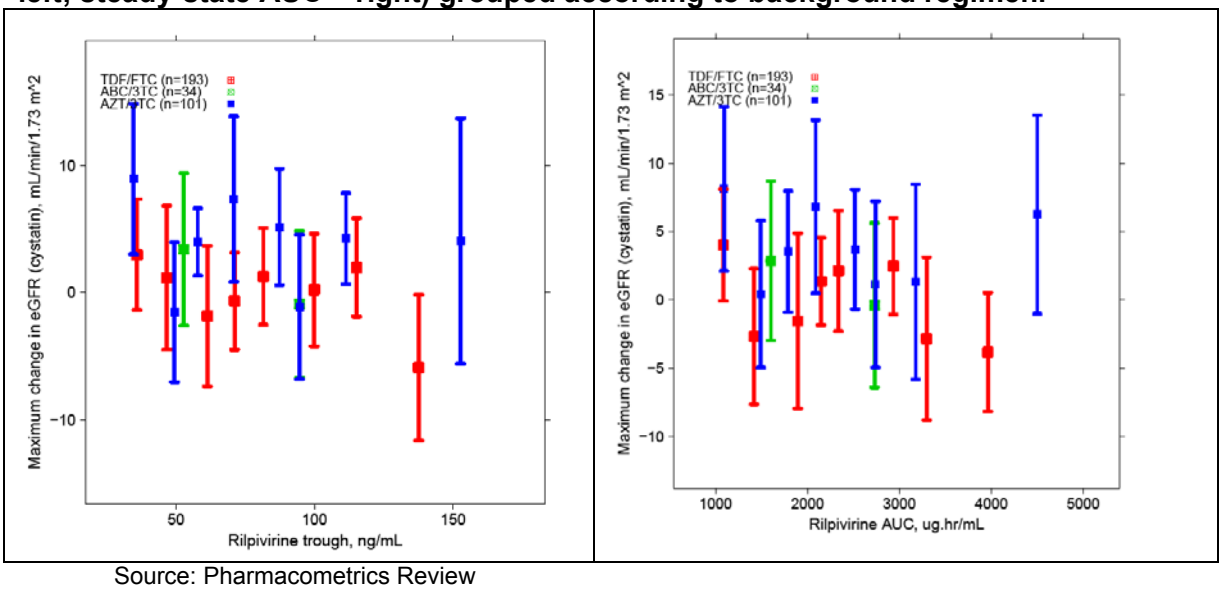
observed for any of the three background regimens (Figure 9). The net change in GFR across all background regimens was 1.3 mL/min/1.73 m^2 (-0.1 mL/min/1.73 m^2 for TDF/FTC).

Figure 8 Estimated GFR based on serum creatinine versus rilpivirine (trough concentration – left; steady-state AUC – right) grouped according to background regimen.



Source: Pharmacometrics Review

Figure 9 Estimated GFR based on cystatin versus rilpivirine exposure (trough concentration – left; steady-state AUC – right) grouped according to background regimen.



Source: Pharmacometrics Review

Finally, no trend was observed in changes in total, indirect, or direct bilirubin with respect to rilpivirine exposure. Similar changes in all bilirubin measurements were observed between those subjects with the highest and lowest rilpivirine exposure.

7.5.2 Time Dependency for Adverse Events

Time to onset analyses was performed for skin events, specifically for rash. Rash occurred with the highest incidence in the first 4 weeks among both rilpivirine and EFV exposed subjects. Refer to Section 7.3.5 for details.

7.5.3 Drug-Demographic Interactions

No unique drug-demographic interactions have been identified. In summary, approximately 25% of subjects in each treatment group were female. The adverse events profiles of rilpivirine and EFV (overall incidence of adverse events, and grade 3 and 4 adverse events) were similar between males and females. In the rilpivirine group, differences were noted in discontinuation rate due to AEs: 5% of women and 3% of men discontinued due to 'adverse events'. In the EFV group, no difference was observed in proportion of subjects who discontinued due to AEs (8% in both men and women).

The majority of subjects in both treatment groups were White (60%); 24% were Black, 13% were Asians and 3% were of other/unknown race. The adverse event profile was similar between Caucasians and Blacks for both treatment groups with regards to overall incidence of AEs, grade 3 and 4 AEs, and discontinuation due to AEs. Because fewer Asian subjects were enrolled, conclusive statements on drug-demographic interactions cannot be made for this subpopulation. However, the overall incidence of AEs was similar to Whites and Blacks in both treatment groups. Less SAEs and discontinuation due to AEs were reported in Asians in both treatment groups.

7.5.4 Drug-Disease Interactions

No definitive drug-disease interactions were observed.

7.5.5 Drug-Drug Interactions

Please refer to Clinical Pharmacology Review by Dr. Stanley Au for discussions on drug-drug interaction studies. An important interaction is with a drug that may increase the exposure of rilpivirine or with a drug known to have risk of Torsade de Pointes. Drugs that alter intra-gastric pH may affect the solubility of rilpivirine and affect its absorption; therefore rilpivirine should not be used in combination with proton pump inhibitors. H2-receptor antagonists should only be administered either 12 hours before or 4 hours after rilpivirine, and antacids should only be administered either 2 hours before or 4 hours after rilpivirine. Co-administration of rilpivirine is contraindicated with drugs where significant decreases in rilpivirine plasma concentrations may occur resulting in loss of therapeutic effect and possible resistance and cross resistance.

7.5.6 Human Carcinogenicity Potential

Carcinogenicity studies in mice and rats were positive for hepatocellular adenomas. Carcinomas were associated with induction of CYP4A (e.g. carcinoma in thyroid gland, hepatocellular adenomas, follicular adenomas). These findings are not reproducible in humans based on this mechanism. Therefore, these finding should not be considered significant for clinical dose of 25mg qd in man. In addition the exposures in mouse and rat carcinogenicity studies are 21 and 3 times higher, respectively, than the recommended 25 mg qd dose.

7.5.7 Human Reproduction and Pregnancy Data

Pregnancy and breastfeeding were exclusion criteria for all clinical trials. Pregnancy was a predefined condition that should lead to discontinuation from the trials. Therefore, no pregnant woman has been studied.

In animal studies, rilpivirine had no effect on fertility and early embryonic and fetal development. Teratogenicity studies in rats and rabbits showed no teratogenic potential.

During the Phase 2b and Phase 3 trials, a total of 6 pregnancies occurred in the rilpivirine group (3 from the Phase 2b trial and 3 from the Phase 3 trial). Two of the pregnancies are ongoing. The remaining 4 pregnancies ended in healthy live births. However, two delivered pre-term, one due to preeclampsia.

In summary, no adequate and well-controlled or pharmacokinetic trials of rilpivirine use in pregnant women have been conducted. Studies in animals have shown no evidence of embryonic or fetal toxicity or an effect on reproductive function. Rilpivirine falls under Category B for use in pregnancy; rilpivirine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

7.5.8 Pediatrics and Effect on Growth

The safety and efficacy of rilpivirine were not been established in pediatrics. Pediatric drug development is currently ongoing. Two pediatric trials are planned: study TMC278-C213 is a trial designed for pediatric patients 12 to 17 years of age. Preparations for the start of C213 are ongoing. The second study, TMC278-C220 will enroll pediatric patients birth to <12 years of age. Initiation of C220 will depend on the data from C213.

7.5.9 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of acute overdose were reported for rilpivirine during clinical trials. There is no known antidote specifically for treatment of rilpivirine overdose. Electrocardiogram monitoring is recommended due to the possibility of QT interval prolongation. Since rilpivirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

Rilpivirine is highly unlikely to have potential for abuse, withdrawal or rebound effect. There were no reports of rilpivirine drug dependence during clinical trials.

7.6 Additional Submissions

Not applicable.

8 Postmarketing Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1-166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
2. Renal Consult: Division of Cardiovascular and Renal Products
3. Endocrinology Consult: Division of Metabolic and Endocrinology Products
4. U.S. Package Insert: Sustiva
5. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

9.2 Labeling Recommendations

The following important revisions were recommended:

- **Usage and Indications Section**: Inclusion of information about the effectiveness of rilpivirine in subjects with high viral load; inclusion of resistance and cross-resistance identified with failure of rilpivirine. See Section 6.1.6 Subpopulations.

- **Contraindications Section**: inclusion of information about drug-drug interactions which may lead to under exposure of rilpivirine and thus pose risk of virologic failure and resistance and cross-resistance. See Section 6.1.6 Subpopulations and Section 7.5.5 Drug-Drug-Interactions

- **Warnings and Precautions Section**: Inclusion of information about increase in exposure when co-administered with drugs known to have Torsade de Point. See Section 7.4.4. Electrocardiogram. Inclusion of Depressive Disorders to communicate serious risks such as suicide attempt. See Section 7.3.5 Submission Specific Primary Safety Concerns.

- **Adverse Reactions Section**: Adverse events which were thought to be significant but infrequent were added under '*Less Common Adverse Reactions'.* See Section 7.3.5 Submission Specific Primary Safety Concerns.

- **Clinical Microbiology Section**: Information about resistance and cross-resistance associated with rilpivirine failure were revised to enhance better communication. See Sections 4.2 Clinical Microbiology and 6.1.6 Subpopulations.

- **Clinical Studies Section**: The efficacy table has been revised to include information by baseline HIV-1 RNA strata. In addition, virologic failure rates are also presented for each baseline HIV-1 RNA stratum. See Section 6.1.6 Subpopulations.

9.3 Advisory Committee Meeting

As discussed before, an Advisory Committee meeting was not held, as rilpivirine was not the first agent in the class of NNRTIs. In addition, no unique safety or efficacy issues were identified that were not already encountered in other ARV reviews that would require input from Advisory Committee members.

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/s/

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03/28/2011

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