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*APPLICATION NUMBER:*

**202022Orig1s000**

**OTHER REVIEW(S)**

## Division of Antiviral Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 202022

**Name of Drug:** Edurant (rilpivirine) 25 mg Tablets

**Applicant:** Tibotec, Inc.

### Labeling Reviewed

**Submission and Receipt Date:** May 18, 2011

FDA's current working version of labeling.

### Background and Summary Description

On July 23, 2010, Tibotec, Inc. (Tibotec) submitted a New Drug Application (NDA) for rilpivirine 25 mg tablets under NDA 202022.

Labeling negotiations began January 13, 2011 with the Sponsor.

The Division sent comments to Tibotec on January 13, 2011, February 1, 2011, March 9, 2011, March 31, 2011, April 13, 2011, April 15, 2011, and April 29, 2011.

Additionally, labeling teleconferences were held with Tibotec on March 14, 2011 and April 7, 2011.

The Sponsor submitted amendments to this application containing draft labeling on February 23, 2011, March 25, 2011, April 8, 2011, April 21, 2011, and May 5, 2011, and May 18, 2011.

The user fee goal date for this NDA is May 23, 2011.

### Review

The following label revisions were relayed to the Sponsor via electronic correspondence on May 13, 2011, May 16, 2011, and May 17, 2011 and incorporated into the final labeling:

1. Section 17 of the Package Insert:



(b) (4)

*Change to:*

Patients should be informed that TRADENAME is not a cure for HIV infection. Patients must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Patient Package Insert (PPI) change:

**TRADENAME does not cure HIV infection or AIDS.**

Always practice safer sex.

Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Never re-use or share needles.

Ask your doctor if you have any questions about how to prevent passing HIV to other people.

*Change to:*

**TRADENAME does not cure HIV infection or AIDS.**

Patients must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Always practice safer sex.

Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Never re-use or share needles.

Ask your doctor if you have any questions about how to prevent passing HIV to other people.

2. Under INDICATIONS AND USAGE, please change (b) (4) to agents in the first sentence to be consistent with the indication in the HIGHLIGHTS OF PRESCRIBING INFORMATION.
3. Please remove the following sentence from section 8.5 geriatric use:

4. Please revise the second bullet under **How should I store TRADENAME?** in the PPI:

**How should I store TRADENAME?**

- Store TRADENAME at 59°F to 86°F (15°C to 30°C).
- Keep TRADENAME in the **original** bottle [redacted] (b) (4) to protect from light.

Based on all labeling comments sent to the Sponsor, there were no significant differences between FDA’s current working version of the label and the Sponsor’s labeling submitted May 18, 2011. Effective May 19, 2011, the Sponsor was sent a Proprietary Name Granted letter and TRADENAME will be replaced by EDURANT in all labeling.

**Recommendations**

The submitted labeling is acceptable based on labeling negotiations with the Sponsor and should be included in the action letter as the approved labeling.

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Robert G. Kosko, Jr., Pharm.D., M.P.H.  
Regulatory Project Manager

May 19, 2011  
Date

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Karen Winestock  
Chief, Project Management Staff

May 19, 2011  
Date

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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Robert G Kosko  
05/19/2011

KAREN D WINESTOCK  
05/20/2011

**ONDQA Pre-Marketing Assessment Division II  
Branch V  
Quality/Chemist Review**

**1. NDA 202022 Review # 2**

Goal Initial Date: July 23, 2010  
Review # 1 GRMP Date: March 28, 2011  
Review # 2 Date: May 19, 2011  
PDUFA Goal Date: May 23, 2011

**2. OND Division:**

Division of Anti-Viral Products

**3. Sponsor and Address:**

TIBOTEC INC  
1125 Trenton-Harbourton Rd  
Titusville, NJ 08580

**4. NDA Reference Documents Covered in this Review**

Type	Supporting Document Number	Date
Labeling/Package Insert Draft	31	08-April-2011
Labeling/Package Insert Draft	32	21-April-2011
Labeling/Package Insert Draft/Container-Carton Draft/Patient Package Insert/Draft	33	05-May-2011
Labeling/Package Insert Draft	37	18-May-2011

**5. ONDQA Review Update**

The NDA 202022 Review # 1 completed on March 28, 2011 recommended and concluded that:

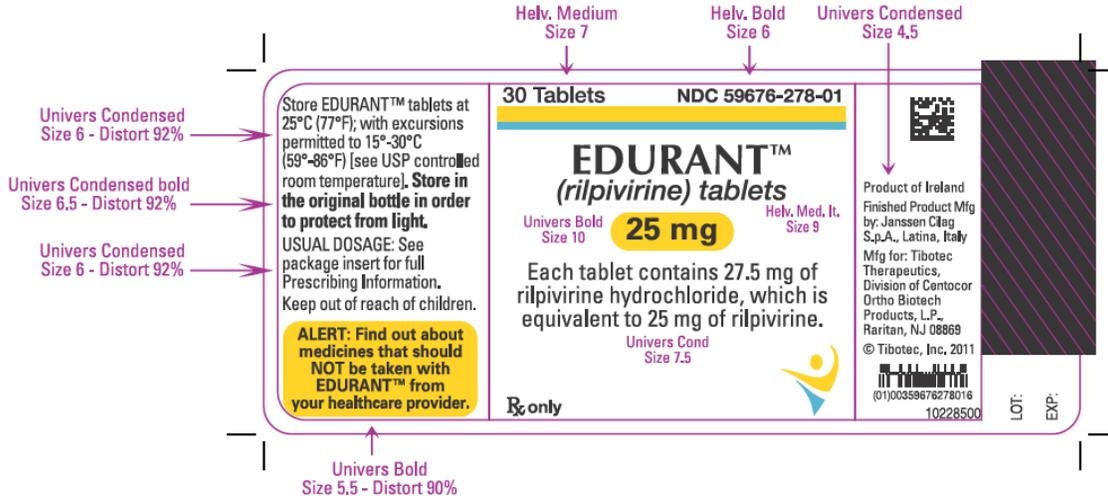
“This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The Sponsor has agreed to all CMC labeling changes proposed. Therefore, from the CMC perspective, this NDA is recommended for approval, pending submission of final labeling documenting agreed-upon revisions to the bottle label and package insert.”

The Sponsor has submitted all changes proposed by ONDQA regarding labeling, therefore no outstanding CMC labeling issues are open for this submission. The conclusion from the CMC perspective continues to recommend approval for this NDA.

Bottle Label

The mock bottle label, as submitted to the NDA, is shown below. The label reflects all changes recommended by ONDQA regarding storage conditions, established name, equivalence statement, and manufacturer information. The Sponsor has also updated country of origin based on external requirements by US Customs.

The proprietary name EDURANT has been found acceptable by DMEPA, as of 19-May 2011. The proposed bottle label is acceptable.



USPI:

The labeling text has been updated to reflect all changes recommended by ONDQA. Below are the relevant sections containing CMC information. The label is acceptable as updated.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use EDURANT safely and effectively. See full prescribing information for EDURANT.**

**EDURANT (rilpivirine) [Tablets]**

**Initial U.S. Approval: 2011**

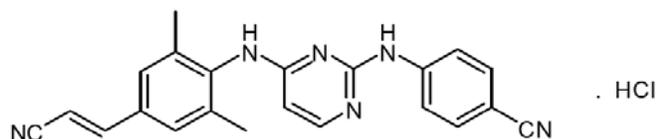
**3 DOSAGE FORMS AND STRENGTHS**

25 mg white to off-white, film-coated, round, biconvex, tablet of 6.4 mm, debossed with “TMC” on one side and “25” on the other side. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine.

**11 DESCRIPTION**

EDURANT (rilpivirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). EDURANT is available as a white to off-white, film-coated, round, biconvex, 6.4 mm tablet for oral administration. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine.

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile monohydrochloride. Its molecular formula is  $C_{22}H_{18}N_6 \cdot HCl$  and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

Each EDURANT tablet also contains the inactive ingredients croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide and triacetin.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

EDURANT (rilpivirine) tablets are supplied as white to off-white, film-coated, round, biconvex, 6.4 mm tablets. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine. Each tablet is debossed with "TMC" on one side and "25" on the other side.

EDURANT tablets are packaged in bottles in the following configuration: 25 mg tablets-bottles of 30 (NDC 59676-278-01).

Store EDURANT tablets in the original bottle in order to protect from light. Store EDURANT tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

**USPPI:**

The labeling text regarding patient information has been updated to reflect all changes recommended by ONDQA, in collaboration with DMEPA. Below are the relevant sections containing CMC information. The label is acceptable as updated.

**How should I store EDURANT?**

- Store EDURANT at 59°F to 86°F (15°C to 30°C).
- Keep EDURANT in the original bottle to protect from light.

**What are the ingredients in EDURANT?**

Active ingredient: rilpivirine.

Inactive ingredients: croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide, and triacetin.

OC Recommendation: The OC recommendation remains “Acceptable” in EES, since January 25, 2011. EES was confirmed as of the date of this review.

## **6. Recommendation and Conclusion on Approvability**

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The Sponsor has agreed to all CMC labeling changes proposed. Therefore, from the CMC perspective, this NDA is recommended for approval

Celia N. Cruz, Ph.D.  
Review Chemist

Maotang Zhou, Ph.D.  
Review Chemist

Stephen P. Miller, Ph.D.  
CMC Lead

Cc:

Reviewer: Celia N. Cruz

Reviewer: Maotang Zhou

CMC Lead: Stephen P. Miller

Branch V Chief: Rapti Madurawe

OND Project Manager: Robert Kosko, Jr.

ONDQA Project Manager: Jeannie David

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/s/  
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CELIA CRUZ  
05/19/2011

MAOTANG ZHOU  
05/19/2011

STEPHEN P MILLER  
05/19/2011

I concur, this NDA continues to be recommended for approval from the CMC perspective; all relevant labeling is now finalized.

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Pediatric study in pediatric subjects from 12 to <18 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission: already submitted	<u>N/A</u>
	Study/Trial Completion:	<u>August 2014</u>
	Final Report Submission:	<u>February 2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies are ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study is a 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 study to evaluate the safety and antiviral activity of rilpivirine in combination with other HIV drugs in pediatric HIV infected subjects age 12 to <18 year old. Safety of rilpivirine in pediatric subjects should be evaluated for a minimum of 48 weeks.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Treatment naïve, HIV-1 infected pediatric subjects 12 to <18 years of age
---

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
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/s/  
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YODIT BELEW  
05/16/2011

KENDALL A MARCUS  
05/16/2011

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Submit the 96 Week safety, efficacy and resistance data from the two ongoing Phase 3 trials (TMC278-C209, TMC278-C215)

---

PMR/PMC Schedule Milestones:	Final Protocol Submission: Protocol already submitted	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	October 2011
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Rilpivirine, a new molecular entity, is an NNRTI for treatment of HIV-1 infection in combination with other antiretroviral drugs in treatment-naïve adult patients. Approval of NDA 202-020 is based on a 48 Week data from two Phase 3 trials. The trials are randomized, double-blinded, designed to continue beyond 48 weeks, for a minimum of Week 96. A PMR is required to assess the safety, efficacy and development of resistance after long-term (e.g. 96 Weeks) treatment with rilpivirine.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Rilpivirine has been shown to be effective treatment for HIV-1 infection in treatment naïve adults. The efficacy was influenced by baseline HIV-1 RNA. At the Week 48 efficacy analysis, more subjects with baseline HIV-1 RNA  $\geq 100,000$  copies/mL had virologic failure compared to subjects with baseline HIV-1 RNA  $< 100,000$  copies/mL. Of those who were virologic failures, 41% (38/92) had evidence of rilpivirine resistance. Importantly, among the subjects who failed treatment with rilpivirine due to development of rilpivirine resistance, most also developed cross-resistance to other NNRTIs: 89% (34/38) were resistant to etravirine and efavirenz, and 63% (24/38) were resistant to nevirapine. The Division considers the development of resistance and cross-resistance a significant safety issue.

The 96 weeks data will further characterize the durability of rilpivirine.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The NDA approval for rilpivirine is based on 48 Week data from two ongoing randomized, blinded, Phase 3 clinical trials. The trials are designed as a 96-weeks safety and efficacy assessment trials. The Division requests the 96 week data be submitted for safety and efficacy evaluation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
The data submitted at the time of approval is a 48 Week data; additional safety and efficacy data are being requested as the trials are ongoing for a minimum of 96 Weeks. The 96 Week data is required for further assessment of safety, efficacy and resistance development.
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other  
Additional data or analysis is required for a previously submitted but ongoing clinical trial. The data submitted at the time of approval is a 48 Week data; additional safety and efficacy data are being requested as the trials are ongoing for a minimum of 96 Weeks. The 96 Week data is required for further assessment of safety, efficacy and resistance development

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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YODIT BELEW  
05/16/2011

KENDALL A MARCUS  
05/16/2011

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Pediatric study in pediatric subjects from **birth to <12 years of age**.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>November 2012</u>
	Study/Trial Completion:	<u>September 2018</u>
	Final Report Submission:	<u>March 2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies are ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study is a deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects birth to <12 years of age. Conduct a pediatric study to evaluate the safety and antiviral activity of rilpivirine in combination with other HIV drugs in pediatric HIV infected subjects age birth to less than 12 year old. Safety of rilpivirine in pediatric subjects should be evaluated for a minimum of 48 weeks.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Treatment naïve, HIV-1 infected pediatric subjects birth to <12 years of age
--

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
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/s/  
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YODIT BELEW  
05/16/2011

KENDALL A MARCUS  
05/16/2011

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: A clinical trial evaluating the P-gp inhibitory effects of rilpivirine on digoxin, a P-gp substrate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2011</u>
	Study/Trial Completion:	<u>05/2012</u>
	Final Report Submission:	<u>10/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The theoretical concern for requesting a trial as a postmarketing requirement to evaluate the P-gp inhibitory effects of rilpivirine on P-gp substrates is the potential for increased P-gp substrate exposures beyond the established safety profile.

The basis for the theoretical concern is information from the in vitro P-gp study. The information from the in vitro study indicates that based on the potential P-gp inhibitory effects of rilpivirine in the GI tract, a human drug-drug interaction trial is recommended.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue is to determine whether the potential P-gp inhibitory effects of rilpivirine 25 mg once daily are clinically relevant. The currently available pharmacokinetic data does not provide an answer to this issue.

The goal of the trial is to determine the magnitude of change in the exposure of a P-gp substrate, digoxin, when coadministered with rilpivirine.

The risk associated with potential rilpivirine inhibition of P-gp is the possibility that the exposure of P-gp substrates when coadministered with rilpivirine will be increased beyond the exposure associated with an established safety profile.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The clinical trial in healthy subjects will 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  $C_{max}$ .

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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STANLEY AU  
05/13/2011  
DCP4 division director (J.Lazor) concurs with PMR.

KENDALL A MARCUS  
05/13/2011

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**Application:** NDA 202022

**Name of Drug:** PROPRIETARY NAME (rilpivirine) Tablets

**Applicant:** Tibotec, Inc.

## Labeling Reviewed

**Submission Date:** April 8, 2011

**Receipt Date:** April 8, 2011

## Background and Summary Description

NDA 202022 was submitted July 23, 2010 as a New Molecular Entity. Initial labeling negotiations began January 13, 2011. Subsequent labeling comments were sent to the Sponsor on February 1, 2011, March 9, 2011, March 31, 2011, and April 13, 2011. The PDUFA goal date for an action on this NDA is May 23, 2011.

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an “X.”

In addition, the following labeling issues were identified:

1. As a suggestion, bullet points were inserted where multiple subheadings were present in the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS subsections of the HIGHLIGHTS OF PRESCRIBING INFORMATION.
2. In the USE IN SPECIFIC POPULATIONS subsection of the HIGHLIGHTS OF PRESCRIBING INFORMATION, [REDACTED] <sup>(b) (4)</sup> was changed to “Pregnancy registry available”.
3. Subsection 13.2 Animal Toxicity and/or Pharmacology was removed from the Table of Contents as there was no corresponding subsection in the Full Prescribing Information.

## Recommendations

All labeling issues identified on the following pages with an “X” will be conveyed to the applicant in an advice letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by April 20, 2011. The resubmitted labeling will be used for further labeling discussions.

Robert G. Kosko, Jr.	4/15/11
Regulatory Project Manager	Date
Karen Winestock	4/15/11
Chief, Project Management Staff	Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## **Contents: Table of Contents (TOC)**

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at

- the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
  - All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
  - When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
    - 8.1 Pregnancy
    - 8.3 Nursing Mothers (not 8.2)
    - 8.4 Pediatric Use (not 8.3)
    - 8.5 Geriatric Use (not 8.4)
  - If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,”

should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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Robert G Kosko  
05/04/2011

KAREN D WINESTOCK  
05/05/2011

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

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**Date:** April 11, 2011

**To:** Robert Kosko, Jr., Pharm.D., DAVP

**From:** Lynn Panholzer, PharmD, DDMAC  
Michelle Safarik, PA-C, DDMAC

**Re:** NDA# 202022  
Rilpivirine hydrochloride Tablets

As requested in your consult dated March 28, 2011, DDMAC has reviewed the draft labeling (package insert [PI], patient package insert [PPI], container label) for rilpivirine hydrochloride Tablets. DDMAC's comments are based on the proposed substantially complete version of the PI and PPI sent to DDMAC via e-mail by DAVP on March 28, 2011, and on the container label submitted by the applicant on March 24, 2011, available in the EDR at <\\CDSESUB1\EVSPROD\NDA202022\0028>.

DDMAC's comments on the PI and PPI are provided directly in the attached copy of the labeling. DDMAC has no comments on the container label.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov). If you have any questions about our comments on the PPI please contact Michelle Safarik at 6-0620 or at [Michelle.Safarik@fda.hhs.gov](mailto:Michelle.Safarik@fda.hhs.gov).

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/s/  
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LYNN M PANHOLZER  
04/14/2011

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: April 11, 2011

TO: Robert Kosko Jr. PharmD., MPH, Regulatory Health Project Manager  
Yodit Belew, M.D., Medical Officer  
Division of Antiviral Products

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-022

APPLICANT: Tibotec, Inc.

DRUG: Oral TMC 278 (rilpivirine)

NME: Yes.

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of HIV-1 adult patients

CONSULTATION REQUEST DATE: September 21, 2010

DIVISION ACTION GOAL DATE: May 23, 2011

PDUFA DATE: May 23, 2011

## I. BACKGROUND:

The sponsor, Tibotec Pharmaceuticals Ltd, submitted a New Drug Application for the use of oral TMC278 (rilpivirine) in HIV-1 infected naive subjects. Human immunodeficiency virus type1 (HIV-1)-infected patients are routinely being treated with combinations of 3 or 4 drugs, including nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) in order to reduce the risk of viral resistance development. Development of new potent antiretroviral (ARV) compounds with increased genetic barriers to development of viral resistance are needed to prolong suppression of viral replication in subjects infected with HIV-1. Currently, etravirine is the only approved NNRTI drug for the use in the treatment-experienced subjects.

According to the applicant, TMC278, is a NNRTI with in vitro activity against both wild-type HIV-1 and NNRTI-resistant mutants. The applicant proposes that TMC278 will combine the convenience of ONCE daily (q.d.) dosing with acceptable antiviral effects and a higher barrier to resistance as compared to currently approved NNRTIs with the exception of etravirine, and that the once daily oral formulation fulfills, a currently unmet medical need.

The sponsor has submitted data for the use of the oral TMC278 formulation from Study TMC278-TiDP6-C215 (C215) to support approval of TMC278 for the following indication:

“TMC278, in combination with other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients.”

### **Study TMC278-TiDP6-C215: “A Phase III, Randomized, Double-Blind Trial of TMC278 75 mg q.d. Versus Efavirenz 600 mg q.d. in Combination with a Background Regimen Consisting of Abacavir and Lamivudine in Antiretroviral-Naïve HIV-1 Infected Subjects”.**

The primary objective of Study TiDP6-C215 was to demonstrate non-inferiority of treatment with TMC278 when administered as 75 mg q.d. compared to the control group (EFV) in regard to the proportion of virologic responders (plasma viral load < 50 HIV-1 RNA copies/ml, according to time to loss of virologic response algorithm) at 48 weeks in ARV-naïve HIV-infected subjects, with a maximum allowable difference of 12%.

The secondary objectives were: 1) to evaluate superiority in efficacy of TMC278 compared to control, efavirenz (EFV), in case non-inferiority is established, 2) to evaluate and compare the safety and tolerability of TMC 278 when administered as 75 mg q.d. versus control (EFV) over 48 weeks and 96 weeks, and 3) to evaluate and compare immunologic changes (as measured) by CD4+ cell count) in the TMC 278 group versus those in the control group (EFV) over 48 and 96 weeks.

The review division requested inspection of four clinical investigators for the pivotal study protocol (4 sites; 3 foreign sites and 1 domestic site to cover Study TMC278-TiDP6-C215) as data from the pivotal protocol are considered essential to the approval process. Three clinical investigators and one domestic investigator were chosen for inspection of the pivotal protocol.

These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, 2) site specific protocol violations, and 3) high virologic success rates. Further, the limited experience with this drug has been from data collected at foreign sites. Since the investigational product is a new molecular entity the sponsor Tibotec Inc. was also targeted for an inspection.

## II. RESULTS (by protocol/site):

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Fredrico Rangel, M.D. Rangel e Gumaraes Assessoria EM pequisa Clinic LTDA R Da hora 559 Recife PE 52020-010 Brazil Site# BR00014	Protocol C215 Number of subjects listed 33	11/ 11 and 12/3/10	NAI
Gisela Herrera-Martinez, M.D. Corporation Ghema S.A. Santa Teresita 200 Metro Al Notre Y 25 Metros Osete Barrio Aranjuez, San Jose Costa Rica Site# CR00004	Protocol C215 Number of subjects listed 27	12/9-15/10	Pending  Preliminary: NAI
Jan Fourie, M.D. Jan Fourie Medical Practice Dundee 3000 South Africa Site#ZA 00028	Protocol C215 Number of subjects listed 35	11/22-24/2010	NAI
Jacob Lalezari, M.D. Quest Clinical Research 2300 Sutter Street Suite 202 San Francisco, CA 94115 Site# 00258	Protocol C215 Number of subjects listed 35	1/18-21/2011	Pending  Preliminary: NAI
Tibotec Pharmaceuticals Ltd. 1125 trenton-harbourton rd,rm K2140 Titusville, NJ 08560	Protocol C215 Number of subjects listed Herrera 27 and Fourie 35	10/14-21/10	NAI

### Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

**Note: Observations noted below for 2 sites are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

Protocol Study C215

**1. Fredrico Rangel, M.D.**

**Brazil**

**a. What Was Inspected:** At this site, a total of 33 subjects were screened, four subjects were reported as screen failures. Twenty nine (29) subjects were randomized into the study, and 3 subjects terminated due to virological failures/endpoint (Subject#215-0134, 215-0134, 215-0773) one subject withdrew consent (Subject#215-0490) and one subject withdrew due to lost-to-follow-up (Subject #215-0439). Currently, the site has 24 subjects remaining in the study and/or extension phase of the study. There were no deaths and one serious adverse event reported. Subject #215-0411 was hospitalized due to severe bronchial spasm. Review of Informed Consent Documents for all subjects records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 4 enrolled subjects were reviewed, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Rangel. The medical records reviewed were found to be in order and the data verifiable. There were no known limitations to the inspection.

**c. Assessment of Data Integrity:** The data, in support of clinical efficacy and safety at Dr. Rangel's site are considered reliable and appear acceptable in support of the pending application.

**2. Gisela Herrera-Martinez, M.D.**

**Costa Rica**

**a. What Was Inspected:** At this site, a total of 27 subjects were screened and seven (7) subjects were reported as screen failures. Twenty (20) subjects were enrolled and currently 16 subjects remaining on the study and/or extension phase of the study. Two subjects were discontinued and one subject was relocated. The reasons were documented. There was one subject who died from AIDS/pulmonary problems. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment. The subjects who continued on the long term treatment were all re-consented.

The medical records/source data for 4 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to e-CRFs and data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Herrera. The medical records reviewed were found to be in order and the data verifiable. One subject developed increased bilirubin levels associated with Gilberts Syndrome. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application

**Assessment of Data Integrity**

The data, in support of clinical efficacy and safety at Dr. Herrera’s site are considered reliable and appear acceptable in support of the pending application.

**3. Jan Fourie, M.D.  
Dundee, South Africa**

**a. What Was Inspected:** At this site, a total of 35 subjects were screened, 12 subjects were reported as screen failures (for not meeting inclusion criteria), 8 subjects were randomized into the study, 3 subjects were discontinued and the reasons were documented and (2 subjects were relocated). Three (3) subjects completed the study and re-consented to enroll in the long term phase of the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria use of concomitant medications; source documents for subjects were compared to case report forms (e-CRFs) and data listings, to include primary efficacy endpoints and adverse events and no discrepancies were noted.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Fourie. The medical records reviewed were found to be in order, verifiable and revealed no violations of the federal regulations. There were no known limitations to the inspection.

**c. Assessment of Data Integrity:** The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. The data generated from Dr. Fourie’s site are considered reliable and appear acceptable in support of the application.

**4. Jacob Lalezari, M.D.  
San Francisco, CA 94115**

**a. What was Inspected:** At this site, a total of 18 subjects were screened, 13 subjects were reported as screen failures, 5 subjects were randomized and 4 subjects completed the study. One subject was relocated to another state before completing the study. Review of Informed Consent Documents, for 18 subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 18 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and current medications, inclusion/exclusion criteria, the use of concomitant medications; source documents for all subjects were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, a 1 item Form FDA 483 was issued to Dr. Lalezari. Our investigation found minor error in drug dispensation date for placebo Subject 215-0071. The drug accountability form identifies that the subject was dispensed medications on 7/12/2008 while the computer printout state the date of dispensation as 8/12/2008. This is an insignificant error and has no likely impact on data validity.

The medical records reviewed disclosed no other adverse findings that would negatively on the reliability of the data. With the exception of the item/error noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity:** Although a minor regulatory violation was noted, the finding is considered isolated in nature and unlikely to significantly impact data reliability. The data from Dr. Lalezari's site are considered reliable and appear acceptable in support of the pending application.

**5. Sponsor Tibotec Inc.  
Titusville, NJ 08560**

**a. What was Inspected:** The inspection audited ProtocolTMC278-TiDP6-C215 and focused on the following clinical investigators: Drs Herrera and Fourie during the course of this sponsor/monitor inspection. Tibotec Pharmaceutical was established in 1996. Tibotec was then acquired by Johnson & Johnson Pharmaceutical Research & development LLC in 2003. As part of J&J's inspection plan Tibotec was fully integrated with J&J companies in 2007. Currently, Tibotec now falls under J&J PRD's therapeutic Virology.

During the inspection the following areas were reviewed: Sponsor's obligation, monitoring plans, monitoring reports, qualifications of clinical investigators, site monitors, adverse event reporting, drug accountability records, and site specific

documents associated with the two clinical investigators noted above. The inspection also focused on other select clinical trials activities to determine whether adequate controls (such as written policies and procedures, training, monitoring, auditing and governance) were in place. The clinical trial activities reviewed included: Clinical protocol development and amendment, development and implementation of study-specific independent review charters, selection, evaluation, and initiation of clinical investigators, clinical monitoring, data quality control and assurance practices, study and program-level quality management, including identification of systemic errors and issue escalation, investigation and management of significant and /or persistent noncompliance, and evaluation of suspected scientific misconduct of the part of CIs.

- b. **General Observations/Commentary:** The inspection found the sponsor in compliance with their SOP's regarding proper monitoring of their clinical investigators. The activities included, but not limited to, trial drug records, subject records, electronic database for entry of study data, protocol adherence, case report forms/source documents and adverse events reporting.
- c. **Assessment of Data Integrity:** The sponsor monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication. In general, the sponsor appears to have fulfilled their regulatory obligations for the study identified above. Therefore, the data generated from the study sites are reliable and can be used in support of the pending application/indication.

### **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four clinical investigator sites, one domestic and three foreign sites were inspected in support of this application. The inspections of Drs. Lalezari, Rangel, Herrera, Fourie and the sponsor revealed no significant problems that would adversely impact data acceptability. Overall the data submitted from these sites are acceptable in support of the pending application.

**Note: Observations noted above for at least 2 inspections are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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ANTOINE N EL HAGE  
04/13/2011

TEJASHRI S PUROHIT-SHETH  
04/13/2011

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

**PATIENT LABELING REVIEW**

Date: April 8, 2011

To: Debra Birnkrant, MD, Director  
**Division of Antiviral Products (DAVP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**  
Barbara Fuller, RN, MSN, CWOCN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Risk Management**

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

Drug Name (established name): TRADENAME (rilpivirine hydrochloride)

Dosage Form and Route: Tablets

Application Type/Number: NDA 202-022

Applicant: Tibotec, Inc.

OSE RCM #: 2010-2395

## 1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (rilpivirine hydrochloride) Tablets. The purpose of the Applicant's submission is to seek approval of their original New Drug Application ( NDA 202-022), for TRADENAME (rilpivirine hydrochloride) Tablets, in combination with other antiretroviral medicinal products for the proposed indication of the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients.

DAVP advised DRISK to use the PPI for Sustiva (efavirenz) capsules (NDA 20-972) and tablets (NDA 21-360) as a comparator. However, the PPI for this product does not meet current patient labeling standards for content and format. Since we were not able to find a previous review indicating that DRISK has reviewed this PPI, we referenced the Sustiva (efavirenz) PPI and several other currently approved HIV product PPIs for this review.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (rilpivirine hydrochloride) Tablets PPI received on July 23, 2010, revised by the Review Division throughout the review cycle, and received by DRISK on March 31, 2011.
- Draft TRADENAME (rilpivirine hydrochloride) Tablets prescribing information (PI) received on July 23, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on March 31, 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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SHARON R MILLS  
04/08/2011

LASHAWN M GRIFFITHS  
04/08/2011

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

Date: March 15, 2011  
Application Type/Number: NDA 202022  
To: Debra B. Birnkrant, MD, Director  
Division of Antiviral Products  
Through: Zachary Oleszczuk, Pharm.D., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis  
From: Yelena Maslov, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis  
Subject: Label and Labeling Review  
Drug Name(s): Rilpivirine Tablets, 25 mg  
Applicant/sponsor: Tibotec, Inc.  
OSE RCM #: 2010-1874

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3	CONCLUSIONS AND RECOMMENDATIONS.....	3
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## 1 INTRODUCTION

This review evaluates the container label, package insert labeling, and container closure system for Tibotec's Rilpivirine Tablets for their potential to contribute to medication errors.

### 1.1 REGULATORY HISTORY

Rilpivirine Tablets, 25 mg is a subject to a 505 (b)(1) application, NDA 202022, submitted to the FDA on July 23, 2010. DMEPA found the two previous proprietary names, (b) (4) unacceptable in OSE-RCM review #2010-1852 and 2010-1852-1 respectively on November 19, 2010. The Applicant submitted the request for proprietary name review for the proposed name (b) (4) to the FDA on December 27, 2010 (See Appendix C for the container label).

DMEPA evaluated Rilpivirine's container label, package insert, and patient information labeling and provided recommendations to the Applicant via email on February 1, 2011 (See Appendix B). The Applicant submitted the revised labels and labeling to the FDA on February 23, 2011.

## 2 METHODS AND MATERIALS

We use Failure Mode and Effects Analysis<sup>1</sup> (FMEA), the principles of human factors, and lessons learned from post-marketing experience to identify potential sources of error with the proposed product labels, insert labeling, and container closure system. We provide recommendations that aim at reducing the risk of medication errors.

This review focused on the Rilpivirine's package insert and patient information labeling submitted by the Applicant on December 27, 2010 and the container label submitted on February 23, 2011 (See Appendices A for the container label image):

- Container Label: 30 Tablets

Additionally, DMEPA reviewed the CMC Section of the NDA to ensure the container closure system is appropriate for this product.

## 3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container closure system found that the unit of use bottle with child resistant cap is appropriate for this product, since the entire manufacturer bottle is intended to be dispensed to the patient.

Additionally, our evaluation of the package insert labeling and patient information did not note any additional areas of needed improvement for minimization the potential for medication errors at this time. However, our evaluation of the container label identified that the expression of the established name should be revised to be consistent with USP recommendations regarding the expression of the established name in terms of the active moiety rather than a salt.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Brantley Dorch at 301-796-0150.

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<sup>1</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

\*\*\* This document contains proprietary and confidential information that should not be released to public

A. Comments to the Applicant

Delete the salt 'Hydrochloride' from the established name. As currently presented, the established name is inconsistent with USP recommendations regarding the expression of the established name in terms of the active moiety rather than a salt. However, DMEPA defers to Labeling and Nomenclature Committee and Richard Lostritto for the final determination of the established name presentation.

**4 REFERENCES**

*Previous OSE Review*

1. Turner, Tara. OSE Review #2010-1852, (b) (4) Proprietary Name Review
2. Turner, Tara. OSE Review #2010-1852-1, (b) (4) Proprietary Name Review

**Appendix A: Container Label submitted to the FDA on 02/23/2011**



**Appendix B: DMEPA's recommendations to the Applicant from February 1, 2011.**

**3.1 COMMENTS TO THE APPLICANT**

**A. Container Label**

1. Unbold the net quantity of the container '30 tablets'. As currently presented, the net quantity competes with the strength of the product for prominence.
2. Revise the statement (b) (4) to read "Store in original bottle" to emphasize the importance of the keeping the medication in the original manufacture's bottle in order to protect from the light. Additionally, this statement is not prominent as it currently appears near the bottom of the side panel. Increase the prominence of this statement by relocating the statement further up on the side panel, bolding the statement or using a different color font for this statement.

**Appendix C: Container Label submitted to the FDA on 12/27/2010**



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/s/  
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YELENA L MASLOV  
03/15/2011

ZACHARY A OLESZCZUK  
03/16/2011

CAROL A HOLQUIST  
03/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**DATE:** March 15, 2011

**FROM:** Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products (DMEP)

**THROUGH:** Dragos Roman, MD, Team Leader, DMEP  
Mary Parks, MD, Division Director, DMEP

**TO:** Yodit Belew, MD, Division of Antiviral Products  
Robert G. Kosko, Jr., Pharm.D., M.P.H, Division of Antiviral Products

**SUBJECT:** Effect of Rilpivirine (TMC278) on adrenal function

**I. Background and basis for consult**

On October 4, 2010, the Division of Metabolism and Endocrinology Products (DMEP) received a consultation request from the Division of Antiviral Products (DAVP) regarding Rilpivirine (TMC278), an anti-retroviral drug being developed by Tibotec for the treatment of HIV-1 infection in combination with other anti-retroviral drugs. Pre-clinical, phase 1 and 2 trials of TMC278, a non-nucleoside reverse transcriptase inhibitor (NNRTI), indicated a drug effect on the adrenal glands. *In vitro* studies suggest that TMC278 may inhibit 21-hydroxylase. A one-month *in vivo* canine study showed dose-related and reversible histopathological changes seen in adrenals exposed to drug.

DMEP was consulted during the TMC278 IND stage to make recommendations on how to assess adrenal function in the Phase 3 trials. These recommendations were incorporated into the protocols for the two pivotal Phase 3 trials (Studies 209 and 215), and based on the clinical data, the sponsor has not included any information on adrenal function in its draft label.

In its consultation request, DAVP has requested that DMEP independently evaluate the safety results of TMC278 in NDA 202022 as they relate to adrenal function. DAVP has submitted the following questions for consideration:

- 1. Please comment on the totality of the adrenal related safety data.*
- 2. Should the drug be approved for marketing, do you recommend routine adrenal function monitoring, such as periodic collection of basal cortisol level? Do you recommend any further evaluation post approval?*
- 3. Currently, Tibotec does not propose any labeling with regard to adrenal function. Should the mean change from baseline for cortisol, 17-OH-progesterone, aldosterone or mean change from baseline in maximum change in cortisol after ACTH stimulation be presented in labeling? What additional labeling, if any, do you propose relating to adrenal function?*

## II. Materials reviewed for consult

1. Clinical trial protocols and clinical study reports for both Phase 3 studies (209 and 215).
2. Previous DMEP consultation reports for IND 67,699
3. Correspondence from sponsor dated 1/13/2011 (response to FDA request for information: Endocrine questions including information on adrenal function in select patients).

## III. DMEP Comments

In its two pivotal phase 3 studies (209 and 215), patients were randomized to receive Rilpivirine (25 mg qd) or an active control, efavirenz (600 mg qd) for 48 weeks. After the initial 48-week study period, patients could enter an additional 48-week extension phase. Based on the assessment of the available data from pre-clinical and clinical data, and through previous consultations with DMEP, the sponsor implemented a pathway for monitoring adrenal function in its phase 3 trials as follows:

- **ACTH Stimulation tests** were performed routinely at Weeks 0 and 48 (and week 96, if patients continued into the extension phase). Cortisol, 17-hydroxyprogesterone (17-OHP), and aldosterone were measured before, 30 and 60 minutes after ACTH stimulation. If the ACTH stimulation test was abnormal (i.e., all stimulated cortisol values < 500 nmol/L), a retest was performed at the next scheduled visit.
- **Basal cortisol levels** were drawn routinely at Weeks 0, 4, 12, 24, 48, and 96. If at any of these time points the value was < 248 nmol/L, a retest was done at the subsequent visit or at least within the next 8 weeks. If the basal cortisol was < 248 nmol/L at two consecutive visits, an ACTH stimulation test was done at the next scheduled visit, as described above.
- **Subject withdrawal** was to be considered in patients who failed a repeat ACTH stimulation test **and** had clinical signs/symptoms of adrenal insufficiency (i.e., tiredness, weakness, mental depression, headache, anorexia, weight loss, dizziness, orthostatic hypotension, abdominal cramps, diarrhea, electrolyte disturbances, hypoglycemia, mild normocytic anemia, lymphocytosis, eosinophilia, loss of body hair in women, hyperpigmentation, and/or hirsutism).

### 1. Adrenal function-related adverse events

Overall, there were no adrenal function-related serious adverse events, deaths, or treatment discontinuations. Fifteen (2.2%) subjects in the TMC278 arm had adverse events described as “blood cortisol decreased,” compared with 7 (1%) subjects in the control arm.

### 2. Biochemical evaluation of adrenal function

The timeline for biochemical evaluation of adrenal function for both pivotal studies is below:

Type of visit	Screening <sup>*</sup>	Randomization & Baseline	Treatment period <sup>**</sup>													Week 96/ withdrawal visit	Post-treatment follow-up period <sup>***</sup>		
	Week -6 to -4		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32 & 40	Week 48	Week 60	Week 72	Week 84	Week 96 <sup>***</sup>			Week 100	
Visit	1	2	3	4	5	6	7	8	9-10	11	12	13	14	15	16				
Basal cortisol (and ACTH stimulation testing if applicable) <sup>†</sup>		X		X			X			X				X			X		X
ACTH stimulation testing and endocrine assessments <sup>‡</sup>		X												X					X

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***Basal cortisol, 17-OHP, and aldosterone: Phase 3 studies***

Sponsor’s Table 53 (below) shows the mean change from baseline to Week 48 in basal cortisol, 17-OHP, and aldosterone. When the results from both trials are pooled, at Week 48 the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the TMC278 group, and an increase of +9.0 nmol/L in the control group.

**Table 53: Descriptive Statistics of Baseline Cortisol, 17-OH-Progesterone and Aldosterone and Change from Baseline at Week 48, Basal Values (T0) (Phase III Week 48 Pooled Analysis)**

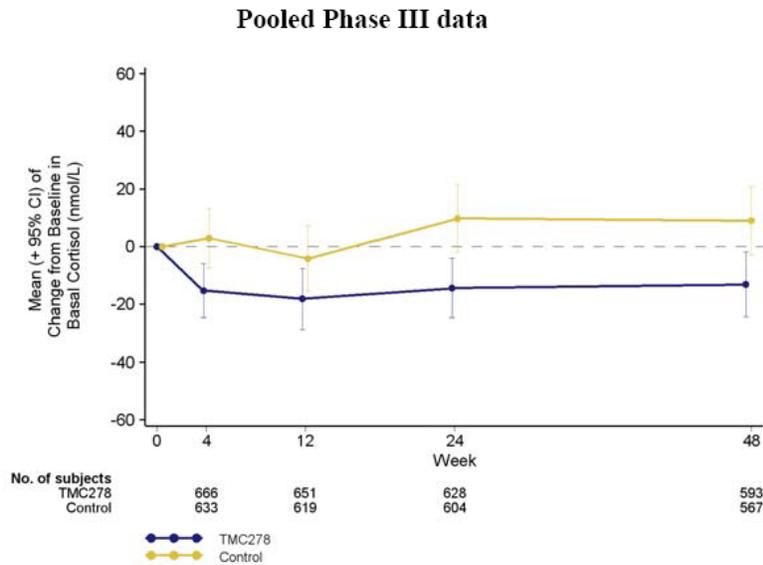
Parameter Time point	C209				C215				Pooled			
	TMC278 N = 346		Control N = 344		TMC278 N = 340		Control N = 338		TMC278 N = 686		Control N = 682	
	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)
<b>Cortisol (nmol/L)</b>												
At baseline	339	340.6 (328.39; 352.71)	338	348.6 (335.23; 361.91)	336	362.3 (348.88; 375.66)	330	381.8 (367.39; 395.95)	675	351.4 (342.31; 360.41)	668	365.0 (355.23; 374.767)
Change from baseline	292	-0.1 (-16.68; 16.57)	287	+22.8 (5.98; 39.66)	301	-25.7 (-40.92; -10.57)	280	-5.3 (-21.81; 11.31)	593	-13.1 (-24.35; -1.84)	567	+9.0 (-2.88; 20.79)
<b>17-OH-progesterone (nmol/L)</b>												
At baseline	341	6.2 (5.82; 6.66)	336	6.3 (5.84; 6.68)	332	6.2 (5.79; 6.58)	327	6.1 (5.75; 6.50)	673	6.2 (5.92; 6.50)	663	6.2 (5.91; 6.47)
Change from baseline	289	+0.4 (-0.14; 0.86)	282	+0.4 (-0.04; 0.76)	292	+0.0 (-0.42; 0.51)	277	+0.4 (-0.12; 0.84)	581	+0.2 (-0.14; 0.54)	559	+0.4 (0.05; 0.67)
<b>Aldosterone (pmol/L)</b>												
At baseline	335	212.7 (195.92; 229.50)	324	216.3 (198.04; 234.49)	330	226.0 (207.90; 244.01)	321	226.6 (208.15; 245.07)	665	219.3 (206.98; 231.58)	645	221.4 (208.47; 234.36)
Change from baseline	278	+22.8 (1.49; 44.06)	267	+9.8 (-16.23; 35.74)	288	+14.8 (-6.12; 35.76)	264	+4.1 (-18.77; 26.97)	566	+18.7 (3.84; 33.61)	531	+6.9 (-10.32; 24.21)

N = number of subjects per treatment group; N' = number of subjects with data.  
 Source: [Module 5.3.5.1/TMC278-C209-W48-Anal-Saf-Endo/Display SAF.22 and Display SAF.23](#); [Module 5.3.5.1/TMC278-C215-W48-Anal-Saf-Endo/Display SAF.23 and Display SAF.24](#); [Module 5.3.5.3/TMC278-C904-Anal-Saf-Endo/Display SAF.37 and Display SAF.38](#).

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The trend in cortisol levels over time is depicted graphically in Sponsor’s Figure 30, below. The figure indicates that there was a small decrease from baseline in mean basal cortisol levels in the first 12 weeks of TMC278 treatment, after which the values remained stable and in the normal range. There was no notable change from baseline in the control group.

**Figure 30: Mean Change (+95%CI) from Baseline in Basal Cortisol (nmol/L) over Time (Phase III Week 48 Pooled Analysis of C209 and C215)**



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**Medical officer’s analysis:** *There is a downward trend in mean basal cortisol levels from baseline to Week 48 in patients on TMC278 compared with control. Although the magnitude of*

***this difference appears small, it is difficult to assess its clinical significance without reviewing the trends over time for individual patients with abnormal results.***

In the pooled Phase 3 trials, small mean increases in 17-OHP levels were seen at Week 48 in both groups (+0.20 nmol/L and +0.4 nmol/L in TMC278 and control group). The mean increase in aldosterone at Week 48 was higher in the TMC278 group than in the control group (+18.7 pmol/L and +6.9 pmol/L, respectively). These results are also seen in Table 53, above.

***Medical officer's analysis: Inhibition of the adrenal enzyme 21-hydroxylase should result in a marked increase in 17-OHP and a decrease in aldosterone. There is no appreciable difference in 17-OHP levels between the TMC278 and control groups, and there is a small, clinically insignificant increase in aldosterone levels in the TMC278 group compared to placebo. The increase in aldosterone is notable, given that inhibition of 21-hydroxylase normally results in a decrease in aldosterone production. Therefore, these findings are not concerning from a clinical standpoint.***

**ACTH-stimulated cortisol, 17-OHP, and aldosterone levels: Phase 3 studies**

At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels<sup>1</sup> was lower in the TMC278 group (+16.5 ±6.14 nmol/L) than in the control group (+58.1 ±6.66 nmol/L). There were no differences between the 2 Phase 3 studies at baseline, nor for the changes from baseline. Small mean increases from baseline in 17-OH-progesterone levels (+1.09 ±5.76 nmol/L and +1.75 ±4.80 nmol/L with TMC278 and control), and in aldosterone concentrations (+31.7 ±206.8 pmol/L and +36.4 ±216.1 pmol/L with TMC278 and control) after ACTH stimulation were observed.

***Medical officer's analysis: Mean ACTH-stimulated cortisol levels increased from baseline to Week 48 in patients in both the TMC278 and control groups, albeit less so in the TCM278 group. Although this may suggest a less vigorous adrenal response in the TCM278 arm, the 17-OH-progesterone and aldosterone changes were not different than those observed in the control group (see also previous comment with respect to expected changes in 17-OH-progesterone and aldosterone in 21-hydroxylase deficiency). Without reviewing the trends over time for individual patients with abnormal results it is difficult to assess further clinical significance.***

**Individual abnormalities in ACTH-stimulated cortisol: Phase 3 studies**

Patients whose cortisol was <500 nmol/L in response to ACTH stimulation were considered to have abnormal test results. In the pooled Phase 3 studies, 38 patients (5.9%) in the TMC278 group had at least one abnormal ACTH test in the course of the 48-week treatment period, compared with 13 patients (2.1%) in the control group. The incidence of at least 2 consecutive abnormal cortisol responses to ACTH stimulation was 1.7% in the TMC278 group compared to none in the control group.

To better understand the long-term effect of TMC278 on adrenal function, DAVP requested that the sponsor provide the following additional data from the pivotal studies for review:

1. All individual values for basal and ACTH-stimulated cortisols at all timepoints on study for patients in the TMC278 group with abnormal basal cortisol values at screening/baseline.

---

<sup>1</sup> Cortisol levels were measured at baseline (T=0), and then at 30 and 60 minutes after ACTH stimulation. The ACTH-stimulated cortisol levels included in this analysis are the greater of the two post-stimulation values.

2. All individual values for basal and ACTH-stimulated cortisols at all timepoints on study for patients in the TMC278 group who developed abnormal basal and/or ACTH-stimulated cortisol values during the treatment period.
3. Present all individual cortisol values for each patient who discontinued.
4. Clinical information on all patients who discontinued and had any symptoms or clinical features consistent with adrenal insufficiency.

- ***Patients with abnormal ACTH-stimulated cortisols at baseline***

To determine the effect of TMC278 on patients with abnormally low ACTH-stimulated cortisols at baseline (i.e., with biochemical evidence of adrenal insufficiency at baseline), the sponsor has provided data on all cortisol values – basal and ACTH-stimulated – for these patients. In total, 24 patients were found to have low baseline ACTH-stimulated cortisol values. Of these, 12 (50%) had normal ACTH-stimulated cortisol values on all subsequent measurements, and therefore are considered to have normal adrenal function by this reviewer. Table 1 below temporally depicts the ACTH-stimulated cortisol values for the remaining 12 patients during the Phase 3 trials. Highlighted in red are the below normal (<500 nmol/L) cortisol values.

**Table 1: ACTH-stimulated cortisol values over time for patients with abnormal ACTH stimulation tests at baseline**

Pt ID	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60
209-0036	54			276			276		524	
209-0119	497								497	
209-0389 <sup>1</sup>	423			639					740	408
209-0612	459			468		606			621	
209-0753	487	364		374					555	
209-0877	469		442						662	
209-0913	464	439			498				451	
215-0115 <sup>2</sup>	497			497			635			
215-0189	110			55					414	
215-0519	469		497						635	
215-0656	442		469						718	
215-0823	476		434			572		487	488	

<sup>1</sup>Patient discontinued due to meeting a virologic endpoint

<sup>2</sup>Patient discontinued – lost to follow up

Two patients who had abnormal ACTH stimulation tests at baseline discontinued the trial. Neither had symptoms suggestive of adrenal insufficiency.

***Medical officer's analysis: As shown in Table 1 above, patients who have baseline abnormalities in ACTH-stimulated cortisol levels do not appear to have significant worsening of cortisol levels over at least 48 weeks of treatment. For some of them the levels normalized on treatment. In patients who have sustained, low ACTH-stimulated cortisol values, it does not appear treatment with TMC278 is associated with clinical symptoms of adrenal insufficiency and there is no evidence of progressive decline on treatment.***

- ***Patients who developed abnormal ACTH-stimulated cortisols during the trial period***

The sponsor has provided data on all cortisol values – basal and ACTH-stimulated – for patients with normal baseline ACTH stimulation test results, but who subsequently had at least one abnormal test during the trial period. In total, 35 patients developed abnormal ACTH-stimulated

cortisol values during the trial. Of these, 12 had a transient abnormality, i.e., with results at the end of trial having normalized. The remaining 23 patients had sustained abnormalities, with the majority (15/23) having mild decreases in ACTH-stimulated cortisol (defined by this reviewer as a decrease from baseline to nadir of <200 nmol/L). The eight patients with significant decreases (>200 nmol/L) had drops in ACTH-stimulated cortisol from baseline to nadir that ranged from 213-497 nmol/L, with the lowest recorded cortisol value of 156 nmol/L. Table 2 below temporally depicts the ACTH-stimulated cortisol values for these 35 patients during the Phase 3 trials, with those who had sustained abnormalities shaded in gray.

**Table 2: ACTH-stimulated cortisol values over time for patients who subsequently had abnormal ACTH stimulation tests during the trial**

Pt ID	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60
209-0082	690								469	
209-0129 <sup>1</sup>	662								497	
209-0160	745								304	745
209-0252	607								442	
209-0309 <sup>2</sup>	533					156				
209-0358	746					380			307	
209-0399	722								310	
209-0474	603				522				474	
209-0478	547								480	
209-0517	597								486	
209-0594 <sup>3</sup>	530	479		587					585	
209-0663	555		445			403			521	
209-0664		533	151	602					565	
209-0713	605	526				493			490	
209-0728	661								477	
209-0745 <sup>4</sup>	573					291				555
209-0824	652	238							569	
209-0841	778								341	
209-0854	602			591					460	
215-0001 <sup>5</sup>	690								469	
205-0397	792								237	748
215-0422	524								359	
215-0463	511		488		495		517		527	
215-0563	592								465	
215-0590	674								210	
215-0606	677				521				464	
215-0661	580						331	635	580	
215-0690	635				635	221			304	
215-0736	544				483		501		469	
215-0777	552								442	
215-0809	745		828						248	
215-0845	607								469	662
215-0859	532			536				471	535	
215-0869	607						497		552	

Pt ID	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60
215-0902	541					460	482		460	

<sup>1</sup> Patient discontinued due to reaching a virologic endpoint

<sup>2</sup> Patient discontinued due to adverse effect of drug: irritability, anxiety, sleep disorder

<sup>3</sup> Patient discontinued due to reaching a virologic endpoint

<sup>4</sup> Patient discontinued due to persistently elevated transaminases

<sup>5</sup> Patient discontinued due to protocol deviation

Five patients who had normal ACTH stimulation tests at baseline discontinued the trial. Of these, only one (209-0309) was discontinued due to clinical symptoms that may be suggestive of adrenal insufficiency, including irritability, anxiety, and a sleep disorder. Of note, this patient had the lowest recorded ACTH-stimulated cortisol value (156 nmol/L) of all the patients included in this analysis.

***Medical officer's analysis: 23 patients (3.4% of the TMC287 treatment group) developed sustained hypocortisolism when treated for 48 weeks. The majority of these patients had mild decreases in ACTH-stimulated cortisol levels; however, 8 patients had significant drops, and one of these patients was discontinued from the trial due to symptoms that could be considered related to adrenal insufficiency.***

#### **IV. DMEP analysis (responses to DAVP questions)**

*1. Please comment on the totality of the adrenal related safety data.*

There is a small decrease in mean basal cortisol levels in patients in the TMC287 group compared with control: when the results from both trials are pooled, at Week 48 the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the TMC278 group, and an increase of +9.0 nmol/L in the control group. In addition, compared with the control group, the cortisol response to ACTH stimulation in the treatment group is attenuated, with a mean change from baseline in ACTH-stimulated cortisol levels in the TMC278 group of +16.5 nmol/L, compared with +58.1 nmol/L in the control group. However, these differences are small and of questionable clinical significance. Furthermore, the data for 17-OHP and aldosterone levels indicate that 21-hydroxylase is not affected by treatment with TMC287.

We have performed an analysis of 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, patients who had an abnormal ACTH stimulation test at baseline did not appear to have a worsening of their hypocortisolism over the 48-week main phase of the Phase 3 trials, and in fact most had normal values for the remainder of the study. The results are less clear for patients who had normal ACTH-stimulated cortisol values at baseline, but who subsequently had abnormal values later in the trial. We have identified 23 patients (3.4% of the TMC287 group) who appear 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 on TMC287. Of the eight patients 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.

Therefore, although the incidence of biochemical adrenal suppression in patients taking TMC287 is low, we think it is important that physicians are made aware – especially when considering patients with HIV/AIDS, who have a higher risk of adrenal insufficiency than the general

population<sup>2</sup> – that observations made in the registration clinical trials suggest that this rare but potentially life-threatening adverse effect may occur.

*2. Should the drug be approved for marketing, do you recommend routine adrenal function monitoring, such as periodic collection of basal cortisol level? Do you recommend any further evaluation post approval?*

Routine adrenal function is performed in patients with HIV/AIDS based on clinical symptomatology rather than as per routine<sup>3</sup>. Given that patients with suspected adrenal insufficiency based on abnormal ACTH stimulation tests (cortisol <500 nmol/L) at baseline did not experience worsening of their cortisol values or clinical signs of adrenal insufficiency over the course of the Phase 3 trials, it is our opinion that based on the available information to date, a fixed routine adrenal function monitoring schedule is not necessary in patients on TMC287. However, if the drug is approved, since it is being used in a larger patient population it is expected that analysis of postmarketing adverse reactions will maintain a high index of suspicion for those related to adrenal safety.

*3. Currently, Tibotec does not propose any labeling with regard to adrenal function. Should the mean change from baseline for cortisol, 17-OH-progesterone, aldosterone or mean change from baseline in maximum change in cortisol after ACTH stimulation be presented in labeling? What additional labeling, if any, do you propose relating to adrenal function?*

Although the decrease in basal cortisol and attenuation of cortisol response to ACTH in the TMC287 group is small (see response to Question 1 above), we would suggest including language describing the adrenal-related safety data in the label. This is due to both the increased baseline risk of adrenal insufficiency in patients with HIV/AIDS, and the significant morbidity and mortality associated with acute adrenal suppression, in general.

We have considered whether the signal described in the Phase 3 trials warrants mention in the WARNINGS AND PRECAUTIONS section. At this point, however, there is no adverse report of adrenal insufficiency in the phase 3 clinical trials, and one patient with biochemically-confirmed adrenal insufficiency was discontinued from the trial with symptoms suggestive of adrenal suppression. In light of the existing data, we do not recommend at this point labeling adrenal insufficiency in the Warnings and Precautions section. This recommendation would change in the face of additional evidence for this adverse reaction. At this point in time, we believe it is more appropriate to include the adrenal safety data in Section 6, ADVERSE REACTIONS. We would propose the following language:

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<sup>2</sup> Membreno L, Irony I, Dere W, Klein R, Biglieri EG, Cobb E. Adrenocortical function in acquired immunodeficiency syndrome. *J Clin Endocrinol Metab.* 1987 Sep;65(3):482-7.

<sup>3</sup> Mayo J, Collazos J, Martínez E, Ibarra S. Adrenal function in the human immunodeficiency virus-infected patient. *Arch Intern Med.* 2002 May 27;162(10):1095-8.

*Adrenal function*

Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Fifteen (2.2%) subjects in the TRADE NAME<sup>TM</sup> arm had adverse events described as “blood cortisol decreased,” compared with 7 (1%) subjects in the control arm.

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 TRADE NAME<sup>TM</sup> group, and an increase of +9.0 nmol/L in the control group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the TRADE NAME<sup>TM</sup> group (+16.5 ±6.14 nmol/L) than in the control 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.

With respect to the data on 17-OH-progesterone and aldosterone, since the data did not reveal a safety signal, we do not believe it is necessary to present this information in the label.

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**Ali Mohamadi, MD**  
**Medical Officer**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALI MOHAMADI  
03/15/2011

DRAGOS G ROMAN  
03/15/2011

MARY H PARKS  
03/15/2011



## Division of Cardiovascular and Renal Products

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Original NDA: 202022  
Sponsor: Tibotec, Inc.  
Purpose of Communication: Renal Consult  
Consult from: Division of Antiviral Products  
Product: rilpivirine, TMC278  
Indication: HIV-1 infection  
Date of NDA submission: 7/23/10  
Date of Consult: 9/28/10  
Date Consult Completed; 03/08/11  
Medical Officer: Melanie J. Blank, MD  
Team Leader: Aliza Thompson, MD  
Division Director: Norman Stockbridge, MD, PhD

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This consult addresses the concerns raised by the Division of Antiviral Products about the renal-related safety of rilpivirine, an NME that is the subject of NDA submission 202022.

### **Questions submitted by the Division of Antivirals**

1. Please comment on the totality of the renal-related safety data
2. Do you concur that the Cystatin C study supports the conclusion that TMC278 does not have an effect on glomerular filtration?
3. Should the drug be approved for marketing, do you recommend any renal monitoring, such as creatinine clearance? Do you recommend any further evaluation post approval?
4. Do you have labeling recommendation for safe use of TMC278?

### **Executive Summary, Answers to Questions and Recommendations**

This consult addresses the significance of the observed and likely mechanism behind pervasive increases in serum creatinine found in the TMC278 arm of the two pivotal studies (C209 and C215) that evaluated the efficacy and safety of TMC278 as a treatment for Human Immunodeficiency Virus-1 (HIV-1).

### Description of data and methods used for analysis

The safety data from the two studies were pooled which was appropriate because the studies were very similar in design. The data analyses included 686 randomized patients who received at least one dose of TMC278 and 682 patients who received at least one dose of an active comparator, efavirenz. Most of the sponsor's analyses covered serum creatinine (SCr) data through week 48 of treatment. My analyses included all lab data available up to 96 weeks of treatment unless otherwise stated.

### Efavirenz nephrotoxicity

With regard to the renal toxicity of the active comparator, it should be noted that while the original efavirenz label did not report renal toxicity, the label has been updated to include postmarketing reports of renal failure and acute renal failure, increased creatinine, acute tubular necrosis and renal insufficiency.

### **Answers to Questions 1 and 2:**

Analyses of the data of the two pivotal trials revealed the following:

1. While most of the TMC278 patients had a rise in serum creatinine at some point during the trial most of the rises in SCr occurred in the first two weeks of treatment and largely stabilized by week 2. There was, however, a small trend toward an increase in mean SCr levels in the TMC278 treatment group starting after week 24.
2. There were no concerning marked increases in serum creatinine during the trials in the TMC278-treated patients or patients who required dialysis while on TMC278. Furthermore, most of the patients in the TMC278 arm who had the greatest rises of SCr also had decreases in SCr during treatment.
3. The SCr rises occurred in the TMC278 treatment group regardless of background antiretroviral therapy used.
4. A small group of patients (61 on TMC278) were followed for two to four weeks following treatment cessation. There was a considerable reduction in the mean SCr in the TMC278 patients during the follow-up period but it did not return to baseline,
5. The renal failure-related adverse events (AEs) were balanced between the TMC278 treatment group and the efavirenz treatment group. The only two cases of life-threatening renal failure during the trial were in the efavirenz treatment group.
7. The estimated glomerular filtration rate for cystatin C equivalent (eGFR<sub>cystC</sub>) analysis was difficult to interpret. The baseline eGFR<sub>cystC</sub> levels were comparable between the two treatment groups. If GFR had decreased during treatment with TMC278, one would have expected a decline in eGFR<sub>cystC</sub> in the TMC278 treatment group and not in the efavirenz group because cystatin C is fully filtered and not secreted. Unexpectedly, eGFR<sub>cystC</sub> increased at week 24 compared to baseline in both treatment groups. However, the increase in eGFR<sub>cystC</sub> was considerably larger in the efavirenz arm than in the TMC278 arm. The fact that cystatin C levels tend to decrease as inflammation decreases is the most plausible explanation for the increase in eGFR<sub>cystC</sub> in both treatment

groups. The difference between the two groups in  $\Delta$  eGFRcystC between baseline and week 24 might reflect a real difference in GFR between treatment groups if one assumes that the production of cystatin C decreased similarly between the treatment groups during the trial.

8. An analysis of BUN levels showed virtually no difference between baseline levels and last visit levels for both treatment groups, making it unlikely that the increase in SCr levels in the TMC278 treatment arm is a result of renal hemodynamic changes.

While there is strong evidence in favor of the hypothesis that tubular secretion is the most likely factor causing the increased levels of SCr (acute rise of SCr rise, some patients with decrease in SCr while continuing on treatment, trend toward recovery after TMC278 is discontinued, no greater incidence of marked increases in SCr in the TMC278 treatment group compared to the efavirenz treatment group, negative BUN findings and absence of decrease in eGFRcystC), there are also data that support the possibility that TMC278 reduces GFR. There was a small trend of SCr increase after week 24, incomplete recovery of SCr at 2-4 weeks of follow-up after discontinuation of treatment, and an unfavorable difference in delta eGFRcyst C between baseline and week 24 in the TMC278 treatment group relative to the efavirenz group. Most of the patients who were enrolled had normal renal function. If there was mild acute renal injury in some of the patients in the TMC278 treatment arm, it is conceivable that these patients could have mobilized their renal reserve (via renal hemodynamic changes) to restore GFR even while on treatment. To further address the concern that TMC278 could be linked to a reduction in eGFR, I have recommended that the sponsor do a post-marketing study (see answer to question 3).

### **Answer to Question 3:**

As with any drug approval, the safety of the drug must be measured against its efficacy. Even if TMC278 caused a small reduction in GFR, this risk could possibly be outweighed by the benefits of treatment. If it is determined that the drug's efficacy is outweighed by the possibility of other safety concerns and the possibility of a small decline in GFR, the renal safety concerns can be addressed by a post-marketing study and labeling.

To differentiate the effects of TMC278 on GFR and tubular secretion, the sponsor should consider doing one of the following studies.

1. Perform a study in patients or normal healthy volunteers on no background nephrotoxic drugs to determine if pre-treatment/concurrent treatment with cimetidine prevents the TMC278 induced rise in mean serum creatinine.<sup>1</sup> If tubular secretion is the predominant mechanism for TMC278 induced rises in mean SCr, there should be no increase in mean SCr levels at 2 to 4 weeks from baseline mean SCr measured after maximum cimetidine inhibition of tubular secretion is reached.

(OR)

2. Perform a study in patients or in normal healthy volunteers on no background nephrotoxic drugs to measure GFR at baseline and then while on treatment with TMC278. Measured GFR should not change if tubular secretion interference is responsible for the observed rises in serum creatinine levels.

### Suggested Labeling

Increases in serum creatinine (mean 0.19 mg/dL with a range of 0 – 0.7 mg/dL) commonly occurred during treatment with TMC278. The increases in serum creatinine occurred within the first two to four weeks of treatment and usually leveled off after that.

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 TMC278, a work up for other causes of renal toxicity should be considered.

eGFR equations will underestimate the degree of renal function and should not be relied upon for dosing other drugs. TMC278 will not interfere with measured GFR.

### Other Comments:

The label should also include information about the two occurrences of glomerulonephritis and the two fold higher incidence of nephrolithiasis/ renal colic in patients in the TMC278 treatment arm.

## **LIST OF ABBREVIATIONS**

ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AZT	zidovudine
CI	confidence interval
eGFR	estimated glomerular filtration rate calculated by MDRD formula
eGFR <sub>cyst</sub>	estimated glomerular filtration rate for cystatin C equivalent
FTC	emtricitabine
GFR	glomerular filtration rate
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects

NNRTI	non-nucleoside reverse transcriptase inhibitor
SAE	serious adverse event
SBP	systolic blood pressure
SCr	serum creatinine
TDF	tenofovir disoproxil fumarate
TMC	Tibotec Medicinal Compound

## 1. Background:

Rilpivirine (referred to as TMC278 throughout this review), a new molecular entity, is an anti-retroviral drug developed for the treatment of HIV-1 infection in combination with other antiretroviral drugs. Rilpivirine belongs to the nonnucleoside reverse transcriptase inhibitor (NNRTI) class of anti-retroviral therapy. Renal toxicity has not been previously described in other drugs that belong to the NNRTI class.

During phase 2 and phase 3 development, treatment with rilpivirine was associated with increases in serum creatinine that occurred and plateaued by week 2. It should be noted that the patients in these trials were often treated with tenofovir, another anti-retroviral drug (not in the NNRTI class) which is known to cause renal toxicity. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir.

In the nonclinical development of rilpivirine, a range of mild to severe multifocal tubular basophilia and minimal to slight glomerulopathy (atrophic glomeruli with thickened Bowman's capsule amidst basophilic tubules), minimal to moderate mononuclear cell infiltration and minimal to slight interstitial fibrosis, minimal tubular dilatation and slight cortical mineralization occurred primarily in female mice exposed to high doses of TMC278. There was an increase in mean BUN levels in the female mice, but no change in mean serum creatinine levels. Nephrotoxicity was not seen in rats. Acute interstitial nephritis was seen in 2 male dogs treated with 25-fold exposure expected in man. There was minimal to slight corticomedullary mineralization in all female dogs sacrificed at the end of the study. In general, creatinine concentration increased in all dogs including the control group, but this was more marked in males that received high doses and females that received moderate to high doses.

Two registrational Phase III trials (TMC278-C209 and TMC278-C215), with a Week 48 cut-off date for analyses were submitted in support of full marketing authorization. The studies were multicenter, international double blind, double-dummy active control studies comparing the investigational drug, rilpivirine (TMC278), 25 mg QD to efavirenz (EFZ) 600 mg QD for 48 weeks. In both studies combined, 1368 HIV-1 infected, antiretroviral treatment-naïve adult subjects were randomized and received treatment. 686 subjects received TMC278 25 mg q.d. and 682 subjects received the active control (EFV). The two clinical trials, TMC278-C209 and TMC278-C215 were very similar except for the type of background regimen used. In C209, subjects received a fixed background regimen consisting of Truvada (tenofovir/emtricitabine (TDF/FTC)). In

C215, the background regimen contained either Epizicom (abacavir/lamivudine (ABC/3TC)), Combivir (zidovudine/lamivudine (AZT/3TC)), or TDF/FTC.

Medication was administered in a double-dummy fashion in trials C209 and C215 to maintain blinding. In both trials, AEs were recorded from the time the subject signed the informed consent form until after the end of the follow-up period. Safety parameters including serum creatinine, serum BUN, urinalysis and AEs were assessed at screening, baseline, and at predefined time points during the treatment phases [baseline, week 2, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, week 56, week 60, week 64, week 68, week 72, week 76, week 80, week 84, week 88, week 92, week 96 (final withdrawal visit), and week 100 (post-treatment follow-up period)]. The Week 48 analysis is the primary safety analysis; however, the Phase 3 trials are ongoing up to Week 96. For the Week 48 analysis, the blind was broken for Tibotec Pharmaceuticals but not for subjects, investigators, and monitors who interact with site personnel.

The safety analysis was done by pooling both studies which I felt was appropriate given the similarity of the studies and the enrollment criteria. Most patients completed 48 weeks with a less than 5% dropout rate (3.8% in the investigational arm and 4.1% in the active control).

A deficiency in the study was the absence of patients with history of chronic kidney disease (CKD). Chronically diseased kidneys have no renal reserve while normal kidneys do. Renal reserve allows kidneys to improve GFR even in the face of injury. Therefore, if there had been renal toxicity in the TMC278-treated CKD patients, SCr would have increased but would not have been able to improve as it did in many of the TMC278 treated patients in these studies, particularly the ones with the greatest rises.

## **2. Exposure**

As shown in Table 1, the exposure was adequate for evaluation of serum creatinine elevation

**Table 1: Phase 3 Exposure to TMC278**

Treatment Duration and Exposure	Pooled	
	TMC278 N = 686	Control N = 682
Subject-years of exposure, Sum	740.1	714.4
Treatment duration (weeks), Median (range)	55.7 (0 -87)	55.6 (0 -88)
Exposure in weeks, n (%)	686	682
< 1 week	1 (0.1)	6 (0.9)
[1 Week -2 weeks]	0	10 (1.5)
[2 weeks -4 weeks]	2 (0.3)	12 (1.8)
[4 weeks -12 weeks]	11 (1.6)	15 (2.2)
[12 weeks -24 weeks]	35 (5.1)	22 (3.2)
[24 weeks -48 weeks]	26 (3.8)	28 (4.1)
[48 weeks -96 weeks]	611 (89.1)	589 (86.4)

N = number of subjects per treatment group; n = number of observations.

Source: [Summary of Clinical Safety, p. 61](#)

Overall, similar percentages of subjects in the TMC278 and control group were still being treated in the Phase III trials at the time of the Week 48 analysis. The proportion of subjects who discontinued study medication was somewhat lower in the TMC278 group (13.7%) than in the control group (16.4%). The lower discontinuation rate in the TMC278 treatment group suggests that there was no informative censoring.

### **3. Renal Adverse Events (AEs)**

Reported AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms using version 11.0 of MedDRA for the Phase III pooled analysis.

There were 4 patients in the TMC278 treatment arm and 3 patients in the efavirenz treatment arm that had AEs of “renal failure” reported. The sponsor provided case report forms for the 7 patients who had renal failure coded as an AE. These are described in Appendix A. It is reassuring that all 3 severity grade 3 (severe)-4 (lifethreatening) acute renal failure AEs occurred in the comparator group

There were no cases of renal failure that required dialysis or death related to renal disease.

2 of the 4 cases of “renal failure” in the TMC278 arm resolved while on treatment. The other two cases of renal failure were classified as serious adverse events (SAEs). One was a case of an acute infection and the renal failure was thought to be related to hemodynamic factors. The other was a patient with membranous glomerulonephritis. He was the only patient on TMC278 who was withdrawn from the study for a renal AE. Another renal related SAE in the TMC278 arm was for a ureteral calculus.

There were 5 renal AEs in the severity grade 3 (severe) to 4 (life-threatening) categories in the TMC278 treatment group (2 nephrolithiasis, 1 pyuria, 1 mesangiocapillary glomerulonephritis (described in Appendix B), 1 proteinuria) and 4 in the efavirenz treatment group (1 nephrolithiasis, 3 acute renal failures).

All renal AEs were designated as recovered except for the 2 occurrences of glomerulonephritis in the TMC278 treatment group.

The renal AEs were nearly equally represented in both treatment groups (Table 2). The exceptions were that there were more cases of nephrolithiasis and colic in the TMC278 group compared to the efavirenz group (8 vs. 4, respectively, RR=2) and the only two cases of glomerulonephritis were in the TMC278 group (discussed in Appendix A). The total number of cases of nephrolithiasis/colic and glomerulonephritis was small but the imbalance between treatment arms raises concern. While glomerulonephritis has been associated with chronic infection including HIV infection since both cases occurred on TMC278, this AE should be noted in the label.

To further address the observed imbalance between treatment groups in events of nephrolithiasis and colic, I analyzed the number and percent of patients that had urinary crystals on urinalysis (using lbad.15 from the September 24, 2010 submission). 80 of 686 (11.7%) patients in the TMC278 treatment arm had urinary crystals (amorphous, oxalate, or uric acid) while 64 of 682 (9.4%) patients in the efavirenz treatment arm had urinary crystals. This difference in frequency in urinary crystals between treatment groups trends with the difference in frequency of kidney stones and supports the possibility that the observed difference in kidney stone formation reflects a real difference between treatments. Therefore, the imbalance between treatment groups in kidney stone formation should also be included in the label.

**Table 2: AEs by treatment group**

ADVERSE EVENTS	TMC 278 N=686(%)	Efavirenz N=682
NEPHROLITHIASIS/COLIC	8(1.2)	4(0.6)
DYSURIA	8(1.2)	6(0.9)
GLOMERULONEPHRITIS	2(0.2)	0(0)
MEMBRANOUSGLOMERULONEPHRITIS	1(0.1)	0(0)
MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS	1(0.1)	0(0)
HAEMATURIA	11(1.6)	11(1.6)
PYURIA	2(0.3)	2(0.3)
NOCTURIA/POLYURIA	10(1.5)	8(1.2)
PROTEINURIA	11(1.6)	9(1.3)
RENAL FAILURE	3(0.4)	3(0.4)
ACUTE RENAL FAILURE	1(0.1)	3(0.4)
UTI	5(0.7)	3(0.4)

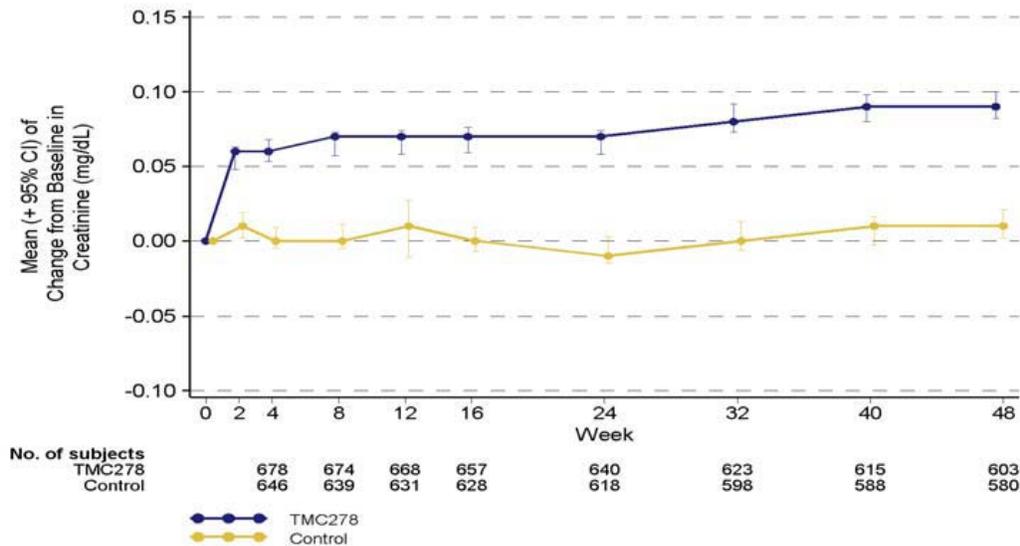
Source: Recoding of sponsor's renal AE data from initial submission

#### 4. Increased Serum Creatinine

The Sponsor provided several graphs that illustrate the observation that the mean serum creatinine rose above baseline in the treatment group but not in the control group. I have renumbered the figures for the sake of simplicity. As shown in Figure 1 the mean SCr levels increased by week 2 in the active treatment arm and stayed relatively stable until week 24 when the mean SCr began to trend slightly upward.

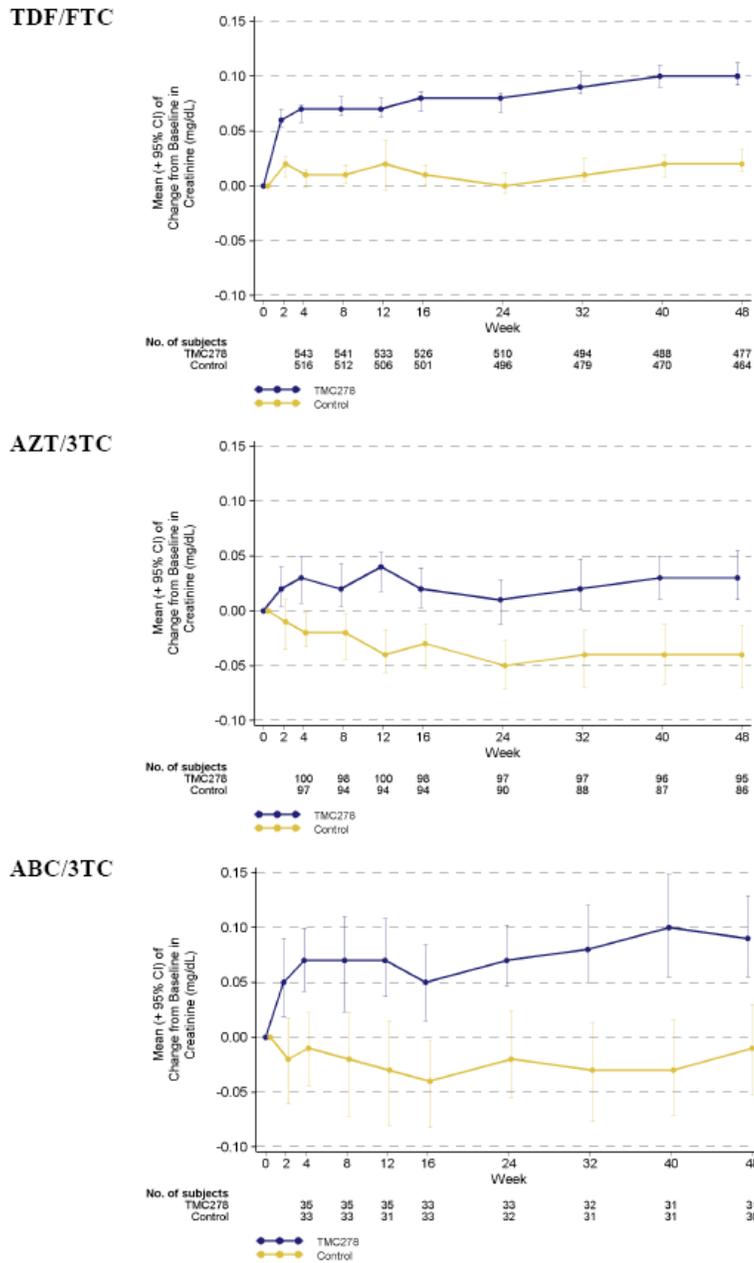
To assess the possibility that TMC278 was potentiating the nephrotoxicity of tenofovir, the sponsor analyzed the creatinine increase over time by background therapy. Since the pattern of consistent differences in SCr persists regardless of background therapy as shown in Figure 2 it is likely that there is no interaction between TMC278 effects on creatinine and background therapy. The change in eGFR as estimated by MDRD is shown in Figure 3. Given that eGFR is based on the serum creatinine measurement, it is not surprising that the results are similar, i.e., the eGFR decreases acutely and then plateaus until week 24 when it gradually starts to decline.

**Figure 1: Mean Change ( $\pm 95\%$  CI) from Baseline in Creatinine over Time (Phase III Week 48 Pooled Analysis of C209 and C215)**



Source: Summary of Clinical Safety

**Figure 2: Mean Change in serum Creatinine by background therapy (TDF/FTC, AZT/3TC, and ABC/3TC) and by treatment**

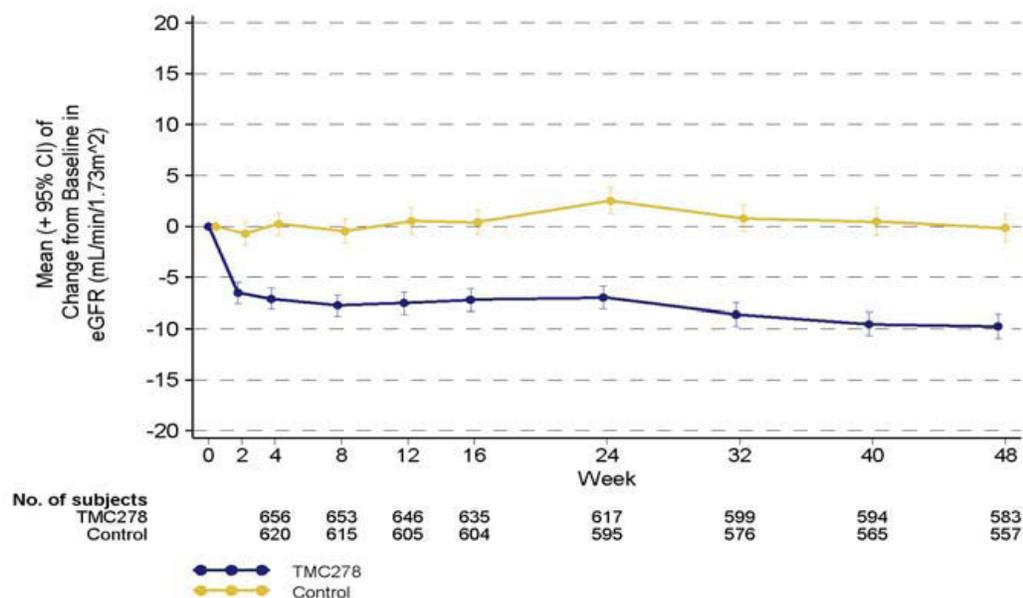


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Source: [Module 5.3.5.3/TMC278-C904-Anal-Saf-Lab/Display SAF.29.](#)

Source: Summary of Clinical Safety

**Figure 3: Mean Change ( $\pm 95\%$  CI) from Baseline in eGFR<sub>creat</sub> Over Time (Phase III Week 48 Pooled Analysis of C209 and C215); calculated based on serum creatinine using MDRA Formula**



Best Available Copy

Source: Summary of Clinical Safety

The mean SCr at baseline, the mean maximum SCr during the trial and the mean delta between each patient’s baseline and maximum SCr are displayed in Table 3. The baselines were nearly the same in each treatment group (0.85 mg/dL mean), the mean maximum serum creatinine levels differed by 0.07 mg/dL and the mean delta between maximum and baseline values differed by 0.06 mg/dL, between the treatment arms, as would be expected given the similar baseline values

**Table 3: Mean SCr at baseline, mean maximum (Max) SCr and mean delta (Max SCr –Baseline SCr) by treatment**

Treatment	N	Mean SCr Baseline (Range) mg/dL	Mean SCr Maximum (range) mg/dL	Mean SCr Delta (range) mg/dL
TMC278	686	0.85 (0.4-1.4)	1.04 (0.53-1.8)	0.19 (0-0.7)
Efavirenz	673	0.85 (0.5-1.6)	0.97 (0.6-6.2)	0.13 (0.-5.4)

Source: Sponsor’s laboratory data (Ibad01.xpt from the Sept 24, 2010 submission)

The Sponsor proposed that the observed pattern of change in average serum creatinine was most compatible with interference with creatinine tubular secretion. The sponsor felt that interference with tubular secretion was the most likely explanation because the creatinine increased rapidly and plateaued at 2 - 4 weeks, and because the majority of TMC278-treated patients had an increase in SCr, few of the increases were large, and those that were mostly recovered while on treatment.

In order to support their hypothesis that TMC278 affects the tubular secretion of creatinine, the sponsor provided additional data. A Cystatin C substudy was conducted in an attempt to demonstrate no decline in eGFR when cystatin C levels were used to estimate renal function. Cystatin C is a freely filtered endogenous substance that does not get secreted and would therefore be unaffected by agents that interfere with tubular secretion. Only patients in study C15 participated in the substudy. Cystatin C levels were drawn at baseline, at week 2 and at week 24. The patients in the TMC278 treatment group that were included in the substudy had a mean baseline serum creatinine of 0.85 (range 0.5-1.36) mg/dL, a mean maximum serum creatinine of 1.03 (range 0.6-1.7) mg/dL and a mean delta serum creatinine (baseline to maximum) of 0.18 (range 0.0-0.6) mg/dL. These values are very close to the values of the entire TMC278 treatment group and therefore the cohort of patients in the eGFR by cystatin C substudy was representative of the whole treatment group. The SCr values of the efavirenz subgroup were also representative.

As can be seen in Table 4, mean eGFR<sub>cyst C</sub> did not decrease in either treatment group (in fact, it increased markedly, which is not what one would expect to occur). Of note, the increase in mean eGFR<sub>cyst C</sub> at 2 and 24 weeks was greater in the efavirenz treatment group than in the TMC278 treatment group. At week 24 (the last eGFR<sub>cyst C</sub> measurement made) there was no overlap of the 95% confidence intervals. It would have been preferable to have later measurements because after week 24 the eGFR by MDRD in the TMC278 treatment arm began to trend downward. It is important to be aware that, serum cystatin C levels have been shown to correlate with inflammation. Inflammation may have decreased during the course of the trial because of the antiviral effects of the treatments. It is likely that the decrease in inflammation caused the apparent improvement in eGFR<sub>cyst C</sub>. Therefore, the absolute values of eGFR<sub>cyst C</sub> may not be reflective of GFR in this setting. For these reasons, the eGFR<sub>cyst C</sub> subgroup analysis did not provide sufficient support to confirm the sponsor's hypothesis that the rise in SCr seen with TMC278 is solely related to an interference with tubular secretion of creatinine. In fact, one could postulate that the relative difference between treatment groups in the  $\Delta$  eGFR<sub>cyst C</sub> between baseline and week 24 is more pertinent and might signify a lower GFR in the TMC278 treatment group. An alternative explanation for the difference between treatment groups in the  $\Delta$  eGFR<sub>cyst C</sub> between baseline and week 24 is that efavirenz decreased inflammation more than TMC278.

**Table 4: Comparison of eGFRcyst C between TMC278 (ripilivine) and efavirenz at week 2 and at week 24**

Glomerular Filtration Rate on Cystatin (mL/min) - Descriptive Statistics

Visit	TMC278					Control				
	n	Mean (95% CI)	SD	SE	Median (Min;Max)	n	Mean (95% CI)	SD	SE	Median (Min;Max)
<b>BASELINE</b>										
Actual Value	330	98.4 (95.76; 101.00)	24.20	1.33	95.5 (45;264)	329	99.3 (96.97; 101.56)	21.18	1.17	98.6 (42;193)
<b>WEEK 2</b>										
Actual Value	325	101.1 (98.43; 103.76)	24.41	1.35	97.9 (47;269)	312	105.0 (102.47; 107.57)	22.87	1.29	104.4 (51;189)
Change from Baseline	321	2.6 (1.15; 3.98)	12.89	0.72	2.8 (-49;78)	308	5.3 (3.75; 6.80)	13.62	0.78	5.2 (-49;65)
<b>WEEK 24</b>										
Actual Value	312	120.2 (116.82; 123.58)	30.31	1.72	114.9 (49;311)	297	130.6 (126.37; 134.77)	36.81	2.14	125.7 (37;385)
Change from Baseline	304	21.6 (18.95; 24.23)	23.40	1.34	17.3 (-52;128)	288	31.3 (27.88; 34.81)	29.88	1.76	25.1 (-21;251)

## 5. Further Analysis

Serum creatinine can increase because of intrinsic renal injury, renal hemodynamic factors (where intraglomerular pressure is reduced resulting in decreased filtration), interference with tubular secretion, increases in body mass, higher protein diet, and postrenal obstructive factors. Since nephrolithiasis occurred in fewer than 2% of patients and anuria and urinary retention did not occur, one can confidently rule out obstructive factors as the reason for the acute rise in SCr. Rapid changes in body mass or diet is also unlikely but weight or dietary intake was not measured at the two week or 4 week point.

I conducted an outlier analysis ensure that there wasn't an imbalance between the treatment groups in patients with large increases in SCr. This analysis is displayed in Figure 4. There were no major outliers in the TMC278 treatment arm. The efavirenz treated group had the largest number of outliers. This analysis suggests the absence of marked TMC-278 induced renal toxicity but does not rule out less severe renal toxicity.

**Figure 4: Maximum SCr in mg/dL in patients during trial and follow-up**

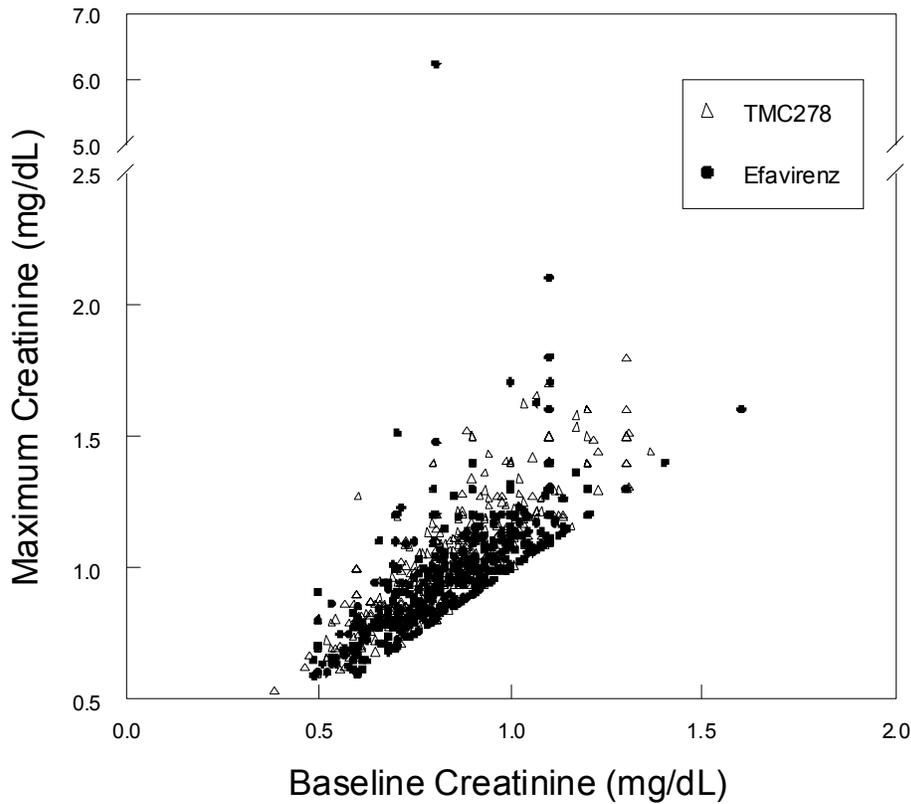
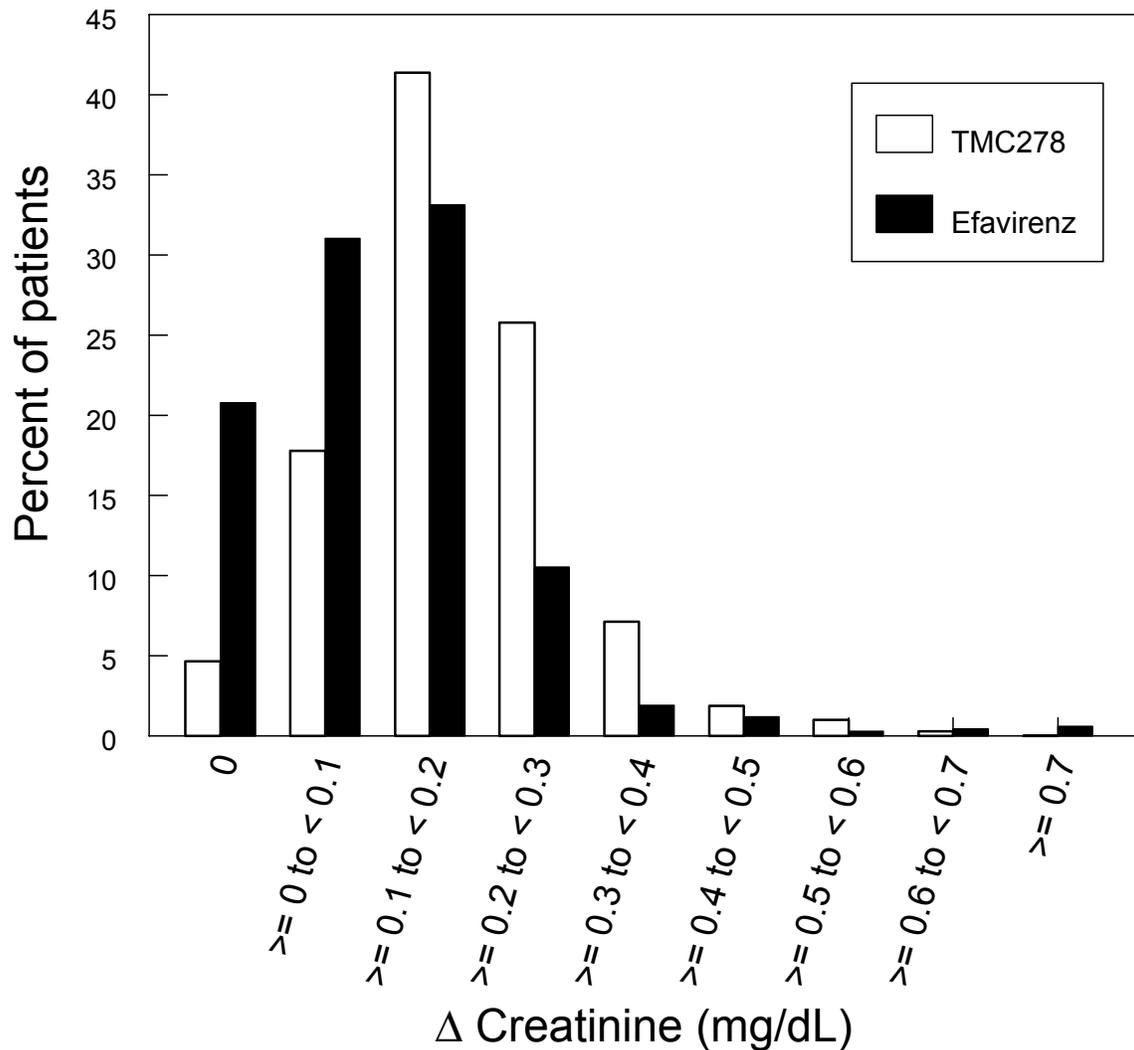


Figure 5 graphically depicts the percent of patients with elevated creatinine levels over baseline by baseline reading at any time during the trial. This analysis shows that the TMC278 treatment group had a shift to the right in percentage of patients with higher changes in SCr compared to the efavirenz treatment group as one would expect. The outliers are also represented in this figure.

**Figure 5: Percent of patients with Increases in Serum Cr in mg/dL by change in SCr in mg/dL**



I then analyzed the recovery period of the patients. This analysis is shown in Table 5. Only 112 patients had recovery periods in which serum creatinine was measured. The patients in the efavirenz group went back to baseline. The patients in the TMC278 arm still had an elevated SCr level compared to baseline but by the end of the trial the average increase was approximately 0.09 mg/dL compared to the 0.04 mg/dL seen in the follow-up period. This analysis demonstrates that the TMC278 effect on serum creatinine is largely but not completely reversible at week 2 or 4 after cessation of treatment. It may have been that the follow-up period was too short to see the average serum creatinine levels return to baseline. While this analysis is limited by small numbers of patients and short follow up periods, the results provide evidence in support of the hypothesis that TMC278 interferes with renal tubular secretion but still do not rule out mild kidney injury. These data would also be compatible with a renal hemodynamic

effect of TMC278 that might decrease intraglomerular pressure and decrease filtration on that basis.

**Table 5: Follow-up period and Elevation in SCr**

	<b>TMC278 25mg QD N=61</b>	<b>Efavirenz 600mg QD N=61</b>
<b>Mean baseline SCr in mg/dL</b>	0.86	0.86
<b>Mean maximum SCr in mg/dL</b>	1.03	0.97
<b>Mean follow-up SCr in mg/dL</b>	0.92	0.85
<b>Mean increase in SCr from baseline in mg/dL</b>	0.044	0.017
<b>Number of patients with higher SCr at follow-up (%)</b>	34(55.7)	27(44.3)
<b>Number of patients with 0 change or lower SCr at follow-up (%)</b>	27(44.3)	34(55.7)

Source: Sponsor's laboratory data (lbad01.xpt from the Sept 24, 2010 submission)

Finally, to investigate the possibility of a renal hemodynamic effect, I analyzed BUN levels. If the etiology for increased creatinine is an effect on renal hemodynamic factors, the blood urea nitrogen (BUN) levels should also have increased in patients treated with TMC278.

I analyzed the BUN data from only those patients who had one or more BUN levels at baseline and at week 48. There were 455 patients in the TMC278 arm and 461 patients in the efavirenz arm who were captured in this analysis. If patients had more than one level at either of the visits I averaged the values for the purpose of the analysis. What I found was that 241/ 455 (53.0%) of the TMC278 treated patients and 215/461 (51.8%) of the efavirenz treated patients had an elevation of their BUN when subtracting the BUN level at baseline from the BUN level at 48 weeks. The average change between BUN at baseline and 48 weeks was 0.42 for TMC278 and 0.12 for efavirenz which is small and not likely to be representative of a clinically meaningful change. For TMC278 there were 43 (9.5%) patients who had increases of BUN between baseline and week 48 of > 5 mg/dL and the highest BUN value was 10.1 mg/dL (seen in only one patient). For efavirenz, there were 38 patients (8.2%) who had increases of BUN between these baseline and week 24 of > 5 mg/dL and there were 2 patients who had an increase of BUN > 10 mg/dL (11 mg/dL and 18 were the actual values). In summary, there were no substantial changes in BUN levels during the trial in either treatment group, making it

unlikely that hemodynamic factors were playing much of a role in causing the increased creatinine values.

## APPENDIX A: Renal Failure - Related AEs

**209-0324:** a 41 y/o white male in the TMC278 treatment group with tenofovir/emtricitabine background therapy had renal failure (verbatim term: renal insufficiency) toxicity grade 3 that occurred on day 228 of treatment and lasted 78 days. The investigator considered the AE to be possibly related to drug. This AE resolved during treatment. This patient's creatinine was 0.9 mg/dL at baseline. It went to 1.2 mg/dL on day 224, and then returned to 1.0 on the next visit, approximately day 336.

**209-0387:** See Appendix B for description

**209-0881:** a 31 y/o white male in the efavirenz arm with tenofovir/emtricitabine background therapy had acute renal failure (verbatim term), toxicity grade 3 that occurred on day 77 for 6 days that resolved during treatment.

**209-0233:** a 33y/o white male in the TMC278 treatment group with tenofovir/emtricitabine background therapy had chronic renal failure (verbatim stage II chronic kidney disease, toxicity grade 2 (moderate) that occurred on day 288 of treatment and lasted 209 days. No follow-up report was provided. The sponsor did not think that this AE was related to drug. The patient's creatinine went from 1.1mg/dL at screening to 1.4 mg/dL at around day 288, increased to 1.5 mg/dL and then came down to 1.2 mg/dL.

**215-0051:** 38 y/o African American female in the efavirenz arm with abacavir/lamivudine background therapy had acute renal failure (verbatim term), which was considered a serious AE, toxicity grade 4 (potentially life-threatening) that occurred on day 183, lasted 3 days and resolved on treatment.

**215-0303:** unknown age African American male in the TMC278 treatment group with tenofovir/emtricitabine background therapy had two episodes of acute renal failure (verbatim term), which were considered serious AEs, toxicity grade 2 (moderate), one on day 351 that lasted 7 days and one on day 371 that lasted 18 days and resolved on treatment. The sponsor did not think that the SAEs were related to drug. The record of serum creatinines suggested that the patient had an earlier episode of increased creatinine. It went from 0.8 mg/dL at baseline to 1.1 mg/dL on day 84, then after coming down to baseline at around day 280, it went to 0.9 mg/dL on day 336. The next creatinine result was 1.2 mg/dL on day 420 and this was the last reading. It is unclear from the records why there is this great of a discrepancy between the report of AEs and the serum creatinine course. There was a 1.5 fold increase in serum creatinine for this patient during treatment. A narrative from the 4-month safety update explained that the patient had prerenal factors that probably accounted for the increased serum creatinine.

**215-0643:** 26 y/o white male in the efavirenz treatment group with tenofovir/emtricitabine background therapy had acute renal insufficiency (verbatim term), toxicity grade 4(potentially life-threatening) that occurred on day 84 and lasted 21

days. The investigator thought that the episode was very likely related to drug and drug was withdrawn temporarily followed by recovery.

## **APPENDIX B: Glomerulonephritis**

**209-0387:** 32 year old white male in the TMC278 treatment group with tenofovir/emtricitabine background therapy developed membranous glomerulonephritis. Membranous glomerulonephritis is an immunologically mediated disease in which deposits of IgG and complement collect in the basement membrane. It can be idiopathic or secondary to drugs, and other diseases and conditions such as HIV-1. The event was considered a serious AE with a toxicity grade of 2 (moderate) and occurred on day 332 of treatment. TMC278 was permanently discontinued. The AE lasted at least 34 days after drug was discontinued (monitoring stopped at day 34). The event was considered to be possibly related to study medication. A biopsy was done. The narrative explained that the biopsy was compatible with drug-induced glomerulonephritis. After TMC278 was withdrawn, glomerulonephritis persisted. While the sponsor decided that the relationship was doubtful at this later point, a relationship between TMC278 and this patient's glomerulonephritis cannot be ruled out.

**209-0142:** a 45 y/o white male in the TMC278 treatment group with tenofovir/emtricitabine background therapy developed mesangioproliferative glomerulonephritis. Mesangioproliferative glomerulonephritis is characterized by glomeruli which are enlarged as a result of proliferation of mesangial cells and irregular thickening of the capillary walls. The event was considered to be not serious with a toxicity grade of 3 (severe). It occurred on day 174, lasted 342 days (the entire time that the patient stayed on drug after AE occurrence) and did not resolve on treatment. The patient continued on treatment and the causal relationship between TMC278 and the event was considered by the investigator to be doubtful. The case report on this patient was not included with the submission. Since this event occurred during treatment, it is reasonable to conclude that the event may possibly have been related to TMC278.

<sup>1</sup> Serdar MA, Kurt I, Ozcelik F, Urhan M, et al, A practical approach to glomerular filtration rate measurements: creatinine clearance estimation using cimetidine, Annals of Clinical and Laboratory Science, Vol 31, no. 3, 2001.

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MELANIE J BLANK  
03/14/2011

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03/14/2011

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03/14/2011

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>NDA</b>	202022
<b>Generic Name</b>	TMC278 (Rilpivirine)
<b>Sponsor</b>	Tibotec Pharmaceuticals Ltd.
<b>Indication</b>	HIV-1 Infection
<b>Dosage Form</b>	Oral Tablets
<b>Drug Class</b>	Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)
<b>Therapeutic Dosing Regimen</b>	25 mg q.d.; 75 mg q.d. and 300 mg q.d.
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not Established
<b>Submission Number and Date</b>	SDN 001, 23-Jul-2010
<b>Review Division</b>	DAVP

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

TMC278 prolongs QTc interval in a dose/exposure-dependent manner. The QT effect following the administration of TMC278 was evaluated in three thorough QT studies (Study TMC278-TiDP6-C131, Study TMC278-TiDP6-C151, and Study TMC278-TiDP6-C152). The overall findings were summarized as follows:

- As shown in Study TMC278-TiDP6-C151, no significant QTc prolongation effect of 25 mg TMC 278 was detected. The largest upper bound of the two-sided 90% confidence interval (CI) for the mean difference between TMC278 (25 mg) and placebo was below 10 ms, the threshold for regulatory concern, as described in ICH E14 guidelines. The moxifloxacin profile, with ECGs collected up to 4 hours post-dose, is displayed in Figure 10. In general, we do not claim that assay sensitivity is established in trials with insufficient sampling time points (e.g., <24 hours post-dose) to verify ECG profile in moxifloxacin arm. However, we accepted the negative results from Study TMC278-TiDP6-C151 for the following reasons: 1.) The lower 90% two-sided confidence interval for the maximum QT effect in moxifloxacin arm in Study TMC278-TiDP6-C151 exceeded 5 ms, which provided some assurance about the ECG results and 2.) The findings from Study TMC278-TiDP6-C152, another thorough QT study with assay sensitivity established (see section 3.4.5 & Figure 11), confirmed the findings in Study TMC278-TiDP6-C151. Study TMC278-TiDP6-C151 was a randomized, double-blind, double-dummy, placebo-controlled and positive-controlled, parallel trial. A total of 36 healthy subjects received TMC278 25 mg q.d. for 11 days, placebo,

and a single oral dose of 400 mg moxifloxacin. The study results were summarized in Table 1.

- Significant QTc prolongation effect of 75 mg and 300 mg TMC 278 was detected in Study TMC278-TiDP6-C131. The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC 278 25 mg and placebo, and between TMC 278 300 mg and placebo were 14 and 27 ms observed at 16 and 4.5 hours post-dose, respectively. In addition, a significant concentration-QT relationship was established using data from Study TMC278-TiDP6-C131. QT-IRT accepts positive results even though assay sensitivity is not established in the trial (Figure 9). Study TMC278-TiDP6-C131 was a phase I, double-blind, double-dummy, randomized, 3-way crossover, placebo-controlled and positive-controlled trial to evaluate QT effect of TMC278. A total of 41 healthy subjects received TMC278 75 mg, 300 mg q.d. for 11 days, and a single oral dose of moxifloxacin. The study results were summarized in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for TMC278 (75 mg, 300 mg, and 25 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Hour	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
TMC278 75 mg (Study TMC278-TiDP6-C131)	16	10.1	(5.7, 14.5)
TMC278 300 mg (Study TMC278-TiDP6-C131)	4.5	22.5	(17.9, 27.1)
TMC278 25 mg (Study TMC278-TiDP6-C151)	6	2.0	(-3.2, 7.2)
Moxifloxacin 400 mg* (75 mg and 300 mg) (Study TMC278-TiDP6-C131)	3.5	2.4	(-0.8, 5.6)
Moxifloxacin 400 mg* (25 mg) (Study TMC278-TiDP6-C151)	3	13.1	(8.3, 17.9)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 2.1 ms (75 mg and 300 mg) and 6.4 ms (25 mg).

The supratherapeutic doses, 300 mg and 75 mg, produces mean  $C_{\text{max}}$  values of 7.3- and 2.8-fold higher than the mean  $C_{\text{max}}$  for the therapeutic dose (25 mg). The most pronounced exposure increase due to drug-drug interaction was observed when TMC278 was coadministered with darunavir/ritonavir (800/100 mg). The maximum exposure (i.e.,  $C_{\text{max}}$ ) was increased by 1.8-fold. Only a modest increase (<50%) in  $C_{\text{max}}$  was observed in patients with mild hepatic impairment and no study was conducted in patients with severe hepatic impairment. Therefore, the maximum exposure at the dose of 75 mg observed from Study 131 was above those for the predicted worst case scenario.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

1. A delayed QTc interval increase following long-term (1 to 3 years) treatment of TMC 278 (25 mg q.d.) was observed in the phase 2B and phase 3 clinical trials (Section 3.4 ). Of note, the increases in QT interval in TMC 278 treated groups were similar with those observed in the control groups.
  - Given the apparent weak potency for hERG trafficking effects observed with TMC278, it seems unlikely that this contributed significantly to the delayed QT effects seen clinically (Section 3.3.).
  - To further explore the delayed increase in QTcF over time observed in the Phase 2B and 3 trials that was observed in both the TMC278 and EFV arms,
    - The Package Inserts for AZT/3TC, TDF/FTC, EFV and abacavir were reviewed. No QT or ECG effects are reported.
    - An MGPS datamining analysis of AERs was conducted for AEs related to QT prolongation. There are reports of TdP and sudden death for all the drugs used for background therapy and EFV. However, the incidence was similar to the background rate in MGPS database. In addition, several of the TdP cases are duplicates or heavily confounded (see Section 5.4.4 for details).
    - Based on the results of Study C-152, mean effects on the QTc interval over the regulatory threshold due to EFV cannot be excluded.
  - It is possible that the QT effects seen in the phase 3 trials are due to the background therapies or active comparator. These results are similar to our experience with palonosetron (NDA 21372). The TQT study results for palonosetron were below the regulatory threshold. However, in a phase 3 study submitted to IND 68213 evaluating a sustained release formulation of granisetron (C2006-01), QT prolongation was observed in both the granisetron and palonosetron arms. Subjects received chemotherapy 30 – 60 minutes after APF530 or palonosetron administration, thereby confounding the results.
  - Another plausible explanation to this observation is additive effects of multiple drugs with small effect size on QTc intervals.
2. It may be worthwhile to further quantify QTc effects of EFV and all background treatments used in these trials. As mentioned earlier, although confounded, there are reports of TdP and sudden death for all these drugs.

## 2 PROPOSED LABEL

### 2.1 SPONSOR PROPOSED LABEL:

#### Section 7: Drug-Drug Interaction

##### QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the electrocardiogram. 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 Clinical Pharmacology (12.2)]. TRADE NAME™ should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes.

### Section 10: OVERDOSAGE

There is no specific antidote for overdose with TRADE NAME™. Human experience of overdose with TRADE NAME™ is limited. Treatment of overdose with TRADE NAME™ consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

*Reviewer's Comment: Acceptable*

### Section 12.2 Pharmacodynamics

#### Effects on Electrocardiogram

The effect of TRADE NAME™ at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. (b) (4)

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of TRADE NAME™ were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 10.7 (15.3) and 23.3 (28.4) milliseconds, respectively. Steady-state administration of TRADE NAME™ 75 mg once daily and 300 mg once daily resulted in a mean steady state C<sub>max</sub> approximately 2.6-fold and 6.7-fold, respectively, higher than the mean C<sub>max</sub> observed with the recommended 25 mg once daily dose of TRADE NAME™.

### 2.2 QT-IRT'S LABELING RECOMMENDATION

QT-IRT recommendations for labeling (Section 12.2) are suggestions only; we defer final decisions related to labeling to the review division:

(b) (4)

### 3 BACKGROUND

#### 3.1 PRODUCT INFORMATION

TMC278 (rilpivirine hydrochloride, RPV), a diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1) under clinical development by Tibotec Inc. The sponsor is seeking approval for TMC278, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients.

#### 3.2 MARKET APPROVAL STATUS

TMC278 is not approved for marketing in any country.

#### 3.3 PRECLINICAL INFORMATION

*Source: eCTD 2.6.3.4-Tabulated Safety Pharmacology Summary*

TMC278 was evaluated for cardiovascular safety in vitro and in vivo. TMC278 tested positive for inhibition of several repolarizing cardiac ionic currents, i.e., hERG, IKs and Ito. Potencies were estimated as <1 µM for hERG (33% inhibition at 0.3 µM and 80% at 3 µM), 3.1 µM for IKs, and >1 µM for Ito (36% inhibition at 1 µM). TMC278 also tested positive for inhibition of hERG channel trafficking, inhibiting channel expression by 29% at 10 µM and 36% at 30 µM. Given the apparent weak potency for trafficking effects, it seems unlikely that this contributed significantly to the delayed QT effects seen clinically.

TMC278 tested negative for QT prolongation in several in vivo canine models. TMC278 also tested negative for QT effects in conscious, telemetered guinea pigs, with drug given daily for 16 days – hence delayed effects seen clinically were not reproduced in this

model. It should be noted that assay sensitivity was not determined for any of the in vivo models evaluated.

Proarrhythmia potential was evaluated in an acute in vitro study using an isolated arterially perfused rabbit ventricular wedge preparation. TMC278 tested negative – however, assay sensitivity was not described and this was an acute study.

#### 2.6.3.4. Safety Pharmacology

Test Article: rilpivirine

Type of Study Organ Systems Evaluated	In vitro System or Species/Strain	Route/ Method of Administration	Gender and no. per Group	Dose (Conc.) (Controls)	Noteworthy Findings	GLP Compliance	Study Number
<i>In Vitro Tests</i>							
Cardiovascular safety (cardiac membrane potassium current)	I <sub>Kr</sub> in transfected CHO cells expressing hERG	In vitro	NA	0.1, 0.3, 3 µM (0.037, 0.111, 1.11 µg/mL) (Positive controls: Astemizole, Terfenadine) (Vehicle: 0.1% DMSO in aqueous buffer)	<b>0.1 µM:</b> 10% inhibition <b>0.3 µM:</b> 33% inhibition <b>3 µM:</b> 80% inhibition	No	TMC278-CPF730
Cardiovascular safety (cardiac membrane potassium current)	I <sub>Ks</sub> in transfected CHO cells expressing KvLQT1/minK	In vitro	NA	0.3, 1, 3, 10 µM (0.111, 0.370, 1.11, 3.7 µg/mL) (Positive control: HMR1556) (Vehicle: 0.3% DMSO in aqueous buffer)	<b>1 µM:</b> 17% inhibition <b>3 µM:</b> 47% inhibition <b>10 µM:</b> 73% inhibition  IC <sub>50</sub> : 3.1 µM (1.15 µg/mL)	No	TMC278-NC342

I<sub>Kr</sub> = rapidly activating rectifying potassium current; I<sub>Ks</sub> = Slowly activating rectifying potassium current, CHO: Chinese hamster ovary, DMSO = dimethylsulfoxide, hERG = human-ether-à-go-go related gene, NA = not applicable, IC<sub>50</sub>: median inhibitory concentration

(Continued)

Type of Study Organ Systems Evaluated	In vitro System or Species/Strain	Route/ Method of Administration	Gender and no. per Group	Dose (Conc.) (Controls)	Noteworthy Findings	GLP Compliance	Study Number
<i>In Vitro Tests (continued)</i>							
Cardiovascular safety (cardiac membrane potassium current)	Direct blocking of wild type hERG(-WT) channel and blocking of trafficking of hERG channel on the basis of overexpression at cell membrane of chaperone-resistant single mutant hERG-SM channel over hERG-WT in transfected HEK293 cells	In vitro	NA	1, 10, 30 µM (0.37, 3.7, 11.1 µg/mL) (Positive controls: Astemizole, Geldanamycin) (Vehicle: 0.1% DMSO in aqueous buffer)	<b>1 µM:</b> 146% expression hERG-SM <b>10 µM:</b> 155% expression hERG-SM 29% block hERG-WT <b>30 µM:</b> 213% expression hERG-SM 36% block hERG-WT	No	TMC278-NC330
Cardiovascular safety (cardiac action potential)	Isolated Guinea pig right atrium	In vitro	NA	0.01, 0.03, 0.1, 1, 3, 10 µM (0.004, 0.011, 0.037, 0.37, 1.11, 3.7 µg/mL) (Vehicle: 0.01 – 10% DMSO in aqueous buffer)	<b>1 µM:</b> RC 86% of baseline <b>3 µM:</b> RC 72% of baseline <b>10 µM:</b> RC 44% of baseline No effects on force of contraction compared to vehicle over the whole conc. range. No effects on ERP compared to vehicle at 0.1 and 10 µM	No	TMC278-N168376
Cardiovascular safety (cardiac action potential)	Isolated arterially perfused rabbit left ventricular wedge	In vitro	NA	0.01, 0.1, 1, 10 µM (0.004, 0.037, 0.37, 3.7 µg/mL) (Vehicle: 0.1% DMSO in aqueous buffer)	<b>1 µM:</b> QT-interval 106% of baseline <b>10 µM:</b> QT-interval 109% of baseline. TdP score 0.5. No EADs, TdP, VT, VF, or in-excitability over the whole conc. range	No	TMC278-NC341

hERG = human-ether-à-go-go related gene, hERG-WT = wild type hERG channel, hERG-SM = chaperone resistant single mutant hERG channel, DMSO = dimethylsulfoxide, HEK293 = human embryonic kidney cell line, NA = not applicable; RC = rate of spontaneous contraction, ERP = effective refractory period = maximal frequency of stimulations not followed by contraction, QT-interval = time between peak Q wave and end T wave, EAD = early afterdepolarization, TdP = torsades des pointes, VT = ventricular tachycardia, VF = ventricular fibrillation

(Continued)

Cardiovascular and pulmonary safety and locomotor activity	Conscious telemetered dog/beagle	Oral/gavage Single dose	4M	20, 80, 160 mg/kg (vehicle: PEG400)	No effects on cardiac hemodynamic, electrophysiological, respiratory, or locomotor activity parameters.	Yes	TMC278-Exp5555
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GLP = good laboratory practices, F = female, M = male, PEG = polyethylene glycol, HPMC = hydroxypropylmethylcellulose, HR = heart rate, MABP = mean arterial blood pressure, ECG = electrocardiogram, BT = body temperature, SVR = systemic vascular resistance, PVR = peripheral vascular resistance, BL = baseline, C<sub>max</sub> = maximal concentration

### 3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety (eCTD 2.7.4) and Module 5.4-White Paper on QT-prolonging and proarrhythmic potentials of TMC278 (rilpivirine), 18 June 2010.

At the time of the cut-off date of the Phase III Week 48 analysis, the clinical safety database consisted of 1736 HIV-1 infected subjects participating in the Phase III trials and the Phase IIb trial, 965 of whom received TMC278.

In total, 5 subjects died during the course of the 2 Phase III trials, 1 in the TMC278 group in trial C215 (due to bronchopneumonia) and 4 in the control group (1 in Trial C209 and 3 in Trial C215).

The potential of TMC278 to influence cardiac repolarization has also been explored in one large Phase IIb dose-finding trial and 2 pivotal Phase III safety and efficacy trials. These are:

- Trial TMC278-C204 (C204) (TMC278 doses of 25 mg, 75 mg and 150 mg q.d.);
- Trial TMC278-TiDP6-C209 (C209) (TMC278 dose of 25 mg q.d.);
- Trial TMC278-TiDP6-C215 (C215) (TMC278 dose of 25 mg q.d.).

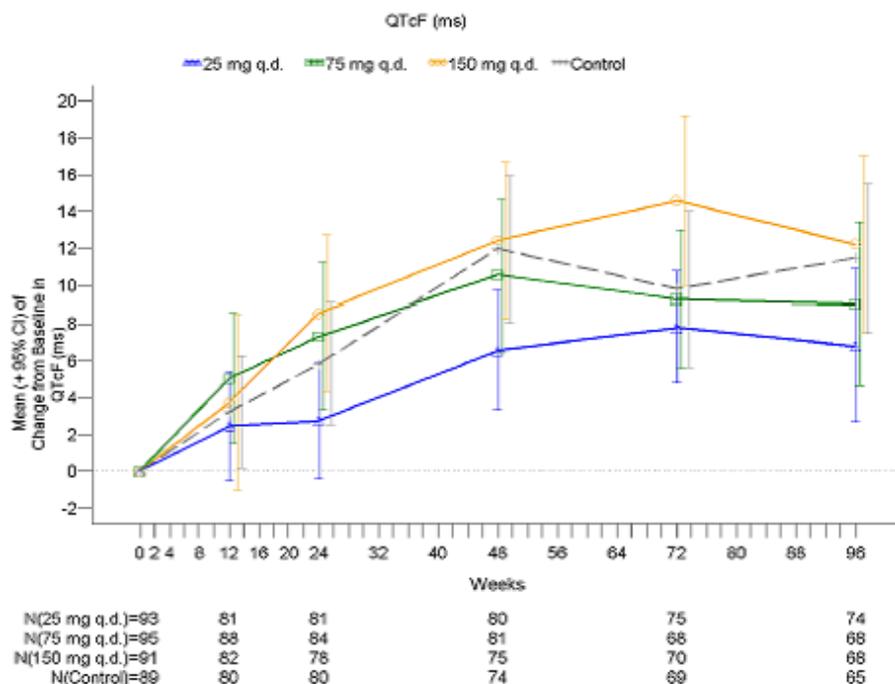
*Based on the efficacy, safety, pharmacokinetics, and pharmacokinetic/pharmacodynamic assessments obtained from the primary analysis (Week 48 data) of the Phase IIb trial (TMC278-C204), the dose of TMC278 75 mg q.d. was initially selected for further development. However, a change in TMC278 dose from 75 mg q.d. to 25 mg q.d. was implemented prior to the start of the Phase III trials. This change in dose was prompted by data that became available from thorough QT trial, TMC278-TiDP6-C131. The choice of 25 mg q.d. as the dose for further development was also supported by Week 96 data obtained from the C204 Phase IIb trial.*

### **3.4.1 ECG DATA FROM TRIAL C204 AT WEEK 96**

Trial C204 is an ongoing Phase II, randomized, active controlled, partially blinded trial. The aim of the dose-ranging part of this trial was to evaluate the efficacy, safety, and tolerability of 3 doses (25 mg q.d., 75 mg q.d., and 150 mg q.d.) of TMC278, compared to EFV (control group), when added to either Combivir (zidovudine[AZT]/lamivudine[3TC]) or Truvada (tenofovir disoproxil fumarate [TDF]/emtricitabine [FTC]). The duration of the dose-ranging part of the trial was 96 weeks and ECG data are available to Week 96.

As shown in the figure below, there was an increase of QTcF at Week 12 and Week 24 for all the TMC278 dose groups, which showed a trend to further increase at Week 48 before stabilizing by Week 96. There was a trend to dose relationship. In the control group, a similar change was observed as in the highest TMC278 dose groups. Categorical changes in QTcF for the TMC278 groups compared to EFV are shown in the sponsor's Table 26. Overall, while an absolute QTcF over 500 ms was only reported with EFV, categorical changes were similar for EFV and 75 mg q.d. of TMC278.

**Figure 4: Mean (95% CI) Change From Baseline in QTcF (ms) in Trial C204**



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Source: Module 5.4, White Paper on QT-prolonging and proarrhythmic potentials of TMC278 (rilpivirine), 18 June 2010

Mean QTcF interval increased from baseline to Week 48, remained stable up to Week 144, but showed a further increase from baseline at Week 192, when maximum mean increases from baseline of 16.4 ms and 14.4 ms were observed in the combined TMC278 and control groups, respectively. Overall, similar proportions of subjects in the combined TMC278 and control groups had a QTcF interval abnormalities or an abnormal increase in QTcF interval during the trial.

**Table 26: Number (and %) of Subjects With Specified Categorical Responses in Trial C204**

Treatment	TMC278			EFV (control)
	25 mg q.d.	75 mg q.d.	150 mg q.d.	600 mg q.d.
Dose	25 mg q.d.	75 mg q.d.	150 mg q.d.	600 mg q.d.
N =	87	93	83	85
<b>Absolute QTcF intervals</b>				
]450-480] ms	1 (1.1%)	1 (1.1%)	4 (4.8%)	3 (3.5%)
]481-500] ms	1 (1.1%)	1 (1.1%)	1 (1.2%)	1 (1.2%)
> 500 ms	0	0	0	1 (1.2%)
<b>Change from baseline resulting in QTcF interval &gt; 450 ms</b>				
Δ 30-60 ms	0	0	3 (3.6%)	1 (1.2%)
Δ > 60 ms	0	2 (2.2%)	2 (2.4%)	1 (1.2%)

Source: Module 5.4, White Paper on QT-prolonging and pro-arrhythmic potentials of TMC278 (rilpivirine), 18 June 2010

In the Week 96 and Week 192 analysis, the sponsor reports greater increases in QTcF interval were seen in AZT/3TC-treated subjects than in TDF/FTC-treated subjects, regardless of TMC278 dose group or control group.

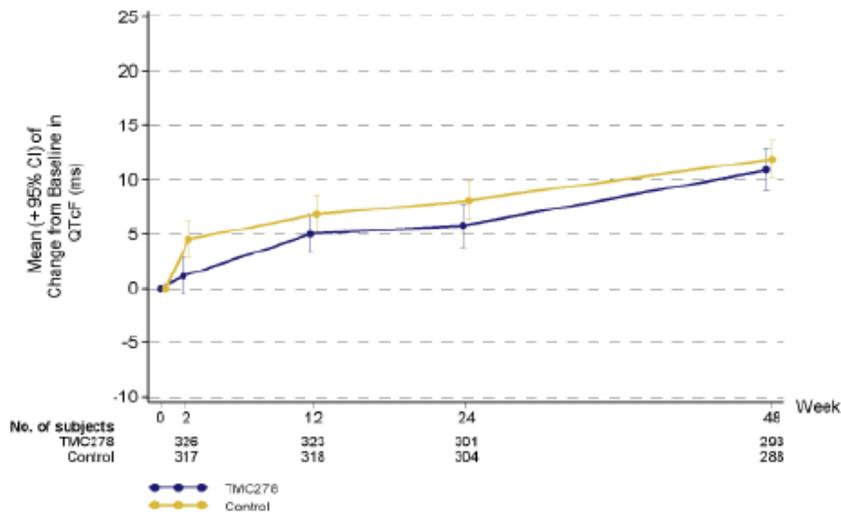
In the TMC278 dose groups and control group, for both male and female subgroups, QTcF interval increased over time, with a greater increase in female subjects seen for all treatment groups compared to male subjects, specifically for the TMC278 75 mg q.d. and 150 mg q.d. groups; the control group showed a similar pattern as the TMC278 75 mg q.d. group.

There were no cardiac AEs indicative of a ventricular tachyarrhythmia reported during the trial.

### 3.4.2 ECG DATA FROM TRIAL C209 AT WEEK 48

This is a 96-week Phase III trial to assess the efficacy, safety and tolerability of TMC278 given at a dose of 25 mg q.d., compared to that observed with EFV 600 mg q.d., each co-administered with TDF/FTC backbone. ECG data are available to Week 48. Exclusion criteria included (QTcF >450 ms). Six hundred and ninety HIV-1 infected subjects who have never received anti-retroviral (ARV) therapy were randomized to one of 2 treatment arms. ECG readings were performed at screening and at weeks 2, 12, 24, 48, 72 and 96 and read by a central ECG laboratory. Mean and categorical changes in QTcF in both groups up to week 48 are as shown below.

**Figure 5: Mean (95% CI) Change From Baseline in QTcF (ms) in Trial C209**



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**Table 28: Overall QTcF Interval Changes in Trial C209**

	TMC278 N = 344	Control N = 338
	<b>Mean changes from baseline</b>	
Mean baseline (95% CI) ms	389.7 (387.74; 391.66)	387.9 (385.85; 389.98)
Maximum increase from baseline (95% CI) ms	16.7 (15.04; 18.42)	18.8 (17.29; 20.33)
	<b>Worst treatment-emergent abnormalities</b>	
QTcF intervals of 450 – 480 ms 481 – 500 ms	3 (0.9%) 1 (0.3%)*	2 (0.6%) 0
QTcF interval increase of 30-60 ms > 61 ms	57 (16.6%) 4 (1.2%)	64 (18.9%) 2 (0.6%)

\* Actual value in this subject was 496 ms

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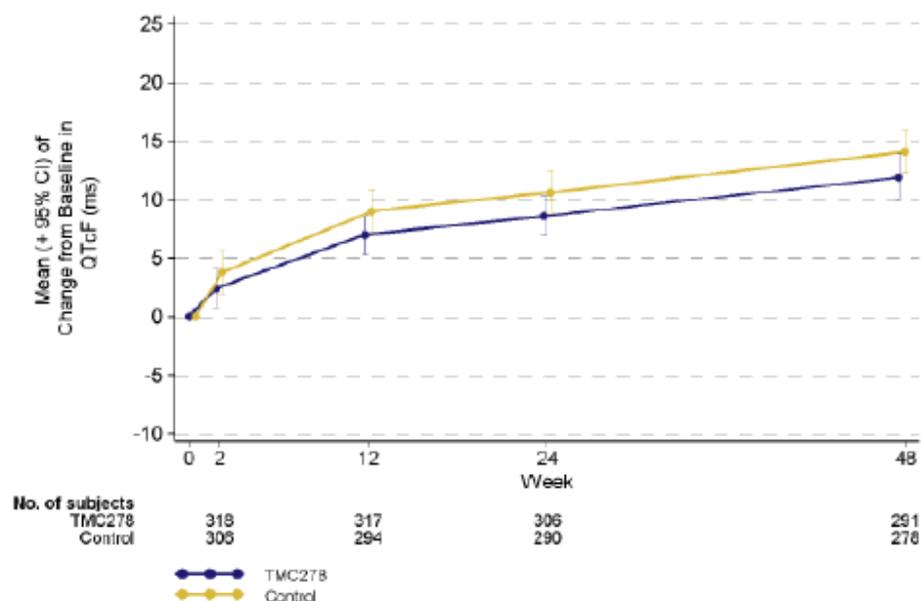
Source: Module 5.4, White Paper on QT-prolonging and proarrhythmic potentials of TMC278 (rilpivirine), 18 June 2010

### 3.4.3 ECG DATA FROM TRIAL C215 AT WEEK 48:

This is a 96-week Phase III trial to assess the efficacy, safety and tolerability of TMC278 given at a dose of 25 mg q.d., compared to that observed with EFV 600 mg q.d., each co-administered in combination with a background regimen of abacavir (ABC)/3TC, AZT/3TC or TDF/FTC. ECG data are available to Week 48. Six hundred and seventy-eight HIV-1 infected subjects who have never received ARV therapy were randomized to one of the 2 treatment arms. ECG readings were performed at screening and at Weeks 2, 12, 24, 48, 72 and 96 and read by central ECG laboratory.

The mean change in QTcF interval over the trial period is shown in Figure 6.

**Figure 6: Mean (95% CI) Change From Baseline in QTcF (ms) in Trial C215**



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**Table 30: Overall QTcF Interval Changes in Trial C215**

	TMC278 N = 338	Control N = 319
<b>Mean changes from baseline</b>		
Mean baseline (95% CI) ms	387.8 (385.90; 389.72)	389.2 (386.94; 391.38)
Maximum increase from baseline (95% CI) ms	19.1 (17.59; 20.69)	19.6 (17.93; 21.22)
<b>Worst treatment-emergent abnormalities</b>		
QTcF intervals of		
450 – 480 ms	7 (2.1%)	12 (3.7%)
481 – 500 ms	1 (0.3%)*	1 (0.3%)**
QTcF interval increase of		
30-60 ms	70 (20.7%)	67 (21.0%)
> 61 ms	4 (1.2%)	4 (1.3%)

\* Actual value in this subject was 486 ms; \*\* Actual value in this subject was 488 ms

Source: Module 5.4, White Paper on QT-prolonging and proarrhythmic potentials of TMC278 (rilpivirine), 18 June 2010

In the TMC278 group, 1 subject developed loss of consciousness but none reported syncope. In contrast, in the control group, none reported loss of consciousness but 2 had syncope. There were no other cardiovascular AEs suggestive of ventricular tachyarrhythmia.

*Reviewer's Comments:* The data were similar in the two phase III trials in terms of mean QTcF change over time and categorical changes. In the pooled phase 3 analysis, the mean maximum change from baseline in QTcF interval in the overall population was +17.9 ms in the TMC278 group and +19.2 ms in the control group. As observed in the phase 2b trial, The QTcF interval increase was lower in the TDF/FTC subgroup than in the AZT/3TC subgroup, with a QTcF interval increase at Week 48 of +10.6 ms and +12.1

ms in the TMC278 group, and +12.1 ms and +17.8 ms and in the control group, respectively

The mean increase from baseline in QTcF interval at Week 48 was smaller in the Phase IIb trials (N = 80, +6.5 ms) than in the Phase III trial (N = 584, +11.4 ms) in the TMC278 2- mg q.d. groups.

### 3.4.4 Events of Interest potentially related to QTc interval prolongation

For the Phase III pooled analysis and the Phase IIb trial, a list of events that could potentially be related to QTc interval prolongation and that originates from a “Standardized MedDRA Query (SMQ)” named “Torsade de Pointes/QT prolongation” was used to identify such events. The incidence of events of interest potentially related to QTc interval prolongation is summarized in sponsor’s Table 37 below.

**Table 37: Events of Interest Potentially Related to QTc Interval Prolongation, Regardless of Severity and Causality (Phase III Week 48 Pooled Analysis)**

System Organ Class Preferred Term, n (%)	C209		C215		Pooled	
	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
Nervous system disorders	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.3)	4 (0.6)
Loss of consciousness	0	0	1 (0.3)	0	1 (0.1)	0
Syncope	1 (0.3)	2 (0.6)	0	2 (0.6)	1 (0.1)	4 (0.6)
Investigations	0	0	1 (0.3)	4 (1.2)	1 (0.1)	4 (0.6)
ECG QT prolonged	0	0	1 (0.3)	4 (1.2)	1 (0.1)	4 (0.6)

N = number of subjects per treatment group; n = number of observations.

Source: [Module 5.3.5.1/TMC278-C209-W48-Anal-Saf-AE/Display SAF.3](#), [Module 5.3.5.1/TMC278-C215-W48-Anal-Saf-AE/Display SAF.3](#) and [Module 5.3.5.3/TMC278-C904-Anal-Saf-AE/Display SAF.5](#).

Source: *Summary of Clinical Safety*

### 3.4.5 TRIAL C152 (25-MG DOSE AND 600-MG EFAVIRENZ)

In addition to trials TMC278-TiDP6-C131 and TMC278-TiDP6-C151, the sponsor completed a third TQT study. The QT-IRT did not perform an independent analysis of this study because the trial results are similar to Trial TMC278-TiDP6-C151. This was a Phase I, double-blind, double-dummy, randomized, placebo-controlled and active controlled, multiple dose (11 days) trial in healthy volunteers to evaluate the effects of TMC278 25 mg q.d. and EFV 600 mg q.d. at steady state on the QT/QTc interval.

The trial was conducted in 2 panels: TMC278 panel and EFV panel. A crossover design was used within each panel. A single oral dose of 400-mg moxifloxacin, administered to subjects in the TMC 278 panel, was used as a positive control. Each subject in TMC278 panel received the following 3 sessions of treatment in a random order.

- A: TMC278 25 mg q.d. on Days 1-11 and moxifloxacin placebo q.d. on Day 11.
- B: TMC278 placebo on Days 1-11 and moxifloxacin placebo q.d. on Day 11.
- C: TMC278 placebo on Days 1-11 and moxifloxacin 400 mg q.d. on Day 11.

The sampling schedule for pharmacokinetic and ECG assessments were similar to that used in the studies TMC278-TiDP6-C131 and TMC278-TiDP6-C151. The sponsor’s results were as follows.

**Table 5: Time-matched Difference Versus Placebo in QTcF Interval on Day 11 at Relevant\* Timepoints for TMC278 25 mg q.d., EFV 600 mg q.d. and Moxifloxacin**

	TMC278 Panel				EFV Panel	
	TMC278 25 mg		Moxifloxacin		EFV 600 mg	
	n	Mean (SE) [90% CI]	n	Mean (SE) [97.5% CI]	n	Mean (SE) [90% CI]
Day 11, 5 hours	56	-2.9 (1.8) [6.0;0.2]	55	9.5 (1.5) [6.1;13.0]	50	4.7 (2.0) [1.3;8.1]
Day 11, 6 hours	54	0.0 (2.0) [-3.3;3.3]	55	8.0 (2.2) [3.0;13.0]	49	5.2 (1.9) [2.0;8.4]
Day 11, 12 hours	55	2.0 (1.8) [-1.0;5.0]	54	7.7 (1.8) [3.7;11.7]	50	3.0 (1.7) [0.1;5.9]

\*For TMC278 and EFV, the timepoint with the highest upper limit of the two-sided 90% CI, and for moxifloxacin the predefined timepoint with the highest lower limit of the two-sided 97.5% CI is shown.

Source: [Display SAF.22](#).

Source: Table 5, CSR for TMC278-TiDP6-C152

*Reviewer's Comments: The QT-IRT did not perform an independent analysis for this study. Similar pharmacokinetic and QTcF profiles of TMC278 were observed as compared to Study C151. Assay sensitivity was established in TMC278 panel. Results for this study confirmed that the QTc interval change (together with the upper 95% one-sided confidence interval) following standard therapeutic dose of 25 mg q.d., was below the regulatory threshold. However moxifloxacin was not included in the EFV panel. Therefore QT effects above the regulatory threshold with EFV 600 mg are possible.*

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of TMC278's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The sponsor performed 3 thorough QT studies (Study TMC278-TiDP6-C131, Study TMC278-TiDP6-C 151, and Study TMC278-TiDP6-C152). QT-IRT reviewed the protocol for Study TMC278-TiDP6-131 (Referred as Study C131) prior to conducting the study under IND 67699. The other 2 thorough QT studies were designed similarly to Study C131 with the focus on different dose levels. The sponsor submitted the study reports for all 3 studies, including electronic datasets and waveforms to the ECG warehouse. Because Study TMC278-TiDP6-151 (Referred as C151) and Study TMC278-TiDP6-152 (Referred as C-152) provide similar information on the QT effect of TMC278, QT-IRT's review focused on Study C131 and Study C151. The results from Study C152 were summarized in the previous clinical experience section (Section 3.4).

### 4.2 TQT STUDY

#### 4.2.1 Title

**C131 Title:**

A Phase I, double-blind, double-dummy, randomized, placebo controlled and active controlled, 3-way crossover trial to evaluate the effect of TMC278 after a single dose and at steady-state on the QT/QTc interval in healthy subjects.

**C151 Title:**

A Phase I, double-blind, double-dummy, randomized, placebo controlled and positive controlled, parallel trial to explore the effect of TMC278 25 mg q.d. at steady-state on the QT/QTc interval in healthy subjects.

**4.2.2 Protocol Number**

TMC278-TiDP6-C131

TMC278-TiDP6-C151

**4.2.3 Study Dates**

**C131:** 20-Apr-2007 to 24-Sep-2007

**C151:** 31-Jan-2008 to 15-Apr-2008

**4.2.4 Objectives**

**C131 Objectives:**

The primary objective of the trial was to evaluate the effect of single dose and steady-state administration of TMC278 versus placebo on the QT/QTc interval with 2 dose regimens, 75 mg q.d. and 300 mg q.d., in healthy subjects.

The secondary objectives were:

- To evaluate and compare the single dose and steady-state pharmacokinetics of 2 dose regimens of TMC278, 75 mg q.d. and 300 mg q.d., in healthy subjects;
- To explore the concentration-effect relationship for TMC278 on the QT/QTc interval in healthy subjects;
- To evaluate trial sensitivity (i.e., evaluate the effect of a positive control, a single 400 mg dose of moxifloxacin, on the QT/QTc interval in healthy subjects);
- To evaluate the safety and tolerability of 2 dose regimens of TMC278, 75 mg q.d. and 300 mg q.d., administered for 11 days in healthy subjects.

**C151 Objectives:**

The primary objective of the present trial was to explore the effect at steady-state of the administration of TMC278 25 mg q.d. versus reference (baseline, Day -1) on the QT/QTc interval in healthy subjects.

Secondary objectives were:

- To explore the effect of the administration at steady-state of TMC278 25 mg q.d. versus placebo on the QT/QTc interval in healthy subjects;
- To evaluate the steady-state pharmacokinetics of TMC278 25 mg q.d. in healthy subjects;
- To explore the concentration-effect relationship of TMC278 25 mg q.d. on the QT/QTc interval in healthy subjects;

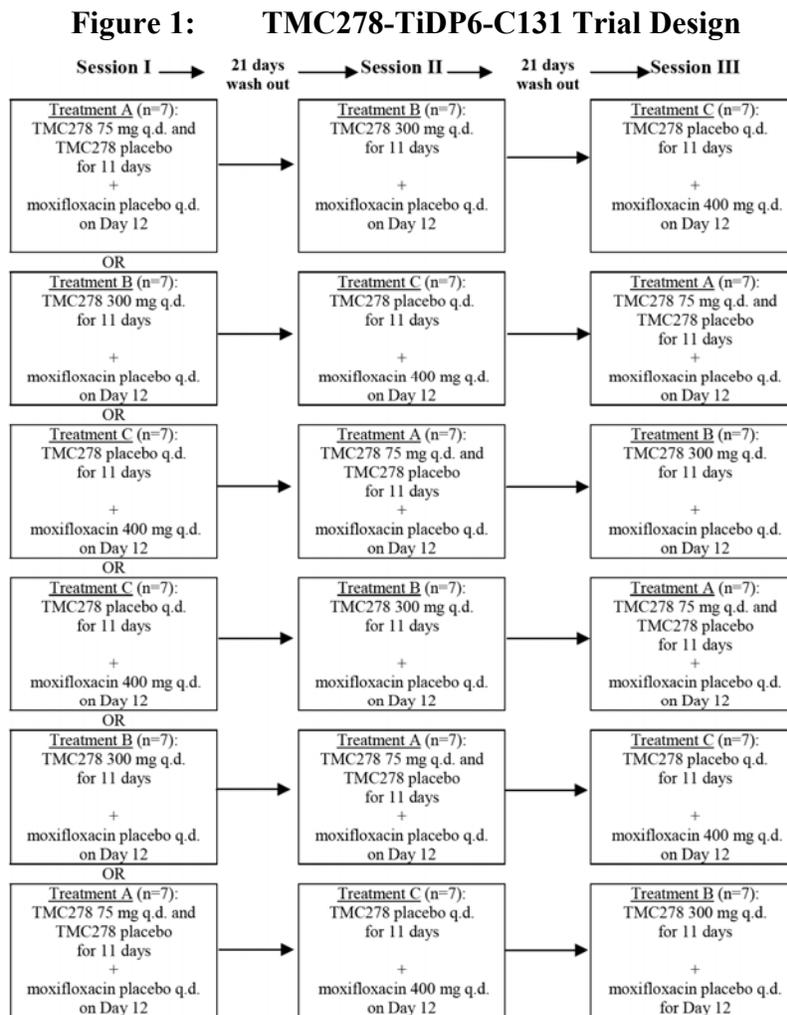
- To evaluate trial sensitivity (i.e., evaluate the effect of a positive control, a single 400 mg dose of moxifloxacin, on the QT/QTc interval in healthy subjects);
- To evaluate the safety and tolerability of TMC278 25 mg q.d., administered for 11 days in healthy subjects.

## 4.2.5 Study Description

### 4.2.5.1 Design

#### C131 Trial Design:

This is a randomized, double-blind, double-dummy, placebo controlled and active controlled, 3-way crossover trial. Each session was followed by a 21-day washout period.



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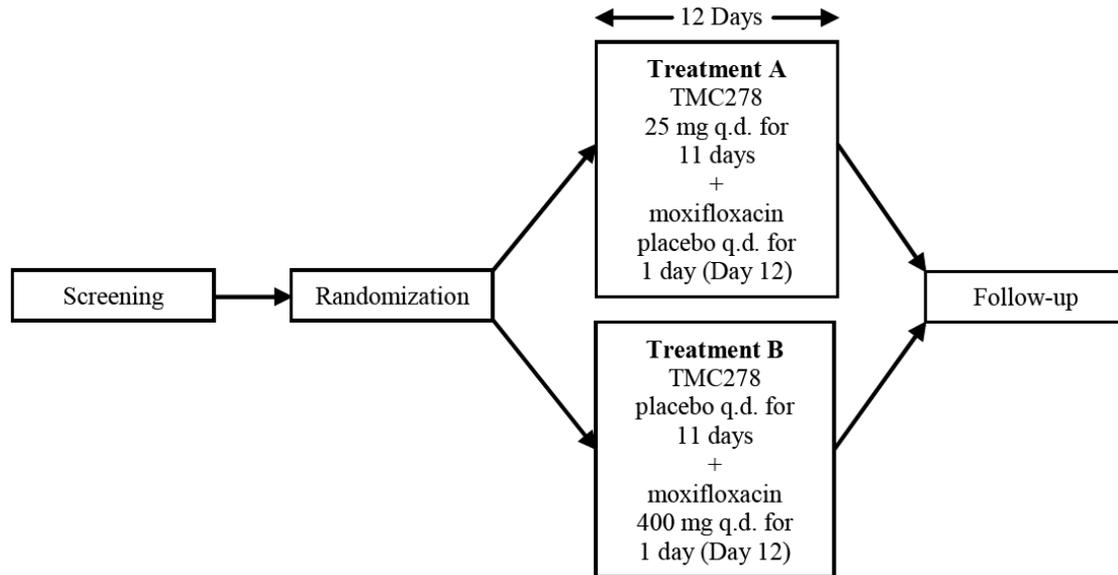
Source: Sponsor's tmc278-c131-crr.pdf page 36, Figure 1: Schematic Overview of the Trial.

Reviewer's comments: Although there should be four arms, there are only three periods. The placebo for the treatment levels is randomized, but the placebo for moxifloxacin is not randomized. TMC278 comparison and moxifloxacin comparison are different.

### C151 Trial Design:

This is a randomized, double-blind, double-dummy, placebo-controlled and positive-controlled, parallel trial.

**Figure 2: TMC278-TiDP6-C151 Trial Design**



Source: Sponsor's *tmc278-c131-crr.pdf* page 27, Figure 1: Schematic Overview of the Trial.

#### 4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls in both studies.

#### 4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

#### 4.2.6 Treatment Regimen

##### 4.2.6.1 Treatment Arms

###### C131:

- TMC278 75 mg q.d.
- TMC278 300 mg q.d.
- Moxifloxacin 400 mg

###### C151:

- TMC278 25 mg q.d.

- Moxifloxacin 400 mg

#### 4.2.6.2 Sponsor's Justification for Doses

##### **Sponsor's Justification for Doses in Study C131:**

“At the time of trial conduct, the dose of 75 mg q.d. was the selected therapeutic dose for further development of TMC278.

“Single doses up to TMC278 300 mg q.d. had been studied in healthy subjects. In this dose ranging trial, the pharmacokinetics of TMC278 were linear up to 200 mg, as  $C_{max}$  and  $AUC_{144h}$  increased proportionally with the dose. A less than dose-proportional increase in exposure was observed between 200 and 300 mg q.d., with only marginal further increases in  $C_{max}$  and  $AUC_{144h}$ . Therefore, as doses higher than 300 mg q.d. would likely not further increase the exposure, this dose was expected to provide exposures in and above the maximum of the range obtained with the therapeutic dose allowing to optimally assess pharmacokinetic-pharmacodynamic relationships with regard to QT/QTc prolongation.

“A dose of TMC278 300 mg q.d. was expected to achieve an exposure that was higher than the maximum exposure achieved with 75 mg q.d., without expected increased safety or tolerability risk for participating subjects.”

*Source: Sponsor's tmc278-c131-crr.pdf page 38, Section 3.1.2 (Discussion of Trial Design and Selection of Doses in the Trial)*

##### **Sponsor's Justification for Doses in Study C151:**

“Based on the dose-response relationship as observed in the TMC278-TiDP6-C131 trial, the anticipated effect of TMC278 on the QTc interval at a dose of 25 mg q.d. was expected to be below the threshold for regulatory concern as defined in the ICH E14 guideline.”

*Source: Sponsor's tmc278-c151-crr.pdf page 29, Section 3.1.2*

##### *Reviewer's Comment:*

- *A 300-mg dose provides 2.6-fold and 7.1-fold higher exposure in TMC278 than a 75-mg and 25-mg dose, respectively.*
- *The 75-mg dose is adequate to cover the anticipated exposure increase in a female Asian patient receiving a 25-mg dose.*
- *Drug-drug interactions with ketoconazole, lopinavir, ritonavir, darunavir, chlorzoxazone, tenofovir disoproxil fumarate have shown increase in TMC278 exposure. The most pronounced exposure increase due to drug-drug interaction was observed when TMC278 is coadministered with darunavir/ritonavir (800/100 mg). The maximum exposure (i.e.,  $C_{max}$ ) is increased by 1.8-fold.*
- *The dose schedule is sufficient to attain steady state exposures for TMC278 on Day 11 of the study.*

#### 4.2.6.3 Instructions with Regard to Meals

“All intakes of TMC278, moxifloxacin, and placebo were under fed conditions. Food increased the exposure (measured as AUC) to TMC278 by about 1.5-fold, as compared to fasting conditions. Therefore, it is recommended to administer TMC278 with food, to improve the oral bioavailability.” “Coadministration with a high fat meal (i.e., 500 calories from fat) did not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin did not significantly affect the extent or rate of systemic absorption (AUC). Therefore administration of moxifloxacin under fed conditions was not expected to influence its absorption or extent of exposure.”

*Source: Sponsor’s tmc278-c131-crr.pdf page 29.*

*Reviewer’s Comment: The schedule for meal intake with regards to TMC278 dosing is acceptable. Previous food effect studies demonstrated 1.5-fold increase of TMC278 AUC under fed conditions as compared to fasting conditions.*

#### 4.2.6.4 ECG and PK Assessments

ECG/PK sampling schedules for the two studies were summarized in Appendix 6.2.

*Reviewer’s Comment: The ECG sampling on Day 11 was acceptable for assessing QT prolongation at steady state TMC278 exposure. However, for Study C131, without any wash-out period after Day 11, the ECG sampling on Day 12 was inadequate for establishing assay sensitivity, because of TMC278’s effect on QT interval and its long half-life (45-50 hours).*

#### 4.2.6.5 Baseline

The sponsor used time-matched QTc values collected on Day -1 as baseline values.

#### 4.2.7 ECG Collection

The ECGs (on Days -1 to 13) were triplicate 10-second recordings collected at 60-second intervals at the time points specified above. Subjects rested in bed for at least 10 minutes prior to each ECG reading

All 12-lead ECG readings were blinded for subject identification, gender, time, and treatment and were taken according to the schedule of assessments and processed, handled, and identified according to the central ECG reader manual, which was provided by the centralized ECG laboratory before the start of the trial.

#### 4.2.8 Sponsor’s Results

##### 4.2.8.1 Study Subjects

###### C-131

Of the 41 subjects who participated in the trial, 40 received TMC278 75 mg q.d., 40 received TMC278 300 mg q.d., 39 received TMC278 placebo, and 39 received moxifloxacin. In all 3 sessions, 38 subjects completed Treatment A, 39 subjects completed Treatment B, and 39 subjects completed Treatment C. Three subjects dropped out before trial completion. Reasons for discontinuation were withdrawal of consent (2

subjects during Treatment A [1 subject during session 1 and 1 subject during session 2]) and AEs (1 subject during Treatment B in session 3).

### C-151

24 subjects were randomized to TMC278 25 mg q.d. followed by a single administration of moxifloxacin placebo (Treatment A), and 12 subjects were randomized to TMC278 placebo q.d. followed by a single administration of moxifloxacin 400 mg (Treatment B). All 36 subjects completed the trial.

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean difference between TMC278 25 mg and placebo, TMC278 75 mg and placebo, and TMC278 300 mg and placebo in QTcF. The sponsor used a mixed effects model. Sponsor's results are in Table 2 and Table 3. The sponsor found that the 75-mg and 300-mg dosages of TMC278 resulted in elongated QT intervals, while the 25-mg dosage of TMC278 did not result in elongated QT intervals.

**Table 2: Sponsor's Result of  $\Delta$ QTcF for TMC278 75 mg and 300 mg  
(Upper 90% Confidence Bounds of the Mean Difference from Baseline)**

Hour	$\Delta$ QTcF: moxifloxacin		Hour	$\Delta$ QTcF: TMC278 75mg		Hour	$\Delta$ QTcF: TMC278 300mg	
	Mean	97.5% CI		Mean	90% CI		Mean	90% CI
5	9.2	(6.2, 12.2)	4.5	10.4	(7.7, 13.1)	5	23.8	(19.3, 28.2)

**Table 3: Sponsor's Result of  $\Delta$ QTcF for TMC278 25 mg  
(Upper 90% Confidence Bounds of the Mean Difference from Baseline)**

Hour	$\Delta$ QTcF: moxifloxacin		Hour	$\Delta$ QTcF: TMC278 25mg	
	Mean	90% CI		Mean	90% CI
3	7.4	(4.2, 10.6)	4	4.8	(1.4, 8.2)

*Reviewer's Comments: In Table 2, the mean difference and confidence intervals for moxifloxacin are given for change from placebo during Day 11. Our independent analysis results are reported in Section 5.2.*

### 4.2.8.2.2 Assay Sensitivity

The reported assay sensitivity results were shown in Table 2 and Table 3.

*Reviewer's comments: Although the maximum lower limit of the 90% CI for  $\Delta$ QTcF moxifloxacin in Table 2 (Study C131) surpasses 5 ms, the establishment of assay*

*sensitivity is still questionable because of the non-randomization of the placebo group for moxifloxacin. Assay sensitivity cannot be established by comparing  $\Delta QTcF$  for moxifloxacin with  $\Delta\Delta QTcF$  for the study drug. In Study C151, our independent analysis agrees with the conclusions that the largest lower confidence limit (after multiple endpoint adjustment) is greater than 5 ms (see Section 5.2).*

#### **4.2.8.3 Safety Analysis**

##### **C131**

No deaths were reported during the trial. One subject, with no medical history of nephrolithiasis nor any known risk factors according to the investigator, was reported with a grade 3 SAE of nephrolithiasis during treatment with TMC278 300 mg q.d. and was hospitalized. This event led to permanent discontinuation of trial medication and withdrawal of the subject from the trial.

Cardiac events of interest were reported in 1 (2.5%) subject during treatment with TMC278 75 mg q.d. (palpitations) and 2 (5.0%) subjects during treatment with TMC278 300 mg q.d. (both chest pain). Asymptomatic QTcF prolongation of >60 ms were observed in 3 (7.5%) subjects, all during treatment with TMC278 300 mg q.d.

##### **C151**

No deaths, SAEs, AEs leading to withdrawal or grade 3 or 4 AEs were reported during the trial. Two subjects experienced AEs associated with ECG readings: 1 subject (4.2%) experienced an AE of QT interval prolongation during treatment with TMC278 25 mg q.d., and 1 subject (4.2%) experienced an AE of PR interval prolongation during TMC278 placebo administration.

#### **4.2.8.4 Clinical Pharmacology**

##### **4.2.8.4.1 Pharmacokinetic Analysis**

###### **C131 Pharmacokinetic Analysis:**

The PK results from Study C131 are presented in Table 4 (TMC278) and Table 5 (moxifloxacin).  $C_{max}$  and AUC values in the thorough QT study were 2.6-fold higher following administration of 300 mg TMC278 compared with 75 mg drug at steady state.

**Table 4: Pharmacokinetic Parameters of TMC278 Administered at 75 mg q.d. (Treatment A) and at 300 mg q.d. (Treatment B) for 11 Days**

<i>Pharmacokinetics of TMC278</i> (mean ± SD, t <sub>max</sub> : median [range])	<b>TMC278 75 mg q.d. Day 1 (reference)</b>	<b>TMC278 300 mg q.d. Day 1 (test)</b>
n	40 <sup>a</sup>	39 <sup>b</sup>
t <sub>max</sub> , h	4.5 (2.0-6.0)	4.5 (2.0-6.0)
C <sub>max</sub> , ng/mL	288.6 ± 97.74	838.2 ± 257.1
AUC <sub>24h</sub> , ng.h/mL	3107 ± 962.1	9119 ± 2987

<sup>a</sup> n=39 for AUC<sub>24h</sub>; <sup>b</sup> n=38 for AUC<sub>24h</sub>

<i>Pharmacokinetics of TMC278</i> (mean ± SD, t <sub>max</sub> : median [range])	<b>TMC278 75 mg q.d. Day 11 (reference)</b>	<b>TMC278 300 mg q.d. Day 11 (test)</b>
n	40	39
t <sub>max</sub> , h	5.0 (2.0-6.0)	5.0 (1.0-6.0)
C <sub>0h</sub> , ng/mL	288.5 ± 99.86	776.3 ± 287.6
C <sub>min</sub> , ng/mL	233.1 ± 69.98	595.5 ± 194.7
C <sub>max</sub> , ng/mL	635.7 ± 196.3	1665 ± 398.1
AUC <sub>24h</sub> , ng.h/mL	8564 ± 2418	22320 ± 5947
C <sub>ss, av</sub> , ng/mL	357.5 ± 101.1	932.2 ± 247.4
FI, %	112.8 ± 30.01	118.5 ± 31.25

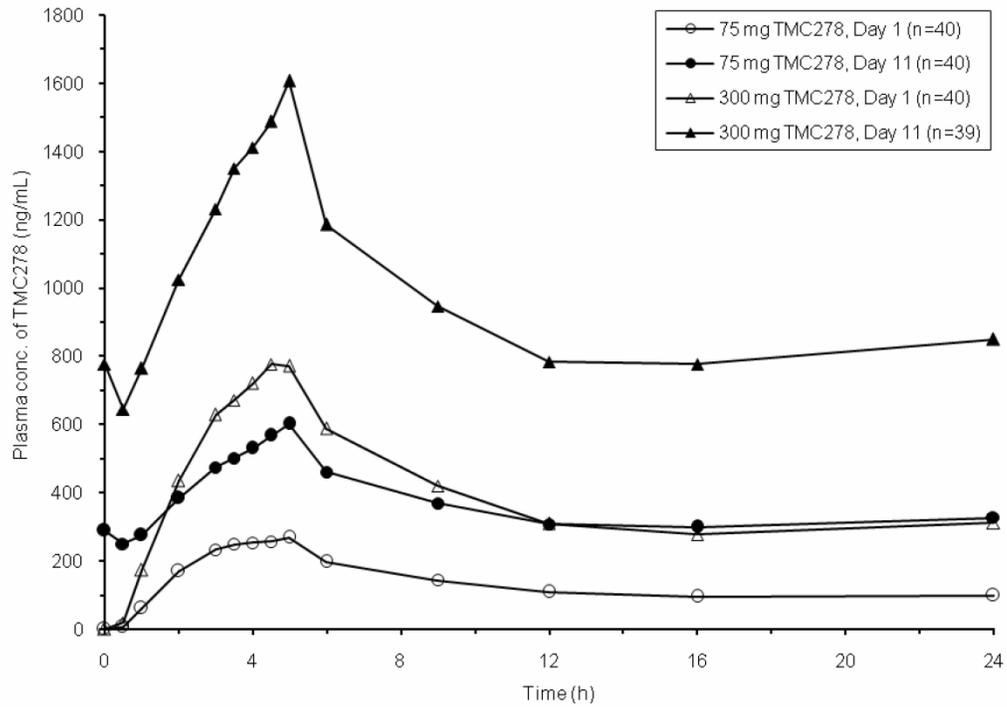
Source: Sponsor's tmc278-c131-crr.pdf page 100, Table 17.

**Table 5: Pharmacokinetic Parameters of Moxifloxacin after Administration of a Single Dose of 400 mg Moxifloxacin (Treatment C, Day 12)**

<i>Pharmacokinetics of moxifloxacin</i> (mean ± SD, t <sub>max</sub> : median [range])	<b>Moxifloxacin 400 mg</b>
n	39
t <sub>max</sub> , h	3.5 (1.0 - 6.0)
C <sub>max</sub> , ng/mL	2982 ± 574.6
AUC <sub>24h</sub> , ng.h/mL	34290 ± 5368
AUC <sub>∞</sub> , ng.h/mL <sup>a</sup>	45380 ± 7690
t <sub>1/2term</sub> , h <sup>a</sup>	11.53 ± 2.018

Source: Sponsor's tmc278-c131-crr.pdf page 103, Table 19.

**Figure 3: Mean Plasma Concentration of TMC278 versus Time after Administration of TMC278 75 mg q.d. and 300 mg q.d. on Days 1 and 11**



Source: Sponsor's tmc278-c131-crr.pdf page 98, Figure 12.

**C151 Pharmacokinetic Analysis:**

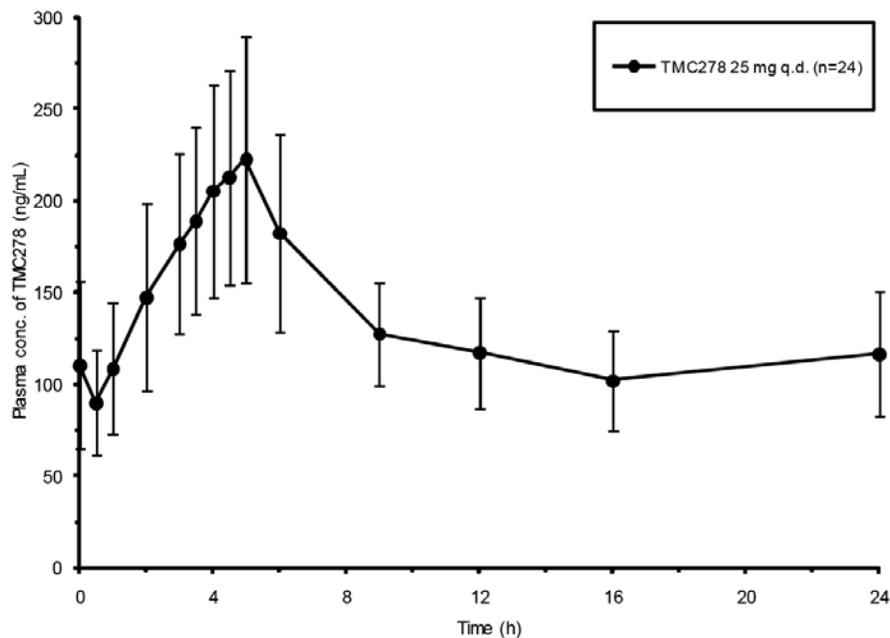
The PK parameters of TMC278 from study C151 are presented in Table 6.

**Table 6: Steady State TMC278 Pharmacokinetic Parameters (Day 11)**

Pharmacokinetics of TMC278 (mean $\pm$ SD, $t_{max}$ : median [range])	TMC278 25 mg q.d.
n	24
<b>Day 9</b>	
$C_{0h}$ , ng/mL	100.7 $\pm$ 48.45
<b>Day 10</b>	
$C_{0h}$ , ng/mL	108.0 $\pm$ 52.02
<b>Day 11</b>	
$C_{0h}$ , ng/mL	110.7 $\pm$ 45.72
$C_{min}$ , ng/mL	87.56 $\pm$ 27.49
$C_{max}$ , ng/mL	229.4 $\pm$ 65.73
$t_{max}$ , h	4.5 (2.0-6.0)
AUC <sub>24h</sub> , ng.h/mL	3146 $\pm$ 758.4
$C_{ss,av}$ , ng.mL	131.1 $\pm$ 31.60
FI, %	108.7 $\pm$ 25.62

Source: Sponsor's tmc278-c151-crr.pdf page 75, Table 9.

**Figure 4: Mean ( $\pm$  SD) Plasma Concentration of TMC278 versus Time after Administration of TMC278 at 25 mg q.d. for 11 Days**



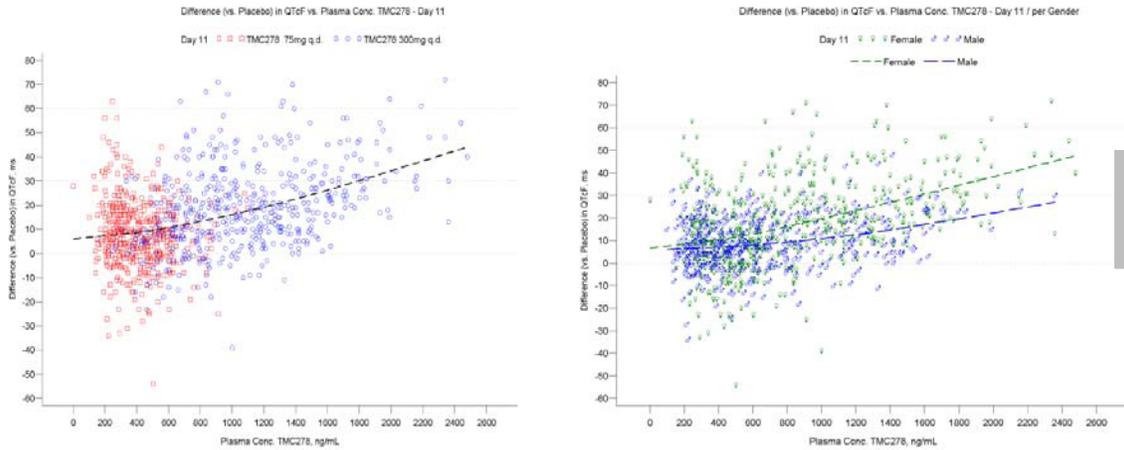
Source: Sponsor's tmc278-c151-crr.pdf page 73, Figure 8.

#### 4.2.8.4.2 Exposure-Response Analysis

##### C131 Exposure-Response Analysis:

Figure 5 presents the time-matched difference from placebo in QTcF interval versus corresponding TMC278 plasma concentration at steady state.

**Figure 5: Scatter Plot of Time-matched Difference from Placebo in QTcF versus Corresponding TMC278 Plasma Concentration**

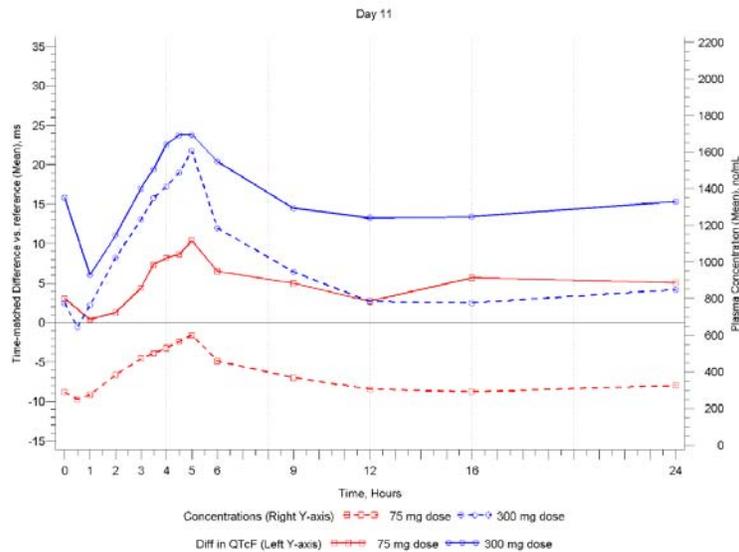


Best Available Copy

Source: Sponsor's tmc278-c131-crr.pdf report page 113, Figure 19.

Figure 6 displays the mean time-matched changes from baseline in QTcF interval (left Y-axis) and mean TMC278 plasma concentration (right Y-axis) versus time on Day 11. The curves of the changes in QTcF interval from baseline follow a similar pattern as the plasma concentration curves.

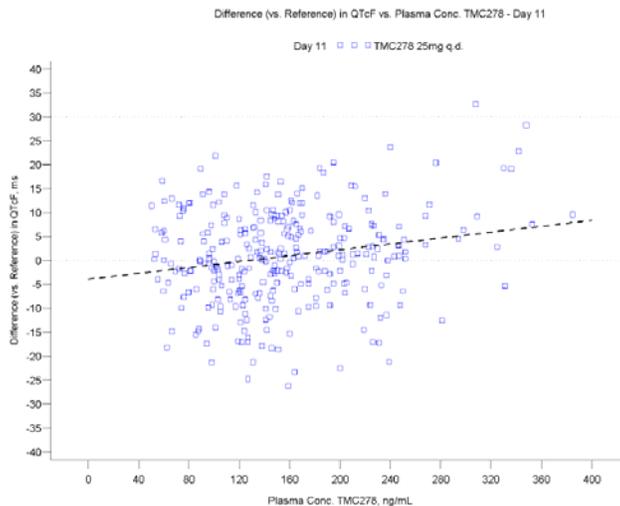
**Figure 6: Mean Difference in QTcF versus Baseline and Mean TMC278 Plasma Concentration over Time at Steady State**



Source: Sponsor's tmc278-c131-crr.pdf page 112, Figure 18.

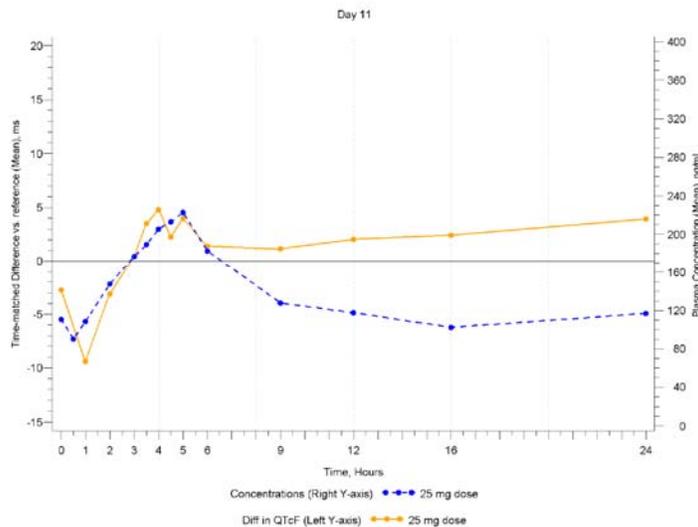
**C151 Exposure-Response Analysis:**

**Figure 7: Scatter Plot of Change from Baseline in QTcF Interval versus Corresponding Time-Matched TMC278 Plasma Concentration on Day 11**



Source: Sponsor’s tmc278-c151-crr.pdf page 78, Figure 12.

**Figure 8: Mean Differences in QTcF Interval versus Baseline (Left Y-axis) and Mean TMC278 Plasma Concentration (Right Y-axis) over Time on Day 11**



Source: Sponsor’s tmc278-c151-crr.pdf page 77, Figure 11.

*Reviewer’s Analysis: The sponsor performed concentration- $\Delta$ QTcF analyses and demonstrated that TMC278 is a QT prolonger at the dose levels of 75 mg q.d. and 300 mg q.d. The sponsor then proposed a new therapeutic dose of 25 mg q.d. and demonstrated in a separate study that no evident relationship between TMC278 concentration and  $\Delta$ QTcF (change from baseline) at the concentration of interest. We performed an independent concentration- $\Delta$ QTcF analysis. Plots of  $\Delta$ QTcF vs. drug concentrations for both studies are presented in Figure 12 and Figure 13, respectively.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods between QTcF and QTcB based on both Study C131 and Study C151. QTcF always performs better than QTcB. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is also consistent with the sponsor's choice of QTcF for their primary analysis.

### 5.2 STATISTICAL ASSESSMENTS

#### 5.2.1 QTc Analysis

##### 5.2.1.1 The Primary Analysis for TMC278

The statistical reviewer used a mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment, sequence, and period as fixed effects and subject as a repeated effect for TCM278 dosages of 75 mg q.d. and 300 mg q.d. (Study C131). The model includes treatment as a fixed effect and subject as a repeated effect for a TCM278 dosage of 25 mg q.d. (Study C151). Baseline values are also included in the model as a covariate. The analysis results are listed in Table 7, Table 8, and Table 9.

**Table 7: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group TMC278 75 mg x 11 days**

Hour	$\Delta$ QTcF: TCM278 75 mg			$\Delta$ QTcF: placebo			$\Delta\Delta$ QTcF			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	40	-0.5	1.9	39	-8.2	1.9	79	7.7	2.4	(3.7, 11.6)
2	39	1.0	1.8	39	-5.0	1.8	78	6.0	2.1	(2.4, 9.6)
3	40	4.0	2.0	39	-2.7	2.0	79	6.7	2.4	(2.6, 10.8)
3.5	40	6.5	2.1	39	-0.8	2.1	79	7.3	2.4	(3.3, 11.3)
4	39	8.1	2.0	39	2.4	2.0	78	5.8	2.7	(1.3, 10.3)
4.5	39	8.5	2.0	39	0.9	2.0	78	7.7	2.7	(3.1, 12.2)
5	40	10.4	1.8	39	1.7	1.8	79	8.7	2.4	(4.6, 12.8)
6	40	6.4	1.8	39	0.2	1.8	79	6.2	2.3	(2.4, 10.0)
9	38	4.6	1.8	39	-4.5	1.8	77	9.1	2.2	(5.4, 12.8)
12	40	2.1	2.3	39	-3.4	2.3	79	5.5	1.9	(2.2, 8.7)
16	40	5.6	1.9	39	-4.5	1.9	79	10.1	2.7	(5.7, 14.5)
24	40	5.0	1.8	39	-2.2	1.8	79	7.1	2.4	(3.1, 11.2)

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group TMC278 300 mg x 11 days**

Hour	$\Delta$ QTcF: TCM278 300 mg			$\Delta$ QTcF: placebo			$\Delta\Delta$ QTcF			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	39	6.4	1.8	39	-8.2	1.9	78	14.6	2.3	(10.7, 18.5)
2	38	11.0	1.8	39	-5.0	1.8	77	16.1	2.1	(12.5, 19.7)
3	39	17.0	2.0	39	-2.7	2.0	78	19.6	2.4	(15.6, 23.7)
3.5	39	19.2	2.1	39	-0.8	2.1	78	20.0	2.3	(16.1, 24.0)
4	38	22.3	2.1	39	2.4	2.0	77	20.0	2.7	(15.4, 24.5)
4.5	38	23.3	2.1	39	0.9	2.0	77	22.5	2.8	(17.9, 27.1)
5	39	23.7	1.8	39	1.7	1.8	78	22.1	2.5	(18.0, 26.1)
6	39	20.3	1.8	39	0.2	1.8	78	20.1	2.3	(16.3, 23.8)
9	39	14.3	1.8	39	-4.5	1.8	78	18.7	2.2	(15.0, 22.4)
12	39	12.9	2.3	39	-3.4	2.3	78	16.3	1.9	(13.0, 19.5)
16	39	13.5	1.9	39	-4.5	1.9	78	18.0	2.6	(13.6, 22.3)
24	39	15.4	1.8	39	-2.2	1.8	78	17.6	2.4	(13.5, 21.6)

**Table 9: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group TMC278 25 mg x 11 days**

Hour	$\Delta$ QTcF: TCM278 25 mg			$\Delta$ QTcF: placebo			$\Delta\Delta$ QTcF			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	24	-9.1	1.6	12	-5.0	2.3	36	-4.1	2.8	(-8.9, 0.7)
2	24	-3.3	1.7	12	-2.0	2.4	36	-1.3	3.0	(-6.3, 3.8)
3	24	0.5	1.6	12	4.7	2.3	36	-4.2	2.9	(-9.0, 0.7)
3.5	24	3.5	2.0	12	5.5	2.8	36	-2.0	3.5	(-7.8, 3.9)
4	24	4.8	1.9	12	6.7	2.7	36	-1.9	3.3	(-7.5, 3.6)
4.5	24	2.3	1.8	12	8.7	2.5	36	-6.5	3.1	(-11.7, -1.2)
5	24	4.0	2.0	12	6.3	2.9	36	-2.4	3.5	(-8.3, 3.6)
6	24	1.3	1.8	12	-0.7	2.5	36	2.0	3.1	(-3.2, 7.2)
9	24	1.2	1.3	12	-0.1	1.9	36	1.3	2.3	(-2.6, 5.2)
12	24	2.1	2.0	12	4.3	2.8	36	-2.3	3.5	(-8.1, 3.6)
16	24	2.3	1.5	12	0.9	2.2	36	1.4	2.7	(-3.1, 5.9)
24	24	4.0	1.3	12	5.6	1.9	36	-1.7	2.3	(-5.5, 2.2)

The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC278 75 mg and placebo, TMC278 300 mg and placebo, and TMC278 25 mg were -14.5 ms, 27.1 ms, and 7.2 ms, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10 (Study C131) and Table 11 (Study C151). For Study C131, the reviewer used the same placebo group as the sponsor (Day 11). The largest unadjusted 90% confidence interval lower bound in Table 10 (Study C131) is 7.1 ms. Using a Bonferroni multiple endpoint adjustment, the largest lower bound is 6.2 ms.

The largest unadjusted 90% confidence interval lower bound in Table 11 (study 151) is 8.3 ms. Using a Bonferroni multiple endpoint adjustment, the largest lower bound is 6.4 ms, which indicates that at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 10: Analysis Results of  $\Delta$ QTcF for Moxifloxacin in Study C131 (TMC278 75 mg and 300 mg)**

Hour	$\Delta$ QTcF*				
	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
1	118	-0.8	1.2	(-2.7, 1.2)	(-3.5, 1.9)
2	118	4.6	1.3	(2.4, 6.8)	(1.6, 7.6)
3	118	7.3	1.2	(5.3, 9.3)	(4.6, 10.1)
3.5	118	8.4	1.3	(6.1, 10.6)	(5.2, 11.5)
4	116	8.3	1.2	(6.2, 10.4)	(5.3, 11.2)
4.5	118	8.6	1.4	(6.3, 11.0)	(5.4, 11.9)
5	116	9.2	1.3	(7.1, 11.3)	(6.2, 12.2)
6	118	5.7	1.1	(3.9, 7.5)	(3.2, 8.2)
9	117	6.5	1.1	(4.7, 8.4)	(3.9, 9.1)
12	118	4.9	1.2	(2.9, 6.9)	(2.2, 7.6)
16	117	7.4	1.4	(5.1, 9.8)	(4.2, 10.7)
24	118	2.2	1.0	(0.4, 3.9)	(-0.2, 4.6)

\* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

*Reviewer's comments: These results are based on data from Day 11 and Day 12 in the same period, in which both moxifloxacin and placebo share the same baseline. Therefore there was almost no baseline contribution when the baseline-adjusted mean difference between moxifloxacin and placebo was considered. Additionally, the placebo used for moxifloxacin is from Day 11 which is only one day apart from the moxifloxacin day (Day 12), in contrast to the 30+ days between the treatments and their placebo. This results in a reduced variance for the moxifloxacin effects (as also shown in Figure 9). Because of the limitation of the design, we can not use the results of moxifloxacin to establish assay sensitivity for study C131.*

**Table 11: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin in Study C151 (TMC278 25 mg)**

Hour	$\Delta$ QTcF: moxifloxacin			$\Delta$ QTcF: placebo			$\Delta\Delta$ QTcF				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
2	12	1.5	2.1	24	-6.9	1.5	36	8.3	2.6	(3.9, 12.8)	(2.1, 14.6)
3	12	12.1	2.3	24	-1.0	1.6	36	13.1	2.8	(8.3, 17.9)	(6.4, 19.8)
4	12	10.5	2.3	24	0.9	1.6	36	9.6	2.8	(4.8, 14.4)	(2.9, 16.3)
5	12	10.1	2.4	24	1.9	1.7	36	8.2	3.0	(3.1, 13.3)	(1.2, 15.2)

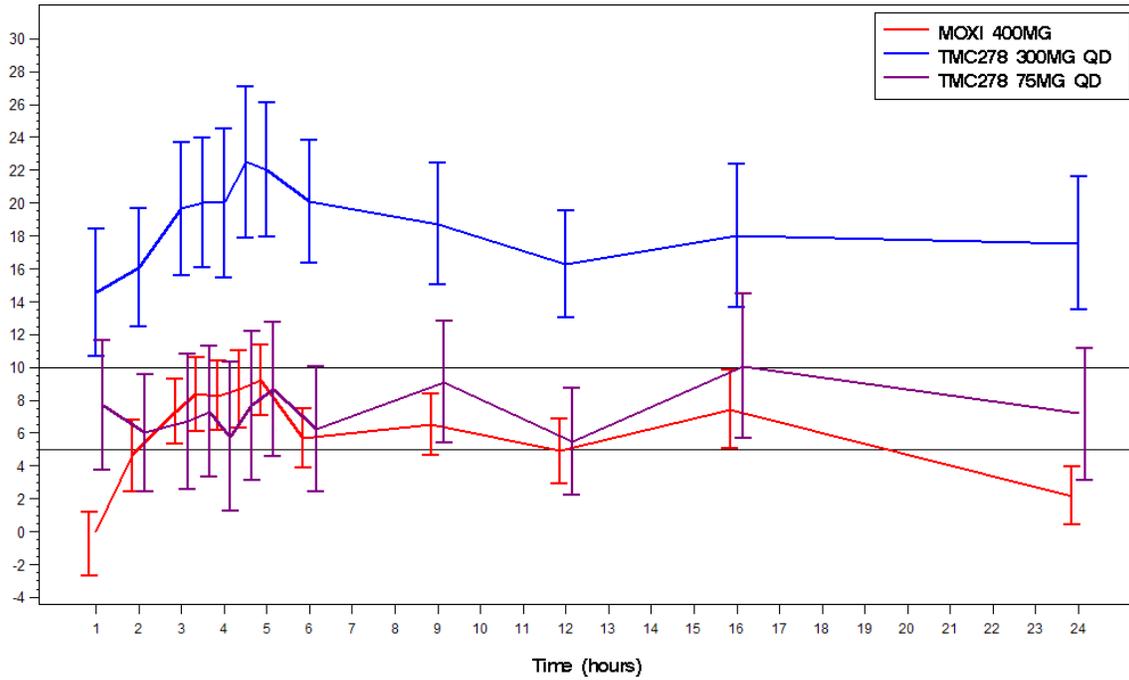
- Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

*Reviewer's comments: Study C151 for TMC278 25 mg q.d did not have enough time points to verify that the moxifloxacin profile over a 24-hour time period was consistent with the expected moxifloxacin time course. We can not claim establishment of assay sensitivity based on study C151.*

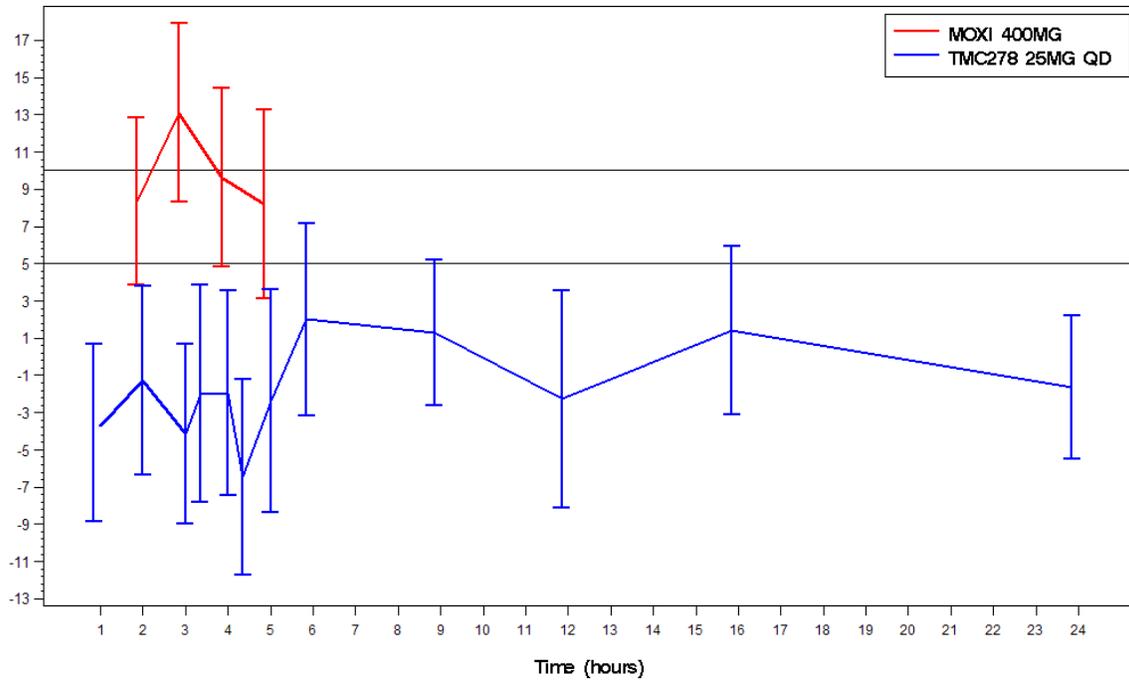
### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 9 (study C131) and Figure 10 (study C151) display the time profile of  $\Delta\Delta$ QTcF for different treatment groups. All confidence intervals are unadjusted, including moxifloxacin.

**Figure 9: Mean and 90% CI  $\Delta\Delta Q_{TcF}$  Time Course in Study C131 (TMC278 75 mg and 300 mg)**



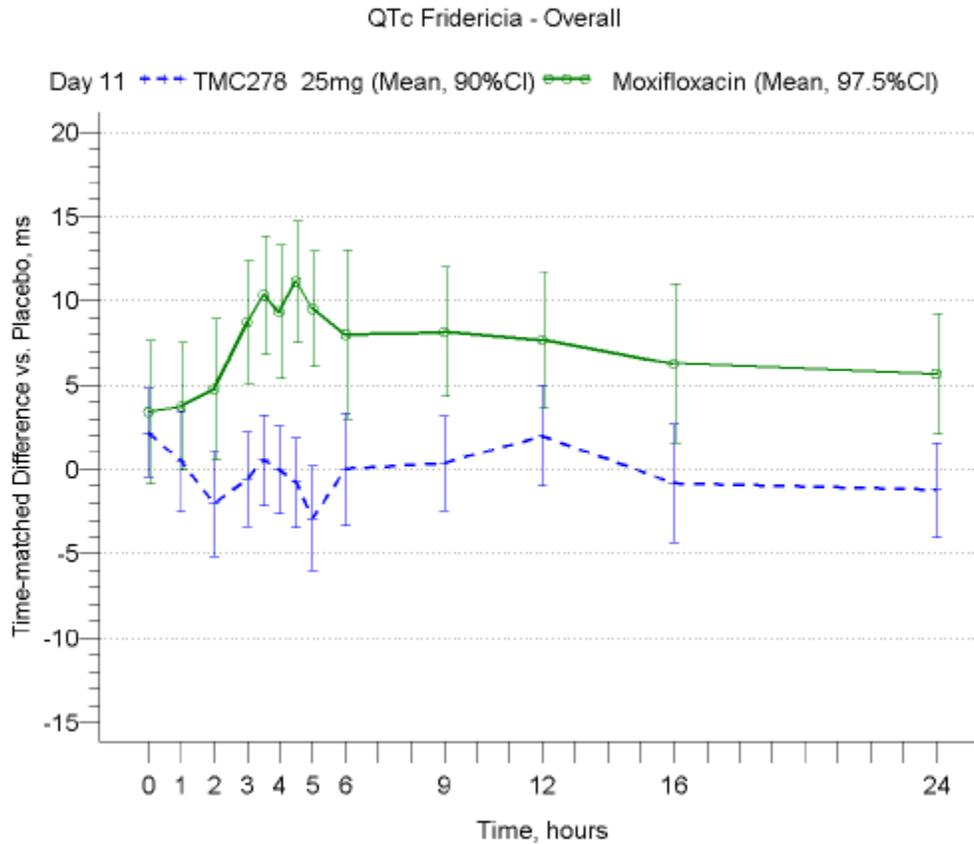
**Figure 10: Mean and 90% CI  $\Delta\Delta Q_{TcF}$  Time Course in Study C151 (TMC278 25 mg)**



*Reviewer's comments: The sponsor performed an additional study (Study C152) on the effects of TMC278 25 mg q.d. In this study, assay sensitivity was established and the results of TMC278 were similar to the results from Study C151. See Figure 11 below*

(reported by the sponsor). The results from Study C152 assured us that QTc interval change following TMC278 25 mg q.d. does not exceed the regulatory threshold and that assay sensitivity was established.

**Figure 11: Time Profile of Moxifloxacin Over a 24 Hour Period (Study C152)**



Source: Sponsor's tmc278-c152-crr.pdf page 90, Figure 5.

### 5.2.1.4 Categorical Analysis

Table 12 (Study C131) and Table 13 (Study C151) list the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcF was above 500 ms for TMC278 dosages 75 mg and 300 mg, and no subject's QTcF was about 480 ms for TMC278 dosage 25 mg.

**Table 12: Categorical Analysis for QTcF in Study C131 (TMC278 75 mg and 300 mg)**

Treatment Group	N	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms	480 ms<Value $\leq$ 500 ms
Baseline	41	38 (92.7%)	3 (7.3%)	0 (0.0%)
Moxifloxacin	39	36 (92.3%)	3 (7.7%)	0 (0.0%)
Placebo for moxifloxacin	40	34 (85.0%)	6 (15.0%)	0 (0.0%)
TMC278 75 mg	40	38 (95.0%)	2 (5.0%)	0 (0.0%)
TMC278 300 mg	39	31 (79.5%)	6 (15.4%)	2 (5.1%)
Placebo for TMC278	39	36 (92.3%)	3 (7.7%)	0 (0.0%)

**Table 13: Categorical Analysis for QTcF in Study C151 (TMC278 25 mg)**

Treatment Group	N	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms
Baseline	36	35 (97.2%)	1 (2.8%)
Moxifloxacin	12	12 (100%)	0 (0.0%)
Placebo for moxifloxacin	24	23 (95.8%)	1 (4.2%)
TMC278 25 mg	24	23 (95.8%)	1 (4.2%)
Placebo for TMC278	12	12 (100%)	0 (0.0%)

Table 14 (Study C131) and Table 15 (Study C151) list the categorical analysis results for  $\Delta$ QTcF. Three subjects' change from baseline were above 60 ms in treatment group TMC278 300 mg, and no subjects' change from baseline were above 60 ms in all other groups.

**Table 14: Categorical Analysis of  $\Delta$ QTcF in Study C131 (TMC278 75 mg and 300 mg)**

Treatment Group	N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	Value>60 ms
Moxifloxacin	39	36 (92.3%)	3 (7.7%)	0 (0.0%)
Placebo for moxifloxacin	40	28 (70.0%)	12 (30.0%)	0 (0.0%)
TMC278 75 mg	40	38 (95.0%)	2 (5.0%)	0 (0.0%)
TMC278 300 mg	39	19 (48.7%)	17 (43.6%)	3 (7.7%)
Placebo for TMC278	39	38 (97.4%)	1 (2.6%)	0 (0.0%)

**Table 15: Categorical Analysis of  $\Delta$ QTcF in Study C151 (TMC278 25 mg)**

Treatment Group	N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms
Moxifloxacin	12	12 (100%)	0 (0.0%)
Placebo for moxifloxacin	24	24 (100%)	0 (0.0%)
TMC278 25 mg	24	23 (95.8%)	1 (4.2%)
Placebo for TMC278	24	24 (100%)	0 (0.0%)

### 5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 16, Table 17, and Table 18. The largest upper limits of 90% CI for the PR mean differences between TMC278 75 mg and placebo, TMC278 300 mg and placebo, and TMC278 25 mg are 4.3 ms, 5.5 ms, and 8.4 ms, respectively.

**There were five subjects who experienced PR intervals greater than 200 ms in the TMC278 25 mg treatment group. The outlier analysis results for PR are presented in**

Table 19. No subjects experienced PR intervals greater than 200 ms in treatment groups TMC278 75 mg and 300 mg.

**Table 16: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group TMC278 75 mg x 11 days**

Hour	$\Delta$ PR: TCM278 75 mg			$\Delta$ PR: placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	39	-0.6	1.2	39	-2.4	1.2	78	1.8	1.5	(-0.8, 4.3)
2	40	-2.8	1.3	39	-0.8	1.3	79	-2.0	1.7	(-4.8, 0.8)
3	40	0.1	1.3	39	0.5	1.3	79	-0.4	1.8	(-3.5, 2.7)
3.5	40	0.5	1.1	39	1.4	1.1	79	-0.8	1.5	(-3.3, 1.7)
4	40	-0.3	1.3	39	0.2	1.3	79	-0.5	1.8	(-3.5, 2.4)
4.5	40	-0.0	1.3	39	1.0	1.3	79	-1.1	1.8	(-4.0, 1.9)
5	39	-0.6	1.4	39	1.1	1.4	78	-1.7	2.0	(-4.9, 1.5)
6	40	-0.5	1.1	39	1.0	1.2	79	-1.5	1.6	(-4.2, 1.1)
9	40	-0.8	1.4	39	0.1	1.4	79	-0.8	1.9	(-4.0, 2.4)
12	40	-0.5	1.1	38	-1.7	1.1	78	1.3	1.5	(-1.2, 3.8)
16	39	0.3	1.3	39	1.0	1.3	78	-0.7	1.6	(-3.4, 2.1)
24	39	1.2	0.9	39	-0.3	0.9	78	1.5	1.3	(-0.7, 3.7)

**Table 17: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group TMC278 300 mg x 11 days**

Hour	$\Delta$ PR: TCM278 300 mg			$\Delta$ PR: placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	39	-1.5	1.2	39	-2.4	1.2	78	0.9	1.5	(-1.6, 3.5)
2	39	-2.3	1.3	39	-0.8	1.3	78	-1.4	1.7	(-4.3, 1.4)
3	38	2.5	1.3	39	0.5	1.3	77	2.0	1.9	(-1.1, 5.1)
3.5	39	-0.6	1.1	39	1.4	1.1	78	-2.0	1.5	(-4.5, 0.5)
4	38	0.3	1.3	39	0.2	1.3	77	0.1	1.8	(-2.9, 3.1)
4.5	39	0.4	1.3	39	1.0	1.3	78	-0.6	1.8	(-3.6, 2.4)
5	39	1.1	1.4	39	1.1	1.4	78	-0.0	1.9	(-3.3, 3.2)
6	39	0.3	1.2	39	1.0	1.2	78	-0.7	1.6	(-3.4, 2.0)
9	39	2.4	1.4	39	0.1	1.4	78	2.3	1.9	(-0.9, 5.5)
12	38	-0.4	1.1	38	-1.7	1.1	76	1.4	1.5	(-1.2, 3.9)
16	39	-0.5	1.3	39	1.0	1.3	78	-1.5	1.6	(-4.2, 1.2)
24	39	0.2	0.9	39	-0.3	0.9	78	0.5	1.3	(-1.7, 2.7)

**Table 18: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group TMC278 25 mg x 11 days**

Hour	$\Delta$ PR: TCM278 25 mg			$\Delta$ PR: placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	24	-2.4	1.9	12	2.3	2.8	36	-4.7	3.4	(-10.5, 1.0)
2	24	-1.0	3.0	12	6.7	4.3	36	-7.7	5.3	(-16.7, 1.2)
3	24	4.0	3.0	12	5.8	4.3	36	-1.8	5.3	(-10.7, 7.2)
3.5	24	6.3	3.5	12	8.5	5.1	36	-2.2	6.3	(-12.9, 8.4)
4	24	3.9	1.5	12	1.9	2.1	36	2.0	2.6	(-2.4, 6.5)
4.5	24	1.1	1.5	12	0.8	2.2	36	0.3	2.8	(-4.3, 5.0)
5	24	2.6	1.4	12	0.4	2.0	36	2.1	2.5	(-2.1, 6.3)
6	24	4.4	1.3	12	8.2	1.9	36	-3.8	2.3	(-7.8, 0.1)
9	24	3.5	1.7	12	4.0	2.4	36	-0.6	3.0	(-5.7, 4.6)
12	24	-1.1	1.4	12	3.4	2.0	36	-4.4	2.5	(-8.7, -0.2)
16	24	-1.7	4.8	12	13.6	6.8	36	-15.3	8.4	(-29.5, -1.1)
24	24	-4.0	1.6	12	-1.2	2.3	36	-2.8	2.8	(-7.6, 2.0)

**Table 19: Categorical Analysis for PR in Study 151 (TMC278 25 mg)**

Treatment Group	N	PR <200 ms	PR >=200 ms
Baseline	36	34 (94.4%)	2 (5.6%)
TMC278 25 mg	24	23 (95.8%)	1 (4.2%)
Placebo	12	10 (83.3%)	2 (16.7%)

### 5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 20, Table 21 and Table 22. The largest upper limits of 90% CI for the QRS mean differences between TMC278 75 mg and placebo, TMC278 300 mg and placebo, and TMC278 25 mg and placebo are 1.8 ms, 2.1 ms, and 5.4 ms, respectively.

The outlier analysis results for QRS are presented in Table 23 (study 131) and Table 24 (study 151). There are 4 subjects who experienced QRS intervals greater than 110 ms in TMC278 75 mg and 300 mg, and 3 subjects who experienced QRS intervals greater than 110 ms in TMC278 25 mg.

**Table 20: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group TMC278 75 mg x 11 days**

Hour	$\Delta$ QRS: TMC278 75 mg			$\Delta$ QRS: Placebo			$\Delta\Delta$ QRS			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	39	-0.2	0.4	39	-0.5	0.4	78	0.3	0.6	(-0.7, 1.3)
2	40	-0.8	0.5	39	-0.7	0.5	78	-0.1	0.8	(-1.4, 1.2)
3	40	-1.1	0.5	39	0.6	0.5	77	-1.6	0.7	(-2.8, -0.5)
3.5	40	-0.3	0.5	39	-0.1	0.5	78	-0.2	0.7	(-1.3, 0.9)
4	40	0.7	0.5	39	0.4	0.5	77	0.3	0.6	(-0.7, 1.3)
4.5	40	0.5	0.4	39	0.8	0.4	78	-0.3	0.6	(-1.3, 0.6)
5	39	1.1	0.5	39	0.4	0.5	78	0.6	0.7	(-0.6, 1.8)
6	40	-0.2	0.5	39	0.4	0.5	78	-0.5	0.7	(-1.6, 0.6)
9	40	-0.1	0.4	39	0.3	0.5	78	-0.4	0.6	(-1.4, 0.7)
12	40	-0.4	0.4	38	-0.7	0.4	76	0.3	0.6	(-0.7, 1.3)
16	40	-0.9	0.6	38	-1.1	0.7	77	0.2	0.7	(-1.0, 1.4)
24	39	0.4	0.5	39	-0.2	0.5	78	0.6	0.7	(-0.5, 1.8)

**Table 21: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group TMC278 300 mg x 11 days**

	$\Delta$ QRS: TMC278 300 mg			$\Delta$ QRS: Placebo			$\Delta\Delta$ QRS			
Hour	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	39	-0.2	0.4	39	-0.5	0.4	78	0.2	0.6	(-0.8, 1.2)
2	39	-0.6	0.5	39	-0.7	0.5	78	0.1	0.8	(-1.2, 1.3)
3	38	0.8	0.5	39	0.6	0.5	77	0.2	0.7	(-0.9, 1.3)
3.5	39	0.5	0.5	39	-0.1	0.5	78	0.5	0.7	(-0.6, 1.7)
4	38	0.1	0.5	39	0.4	0.5	77	-0.3	0.6	(-1.3, 0.7)
4.5	39	0.6	0.4	39	0.8	0.4	78	-0.2	0.6	(-1.2, 0.8)
5	39	0.7	0.5	39	0.4	0.5	78	0.3	0.7	(-0.9, 1.5)
6	39	1.3	0.5	39	0.4	0.5	78	1.0	0.7	(-0.1, 2.1)
9	39	0.5	0.5	39	0.3	0.5	78	0.3	0.6	(-0.8, 1.3)
12	38	-0.2	0.4	38	-0.7	0.4	76	0.5	0.6	(-0.5, 1.6)
16	39	-0.2	0.6	38	-1.1	0.7	77	0.9	0.7	(-0.2, 2.1)
24	39	0.2	0.5	39	-0.2	0.5	78	0.5	0.7	(-0.7, 1.6)

**Table 22: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group TMC278 25 mg x 11 days**

	$\Delta$ QRS: TMC278 25 mg			$\Delta$ QRS: Placebo			$\Delta\Delta$ QRS			
Hour	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
1	24	-1.6	0.7	12	-2.2	1.0	36	0.6	1.2	(-1.3, 2.6)
2	24	-1.0	0.6	12	-1.5	0.9	36	0.5	1.1	(-1.3, 2.4)
3	24	-1.5	0.8	12	-0.2	1.2	36	-1.3	1.4	(-3.8, 1.1)
3.5	24	0.5	0.7	12	-1.0	1.0	36	1.5	1.3	(-0.7, 3.7)
4	24	-1.3	0.9	12	-0.1	1.3	36	-1.2	1.5	(-3.8, 1.4)
4.5	24	-0.8	0.7	12	-0.3	1.0	36	-0.5	1.3	(-2.6, 1.6)
5	24	-0.2	0.9	12	-1.5	1.2	36	1.4	1.5	(-1.2, 3.9)
6	24	-0.9	0.7	12	0.1	1.0	36	-1.0	1.2	(-3.0, 1.0)
9	24	0.5	0.7	12	-1.7	0.9	36	2.2	1.2	(0.3, 4.2)
12	24	0.2	0.7	12	0.2	1.0	36	-0.0	1.3	(-2.1, 2.1)
16	24	1.5	0.8	12	-1.6	1.1	36	3.1	1.4	(0.8, 5.4)
24	24	0.6	0.7	12	-0.9	1.0	36	1.5	1.3	(-0.6, 3.7)

**Table 23: Categorical Analysis for QRS in Study 131 (TMC278 75 mg and 300 mg)**

Treatment Group	N	QRS <110 ms	QRS >= 110 ms
TMC278 75 mg	40	39 (97.5%)	1 (2.5%)
TMC278 300 mg	39	38 (97.4%)	1 (2.6%)
Placebo	39	38 (97.4%)	1 (2.6%)
Baseline	41	40 (97.6%)	1 (2.4%)

**Table 24: Categorical Analysis for QRS in Study 151 (TMC278 25 mg)**

Treatment Group	N	QRS <110 ms	QRS >= 110 ms
Baseline	36	35 (97.2%)	1 (2.8%)
TMC278 25 mg	24	23 (95.8%)	1 (4.2%)
Placebo	12	11 (91.7%)	1 (8.3%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

#### C131:

The mean drug concentration-time profile is illustrated in Figure 3.

The relationship between  $\Delta\Delta\text{QTcF}$  and TMC278 concentrations was investigated by linear mixed-effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

A linear concentration- $\Delta\Delta\text{QTcF}$  relationship was identified for TMC278 with results of the analyses summarized in Table 25.

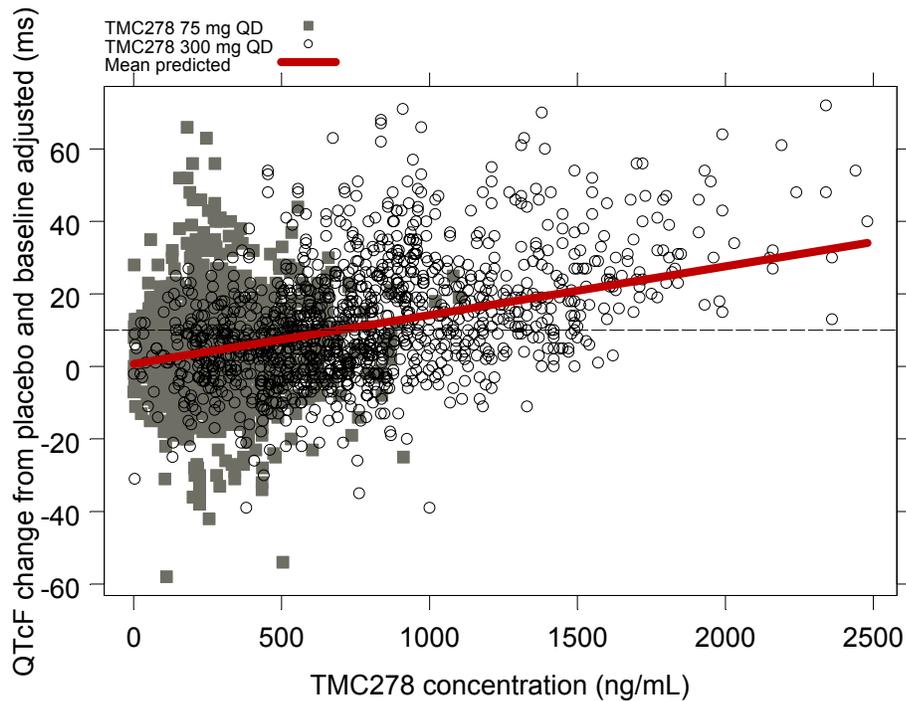
**Table 25: Exposure-response Analysis of TMC278 Associated  $\Delta\Delta\text{QTcF}$  Prolongation (Study C131)**

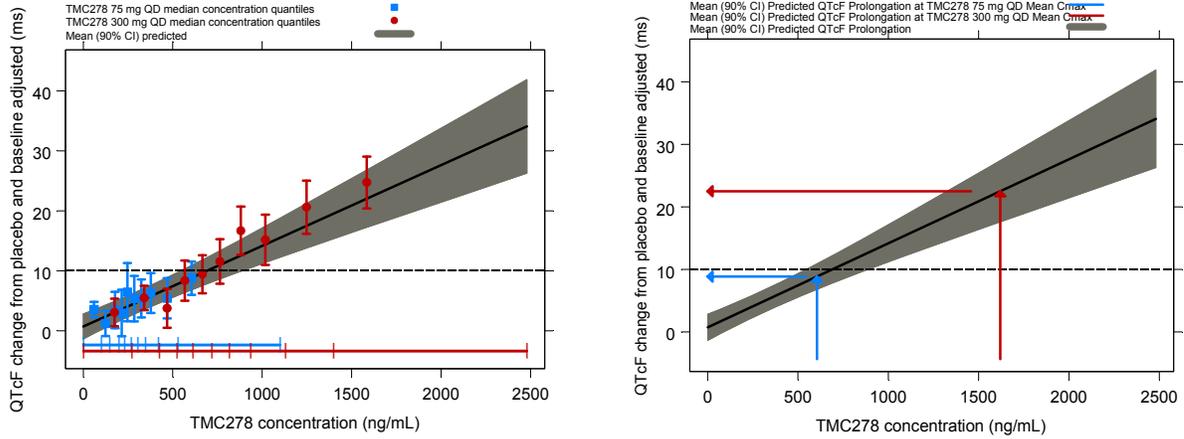
Parameter	Estimate	P-value	IIV
<b>Model 1: <math>\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \text{TMC278 Concentration}</math></b>			
Intercept (ms)	0.71 (-1.38; 2.81)	0.5706	NA
Slope (ms per ng/mL)	0.0134 (0.00993; 0.017)	<.0001	NA
Residual Variability (ms)	NA		
<b>Model 2: <math>\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \text{TMC278 Concentration (Fixed Intercept)}</math></b>			
Intercept (ms)	0		NA
Slope (ms per ng/mL)	0.0141 (0.0111; 0.0171)	<.0001	NA
Residual Variability (ms)	NA		

<b>Model 3: <math>\Delta\Delta\text{QTcF} = \text{slope} * \text{TMC278 Concentration (No Intercept)}</math></b>			
Slope (ms per ng/mL)	0.0155 (0.0125; 0.0185)	<.0001	NA
Residual Variability (ms)	NA		

The relationship between  $\Delta\Delta\text{QTcF}$  and TMC278 concentrations is visualized in Figure 12 (top). The goodness-of-fit plot in Figure 12 (bottom left) shows the observed median-quantile TMC concentrations and associated mean (90% CI)  $\Delta\Delta\text{QTcF}$ . The predicted  $\Delta\Delta\text{QTcF}$  at the mean peak TMC concentrations can be visualized in Figure 12 (bottom, right). Predicted  $\Delta\Delta\text{QTcF}$  at 75 mg/day and 300 mg/day TMC278 peak concentration was 8.85 ms (90% CI: 6.82; 10.9) and 22.5 ms (90% CI: 17.6; 27.4).

**Figure 12: Observed  $\Delta\Delta\text{QTcF}$  vs. TMC278 concentrations Together with the Population Predictions (Red Line, Top). Observed Median-Quantile TMC278 Concentrations and Associated Mean (90% CI)  $\Delta\Delta\text{QTcF}$  Together with the Mean (90% CI) Predicted  $\Delta\Delta\text{QTcF}$  (Black Line with Shaded Grey Area, Bottom Left). Mean (90% CI) Predicted  $\Delta\Delta\text{QTcF}$  at Mean  $C_{\text{max}}$  (Bottom Right) (Study TMC278-TiDP6-C131).**





**Table 26: Predicted  $\Delta\Delta$ QTcF Interval at Mean Peak TMC278 Concentration Using Model 1 (Study TMC278-TiDP6-C131)**

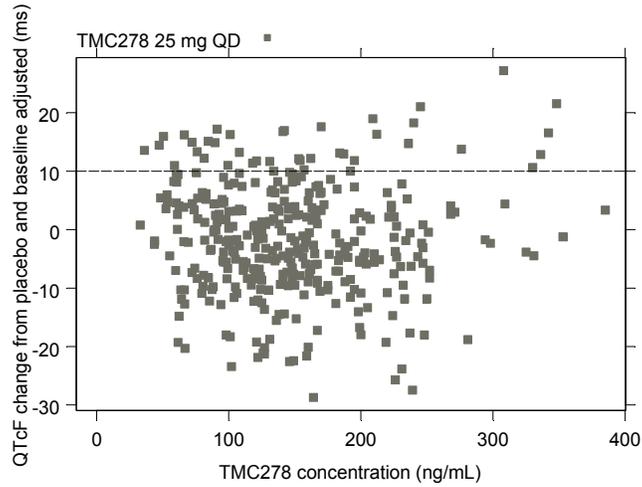
Treatment	Conc	Pred	CI
TMC278 75 mg QD	605 ng/mL	8.85	(6.82; 10.9)
TMC278 300 mg QD	1620 ng/mL	22.5	(17.6; 27.4)

**C151:**

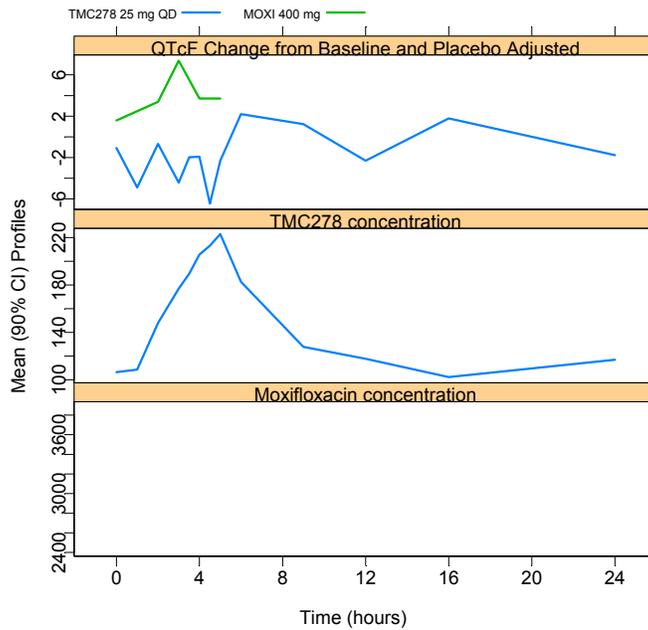
The mean drug concentration-time profile is illustrated in Figure 4.

The relationship between  $\Delta\Delta$ QTcF and TMC278 concentrations is visualized in Figure 13 with no evident of exposure-response relationship under the exposure of interest.

**Figure 13:  $\Delta\Delta$  QTcF vs. TMC278 concentration (Study TMC278-TiDP6-C151)**



**Figure 14: Mean TMC278 Concentration and Mean  $\Delta\Delta$  QTcF Interval (Study TMC278-TiDP6-C151)**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in both studies. Two subjects experienced a post-treatment QTcF between 480- 500 ms and 3 subjects had a change from baseline over 60 ms post-treatment with TMC278 300 mg.

#### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed.

##### **C131**

The global median beat with 12-lead overlay was annotated. Less than 0.4% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

##### **C151**

The global median beat with 12-lead overlay was annotated. Less than 0.3% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

##### **C152**

The global median beat with 12-lead overlay was annotated. Less than 0.4% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

#### **5.4.3 PR and QRS Interval**

There were no clinically relevant effects on the PR and QRS intervals.

#### **5.4.4 MGPS data mining analyses**

We conducted an MGPS data mining analyses of AERS for AEs related to QT prolongation with EFV and all other ARV agents used as background therapy in the phase 3 program. There are reports of TdP and sudden death with all the drugs but the signal scores (EBGM and EB 05 values) were all less than 2 indicating incidence similar to background rate. Also, on review of the TdP narratives, there were several replicates, several cases on methadone and other confounders like co-morbidities etc. The remaining cases were could not be associated to a single drug since all subjects were on multiple antiviral therapies.

**Configuration:** CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 4712  
**Dimension:** 2 **Selection Criteria:** Generic name(...) + PT(...) **Where:** EBGGM > 1.0  
**18 rows** Sorted by Generic name, EBGGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Abacavir	Sudden death	Death and sudden death	15	1.28	0.831	1.91
Abacavir	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	5	1.18	0.557	2.24
Abacavir	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	8	1.02	0.566	1.74
Efavirenz	Ventricular arrhythmia	Ventricular arrhythmias and cardiac arrest	5	1.54	0.731	2.94
Efavirenz	Sudden death	Death and sudden death	19	1.17	0.796	1.67
Efavirenz	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	7	1.11	0.588	1.94
Lamivudine	Cardiac arrest neonatal	Ventricular arrhythmias and cardiac arrest	3	1.54	0.597	3.39
Lamivudine	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	14	1.39	0.886	2.10
Lamivudine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	21	1.11	0.770	1.56
Lamivudine	Ventricular arrhythmia	Ventricular arrhythmias and cardiac arrest	5	1.01	0.479	1.93
Lamivudine	Sudden death	Death and sudden death	24	1.01	0.714	1.39
Tenofovir	Electromechanical dissociation	Ventricular arrhythmias and cardiac arrest	7	2.33	1.24	4.09
Tenofovir	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	8	1.83	1.01	3.11
Tenofovir	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	10	1.30	0.765	2.10
Tenofovir	Cardio-respiratory arrest neonatal	Ventricular arrhythmias and cardiac arrest	1	1.21	0.280	3.78
Zidovudine	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	12	2.12	1.30	3.30
Zidovudine	Cardiac arrest neonatal	Ventricular arrhythmias and cardiac arrest	6	1.77	0.892	3.22
Zidovudine	Sudden death	Death and sudden death	17	1.19	0.790	1.73

<b>ID:</b>	4712
<b>Type:</b>	MGPS
<b>Name:</b>	Generic (S)
<b>Description:</b>	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
<b>Project:</b>	CBAERS Standard Runs
<b>Configuration:</b>	CBAERS BestRep (S) (v2)
<b>Configuration description:</b>	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
<b>As of date:</b>	01/27/2011 00:00:00

<b>Item variables:</b>	Generic name, PT
<b>Stratification variables:</b>	Standard strata
<b>Highest dimension:</b>	2
<b>Minimum count:</b>	1
<b>Calculate PRR:</b>	Yes
<b>Calculate ROR:</b>	Yes
<b>Base counts on cases:</b>	Yes
<b>Use "all drugs" comparator:</b>	No
<b>Apply Yates correction:</b>	Yes
<b>Stratify PRR and ROR:</b>	No
<b>Fill in hierarchy values:</b>	Yes
<b>Exclude single itemtypes:</b>	Yes
<b>Fit separate distributions:</b>	Yes
<b>Save intermediate files:</b>	No
<b>Created by:</b>	Empirica Signal Administrator
<b>Created on:</b>	02/05/2011 09:49:58 EST
<b>User:</b>	Suchitra Balakrishnan
<b>Source database:</b>	Source Data: CBAERS data from Extract provided by CBER as of 01/27/2011 00:00:00 loaded on 2011-02-03 06:15:35.0

**Dimension: 2 Selection Criteria:** Generic name(Abacavir, Efavirenz, Lamivudine, Tenofovir, Zidovudine) + PT (Accelerated idioventricular rhythm, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Convulsion, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electromechanical dissociation, Parasystole, Presyncope, Rhythm idioventricular, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGM > 1.0

```
SELECT * FROM OutputData_4712 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Abacavir','Efavirenz','Lamivudine','Tenofovir','Zidovudine') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Convulsion','Electrocardiogram QT interval','Electrocardiogram QT interval abnormal','Electrocardiogram QT prolonged','Electromechanical dissociation','Parasystole','Presyncope','Rhythm idioventricular','Sudden cardiac death','Sudden death','Syncope','Torsade de pointes','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

## 6 APPENDIX

## 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	<p><a href="#">Include maximum proposed clinical dosing regimen.</a></p> <p>The selected therapeutic dose for TMC278 is 25 mg q.d.</p> <p>For the TQT study TMC278-TiDP6-C152, the dose used for TMC278 was 25 mg q.d. (in a previous completed TQT study (TMC278-TiDP6-C131), doses of 75 mg q.d. and 300 mg q.d. were tested)</p>	
Maximum tolerated dose	<p><a href="#">Include if studied or NOAEL dose</a></p> <p>The maximum tolerated dose in humans has not been established. A maximum dose of 300 mg has been studied after single-dose and multiple dose (q.d.) administration in healthy subjects. TMC278 was generally well tolerated in these studies.</p> <p>The maximum exposure to TMC278 was observed after co-administration of steady-state TMC278 150 mg q.d. and darunavir/ritonavir 800/100 mg q.d. in healthy subjects. In this study (TMC278-C112), the TMC278 AUC<sub>24h</sub> was increased 2.3-fold compared to administration of TMC278 150 mg q.d. alone (LS means ratio 2.30, 90% CI 1.98-2.67). TMC278 was generally well tolerated during co-administration with darunavir/ritonavir for 11 days.</p>	
Principal adverse events	<p><a href="#">Include most common adverse events; dose limiting adverse events</a></p> <p>In the pooled safety analysis of 27 Phase I trials with a total of 714 subjects of whom 615 received at least 1 dose of oral TMC278, the most common adverse events (AEs) by system organ class were nervous system disorders (32%) and gastrointestinal events (22%). The most common AE by preferred term was headache (27% in multiple dose trials). There were no apparent differences between the different doses (single doses of 12.5 mg-300 mg, multiple doses of 25 mg-150 mg for a maximum of 14 days) of TMC278 with respect to incidence of AEs.</p> <p>In the Week 96 analysis of the Phase IIb trial TMC278-C204 with a total of 279 ARV-naïve HIV-infected subjects treated with 1 of 3 doses of TMC278 (25 mg q.d., 75 mg q.d. and 150 mg q.d.), the most common AEs by system organ class during TMC278 treatment were gastrointestinal events, infections and infestations, and nervous system disorders. The most common AEs by preferred term were nausea (36%), headache (20%), upper respiratory tract infection (15%), vomiting (12%), anemia (10%), dizziness (11%) and dyspepsia (10%). There were no real dose limiting toxicities observed. However, the 150 mg dose showed a slightly higher incidence of AEs leading to discontinuation and of rash.</p> <p>In the 2 Phase III studies (TMC278-TiDP6-C209 and -C215), 686 HIV-1 infected, ARV treatment-naïve adults received TMC278 25 mg q.d. The most commonly reported AEs in subjects on TMC278 were: headache (13.8%), nausea (13.4%), diarrhea (11.4%) and nasopharyngitis (10.1%). The majority of AE's was mild or moderate in severity.</p> <p>Following AEs are considered drug related due to a suspected causal relationship to the administration of TMC278: headache, dizziness, somnolence, abnormal dreams, insomnia, sleep disorders, depression, depressed mood, nausea, abdominal pain, abdominal discomfort, vomiting, dry mouth, rash, fatigue, decreased appetite, immune reconstitution syndrome, transaminases increased.</p>	
Maximum dose tested	Single Dose	<p><a href="#">Specify dose:</a></p> <p>300 mg</p>
	Multiple Dose	<p><a href="#">Specify dosing interval and duration:</a></p> <p>300 mg q.d. for 11 days in healthy subjects (TMC278-TiDP6-C131)</p> <p>150 mg q.d. for at least 96 weeks in HIV-1-infected patients (TMC278-C204)</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p><a href="#">Mean (%CV) C<sub>max</sub> and AUC:</a></p> <p>Data from trial R278474-CDE-103:</p> <p>Mean C<sub>max</sub> ± SD: 944 ± 172 ng/mL (%CV 18.2)</p> <p>Mean AUC<sub>14h</sub> ± SD: 27910 ± 7298 ng.h/mL (%CV 26.1)</p> <p>Mean AUC<sub>∞</sub> ± SD: 32794 ± 10352 ng.h/mL (%CV 31.6)</p>
	Multiple Dose	<p><a href="#">Mean (%CV) C<sub>max</sub> and AUC:</a></p> <p>Data from trial TMC278-TiDP6-C131:</p> <p>Mean C<sub>max</sub> ± SD: 1665 ± 398.1 ng/mL (%CV 23.9)</p> <p>Mean AUC<sub>24h</sub> ± SD: 22320 ± 5947 ng.h/mL (%CV 26.6)</p>
Range of linear PK	<p><a href="#">Specify dosing regimen:</a></p> <p>50-200 mg after single-dose administration in healthy subjects</p> <p>25-150 mg q.d. after repeated administration in healthy subjects</p> <p>In HIV-1-infected patients, a less than proportional increase in exposure was observed: the exposure to TMC278 in the 75 mg q.d. and 150 mg q.d. dose groups was, respectively, 2.1-fold and 3.7-fold higher as compared to the 25 mg q.d. dose group.</p>	
Accumulation at steady state	<p><a href="#">Mean (%CV); specify dosing regimen</a></p> <p>Data from trial TMC278-C103 (dosing regimen: 25-150 mg q.d.):</p> <p>The ratio of AUC<sub>24h</sub> (mean ± SD) on Day 14 to Day 1 ranged from 2.07 ± 0.75 (%CV 36.2) to 3.02 ± 1.97 (%CV 65.1).</p>	
Metabolites	<p><a href="#">Include listing of all metabolites and activity</a></p> <p>In human subjects, TMC278 was metabolized by both oxidative pathways and conjugation. Main metabolites identified in plasma were TMC278-N-glucuronide (4-10%), hydroxymethyl-TMC278 (2%-5%) and a tricyclic metabolite (6%-10%). In urine, GSH conjugation-derived metabolites (1.2% of the dose), TMC278-N-glucuronide (0.6% of the dose) and 2 glucuronides of hydroxy-metabolites (0.9% of the dose) were found together with trace amounts of the carboxylic acid derivative. In feces, 5-hydroxypyrimidinyl-TMC278 (16% of the dose) was the most prominent</p>	

Maximum dose tested	Single Dose	Specify dose: 300 mg
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Range of linear PK	Specify dosing regimen: 50-200 mg after single-dose administration in healthy subjects 25-150 mg q.d. after repeated administration in healthy subjects In HIV-1-infected patients, a less than proportional increase in exposure was observed: the exposure to TMC278 in the 75 mg q.d. and 150 mg q.d. dose groups was, respectively, 2.1-fold and 3.7-fold higher as compared to the 25 mg q.d. dose group.	
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	metabolite. Hydroxymethyl-TMC278 (3.0%), the carboxylic acid derivative (2.7%), and a metabolite of unknown identity (2.2%) were noted together with some minor metabolites resulting from further biotransformation of hydroxymethyl-TMC278 (ring closure, formation of a carboxylic acid derivative). The 50% effective concentration in cell-based assays (EC50) for wild type virus of hydroxymethyl-TMC278 (0.4 nM) was comparable to the EC50 of TMC278 while it was 36-fold higher (less active) for hydroxypyrimidinyl-TMC278 (18 nM). Both metabolites lost activity on the resistant virus strains tested.	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) The absolute bioavailability of TMC278 in humans has not been established.
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Median (range) for parent Median T<sub>max</sub> is 4.0h (range 2.0-12.0h).</li> <li>• Median (range) for metabolites No data are available for individual metabolites. In the mass-balance study (TMC278-C119), the median T<sub>max</sub> of total radioactivity in plasma was 4.0h (3.0-4.0h) and the median T<sub>max</sub> of unchanged TMC278 was 3.5h (range 3.0-4.0h) after single-dose administration of TMC278 150 mg.</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Mean (%CV) The apparent volume of the central compartment in HIV-1 infected patients was estimated to be 152 L (inter-individual variability 117%) with the Phase III population pharmacokinetic model.
	% bound	Mean (%CV) TMC278 is extensively bound to plasma proteins (primarily albumin). More than 99% is protein bound across concentrations ranging from 10 to 3000 ng/mL. At a concentration of 100 ng/mL, the mean ± SD protein binding is 99.64 ± 0.01% (%CV 0.01).
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated The primary route of elimination of TMC278 is via the feces. After single-dose oral administration of TMC278 150 mg, the mean ± SD of total radioactivity recovered in feces was 85.1 ± 4.0% of the dose. The mean recovery of unchanged TMC278 in the feces was 25.5%, range 12.1-33.4%.</li> <li>• Other routes Renal clearance is a minor route for elimination of TMC278. After single-dose oral administration of TMC278 150 mg, the mean ± SD of total radioactivity recovered in the urine was 6.1 ± 2.1% of the dose, with only trace amounts of unchanged TMC278.</li> </ul>

Race	<p>Specify mean changes in C<sub>max</sub> and AUC</p> <p>The exposure to TMC278 was somewhat higher in Asian HIV-1-infected patients compared to the rest of the population (majority Caucasians and Blacks/African Americans). In the covariate analysis of the pooled Phase III pharmacokinetic data, a statistically significant effect of race on the CL/F of TMC278 was observed, resulting in a slightly lower CL/F in Asian subjects (17.2% lower) compared to the rest of the population. This covariate-induced difference in CL/F is considered not to be of clinical relevance and was not retained in the final population pharmacokinetic model. Data on C<sub>max</sub> were not obtained in this population pharmacokinetic analysis. A similar observation was made in the Phase IIb trial, where Asian subjects had a somewhat higher exposure to TMC278.</p>
Hepatic & Renal Impairment	<p>Specify mean changes in C<sub>max</sub> and AUC</p> <p>TMC278 is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of TMC278 was 47% (AUC<sub>24h</sub>) and 27% (C<sub>max</sub>) higher in subjects with mild hepatic impairment and 5% higher (AUC<sub>24h</sub>) and 5% lower (C<sub>max</sub>) in subjects with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. TMC278 has not been studied in subjects with severe hepatic impairment (Child-Pugh score C).</p> <p>The pharmacokinetics of TMC278 have not been evaluated in subjects with renal impairment. Renal elimination of TMC278 is negligible, and therefore, the impact of renal impairment on TMC278 elimination is expected to be minimal.</p>

Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in C<sub>max</sub> and AUC</p> <p><b>Summary of Drug-Drug Interactions: the Effect of Steady-state TMC278 on the Pharmacokinetics of Coadministered Drugs</b></p>																																																																																																																																			
		<table border="1"> <thead> <tr> <th rowspan="2">Coadministered drug</th> <th colspan="2">Dosage</th> <th rowspan="2">n</th> <th rowspan="2">effect</th> <th colspan="3">Ratio<sup>a</sup> (90% CI) of the pharmacokinetic parameters of the coadministered drug with/without TMC278</th> </tr> <tr> <th>Coadmin. drug</th> <th>TMC278 mg q.d.</th> <th>C<sub>max</sub></th> <th>AUC<sub>t</sub></th> <th>C<sub>min</sub></th> </tr> </thead> <tbody> <tr> <td>Atorvastatin</td> <td>40 mg q.d.</td> <td>150</td> <td>16</td> <td>↔</td> <td>1.35 (1.08-1.68)</td> <td>1.04 (0.97-1.12)</td> <td>0.85 (0.69-1.03)</td> </tr> <tr> <td>Chlorzoxazone</td> <td>500 mg*</td> <td>150</td> <td>16</td> <td>↔</td> <td>0.98 (0.85-1.13)</td> <td>1.03 (0.95-1.13)</td> <td>NA</td> </tr> <tr> <td>darunavir ritonavir</td> <td>800 mg q.d. 100 mg q.d.</td> <td>150</td> <td>14</td> <td>↔</td> <td>0.90 (0.81-1.00) 0.83 (0.72-0.95)</td> <td>0.89 (0.81-0.99) 0.85 (0.78-0.91)</td> <td>0.89 (0.68-1.16) 0.78 (0.68-0.90)</td> </tr> <tr> <td>Didanosine</td> <td>400 mg q.d.</td> <td>150</td> <td>13</td> <td>↔</td> <td>0.96 (0.80-1.14)</td> <td>1.12 (0.99-1.27)</td> <td>NA</td> </tr> <tr> <td>Ketoconazole</td> <td>400 mg q.d.</td> <td>150</td> <td>14</td> <td>↓</td> <td>0.85 (0.80-0.90)</td> <td>0.76 (0.70-0.82)</td> <td>0.34 (0.25-0.46)</td> </tr> <tr> <td>lopinavir (LPV)<sup>b</sup> ritonavir<sup>b</sup></td> <td>400 mg b.i.d. 100 mg b.i.d.</td> <td>150</td> <td>15</td> <td>↔</td> <td>0.96 (0.88-1.05) 0.89 (0.73-1.08)</td> <td>0.99 (0.89-1.10) 0.96 (0.84-1.11)</td> <td>0.89 (0.73-1.08) 1.07 (0.89-1.28)</td> </tr> <tr> <td>Omeprazole</td> <td>20 mg q.d.</td> <td>150</td> <td>15</td> <td>↔</td> <td>0.86 (0.68-1.09)</td> <td>0.86 (0.76-0.97)</td> <td>BLOQ</td> </tr> <tr> <td>oral contraceptive ethinylestradiol<sup>f</sup> norethindrone<sup>c</sup></td> <td>35 µg q.d. 1.0 mg q.d.</td> <td>150</td> <td>15</td> <td>↔ ↓</td> <td>1.12 (1.01-1.24) 0.67 (0.60-0.74)</td> <td>0.99 (0.93-1.06) 0.59 (0.56-0.61)</td> <td>0.83 (0.75-0.91) 0.54 (0.49-0.59)</td> </tr> <tr> <td>oral contraceptive ethinylestradiol<sup>f</sup> norethindrone<sup>c</sup></td> <td>35 µg q.d. 1.0 mg q.d.</td> <td>25</td> <td>17</td> <td>↔↔↔</td> <td>1.17 (1.06-1.30) 0.94 (0.83-1.06)</td> <td>1.14 (1.10-1.19) 0.89 (0.84-0.94)</td> <td>1.09 (1.03-1.16) 0.99 (0.90-1.08)</td> </tr> <tr> <td>Paracetamol</td> <td>500 mg*</td> <td>150</td> <td>16</td> <td>↔</td> <td>0.97 (0.86-1.10)</td> <td>0.92 (0.85-0.99)</td> <td>NA</td> </tr> <tr> <td>Rifabutin</td> <td>300 mg q.d.</td> <td>150</td> <td>17</td> <td>↔</td> <td>1.03 (0.93-1.14)</td> <td>1.03 (0.97-1.09)</td> <td>1.01 (0.94-1.09)</td> </tr> <tr> <td>rifampin<sup>d</sup></td> <td>600 mg q.d.</td> <td>150</td> <td>16</td> <td>↔</td> <td>1.02 (0.93-1.12)</td> <td>0.99 (0.92-1.07)</td> <td>BLOQ</td> </tr> <tr> <td>tenofovir disoproxil fumarate (TDF)</td> <td>300 mg q.d.</td> <td>150</td> <td>16</td> <td>↑</td> <td>1.19 (1.06-1.34)</td> <td>1.23 (1.16-1.31)</td> <td>1.24 (1.10-1.38)</td> </tr> <tr> <td>R(-) methadone</td> <td>60 to 100 mg q.d. individualized dose</td> <td>25</td> <td>13</td> <td>↓</td> <td>0.86 (0.78-0.95)</td> <td>0.84 (0.74-0.95)</td> <td>0.78 (0.67-0.91)</td> </tr> <tr> <td>Sildenafil</td> <td>50 mg*</td> <td>75</td> <td>16</td> <td>↔</td> <td>0.93 (0.80-1.08)</td> <td>0.98 (0.87-1.08)</td> <td>NA</td> </tr> </tbody> </table> <p>n = number of subjects; AUC<sub>t</sub> = AUC over the dosing interval; BLOQ = below limit of quantification; AUC = AUC<sub>0-∞</sub>;  CI = confidence interval; NA = not applicable, *single dose administration, ↔ = no change, ↓ = reduced exposure, ↑ = increased exposure  <sup>a</sup>Ratio of the least square means (a ratio of 1.00 indicates absence of an interaction)  <sup>b</sup>LPV/r administered as co-formulation (Kaletra<sup>®</sup> soft-gel capsules)  <sup>c</sup>Ethinylestradiol and norethindrone administered as co-formulation (Ortho-Novum<sup>®</sup> or Ovysmen<sup>®</sup>)  <sup>d</sup>TMC278 coadministered as oral solution</p>	Coadministered drug	Dosage		n	effect	Ratio <sup>a</sup> (90% CI) of the pharmacokinetic parameters of the coadministered drug with/without TMC278			Coadmin. drug	TMC278 mg q.d.	C <sub>max</sub>	AUC <sub>t</sub>	C <sub>min</sub>	Atorvastatin	40 mg q.d.	150	16	↔	1.35 (1.08-1.68)	1.04 (0.97-1.12)	0.85 (0.69-1.03)	Chlorzoxazone	500 mg*	150	16	↔	0.98 (0.85-1.13)	1.03 (0.95-1.13)	NA	darunavir ritonavir	800 mg q.d. 100 mg q.d.	150	14	↔	0.90 (0.81-1.00) 0.83 (0.72-0.95)	0.89 (0.81-0.99) 0.85 (0.78-0.91)	0.89 (0.68-1.16) 0.78 (0.68-0.90)	Didanosine	400 mg q.d.	150	13	↔	0.96 (0.80-1.14)	1.12 (0.99-1.27)	NA	Ketoconazole	400 mg q.d.	150	14	↓	0.85 (0.80-0.90)	0.76 (0.70-0.82)	0.34 (0.25-0.46)	lopinavir (LPV) <sup>b</sup> ritonavir <sup>b</sup>	400 mg b.i.d. 100 mg b.i.d.	150	15	↔	0.96 (0.88-1.05) 0.89 (0.73-1.08)	0.99 (0.89-1.10) 0.96 (0.84-1.11)	0.89 (0.73-1.08) 1.07 (0.89-1.28)	Omeprazole	20 mg q.d.	150	15	↔	0.86 (0.68-1.09)	0.86 (0.76-0.97)	BLOQ	oral contraceptive ethinylestradiol <sup>f</sup> norethindrone <sup>c</sup>	35 µg q.d. 1.0 mg q.d.	150	15	↔ ↓	1.12 (1.01-1.24) 0.67 (0.60-0.74)	0.99 (0.93-1.06) 0.59 (0.56-0.61)	0.83 (0.75-0.91) 0.54 (0.49-0.59)	oral contraceptive ethinylestradiol <sup>f</sup> norethindrone <sup>c</sup>	35 µg q.d. 1.0 mg q.d.	25	17	↔↔↔	1.17 (1.06-1.30) 0.94 (0.83-1.06)	1.14 (1.10-1.19) 0.89 (0.84-0.94)	1.09 (1.03-1.16) 0.99 (0.90-1.08)	Paracetamol	500 mg*	150	16	↔	0.97 (0.86-1.10)	0.92 (0.85-0.99)	NA	Rifabutin	300 mg q.d.	150	17	↔	1.03 (0.93-1.14)	1.03 (0.97-1.09)	1.01 (0.94-1.09)	rifampin <sup>d</sup>	600 mg q.d.	150	16	↔	1.02 (0.93-1.12)	0.99 (0.92-1.07)	BLOQ	tenofovir disoproxil fumarate (TDF)	300 mg q.d.	150	16	↑	1.19 (1.06-1.34)	1.23 (1.16-1.31)	1.24 (1.10-1.38)	R(-) methadone	60 to 100 mg q.d. individualized dose	25	13	↓	0.86 (0.78-0.95)	0.84 (0.74-0.95)	0.78 (0.67-0.91)	Sildenafil	50 mg*	75	16	↔	0.93 (0.80-1.08)
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Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in C<sub>max</sub> and AUC</p> <p><b>Summary of Drug-Drug Interactions: the Effect of Steady-state TMC278 on the Pharmacokinetics of Coadministered Drugs</b></p>																																																																																																																																													
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C <sub>max</sub>	AUC <sub>t</sub>	C <sub>min</sub>	Atorvastatin	40 mg q.d.	150	16	↔	1.35 (1.08-1.68)	1.04 (0.97-1.12)	0.85 (0.69-1.03)	Chlorzoxazone	500 mg*	150	16	↔	0.98 (0.85-1.13)	1.03 (0.95-1.13)	NA	darunavir ritonavir	800 mg q.d. 100 mg q.d.	150	14	↔	0.90 (0.81-1.00) 0.83 (0.72-0.95)	0.89 (0.81-0.99) 0.85 (0.78-0.91)	0.89 (0.68-1.16) 0.78 (0.68-0.90)	Didanosine	400 mg q.d.	150	13	↔	0.96 (0.80-1.14)	1.12 (0.99-1.27)	NA	Ketoconazole	400 mg q.d.	150	14	↓	0.85 (0.80-0.90)	0.76 (0.70-0.82)	0.34 (0.25-0.46)	lopinavir (LPV) <sup>b</sup> ritonavir <sup>b</sup>	400 mg b.i.d. 100 mg b.i.d.	150	15	↔	0.96 (0.88-1.05) 0.89 (0.73-1.08)	0.99 (0.89-1.10) 0.96 (0.84-1.11)	0.89 (0.73-1.08) 1.07 (0.89-1.28)	Omeprazole	20 mg q.d.	150	15	↔	0.86 (0.68-1.09)	0.86 (0.76-0.97)	BLOQ	oral contraceptive ethinylestradiol <sup>c</sup> norethindrone <sup>c</sup>	35 µg q.d.	150	15	↔	1.12 (1.01-1.24)	0.99 (0.93-1.06)	0.83 (0.75-0.91)	1.0 mg q.d.	↓	0.67 (0.60-0.74)	0.59 (0.56-0.61)	0.54 (0.49-0.59)	oral contraceptive ethinylestradiol <sup>c</sup> norethindrone <sup>c</sup>	35 µg q.d.	25	17	↔↔	1.17 (1.06-1.30) 0.94 (0.83-1.06)	1.14 (1.10-1.19) 0.89 (0.84-0.94)	1.09 (1.03-1.16) 0.99 (0.90-1.08)	1.0 mg q.d.					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Food Effects	<p>Specify mean changes in C<sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <p>Data from trial TMC278-TiDP6-C137 :</p> <p><b>Pharmacokinetic Parameters of TMC278 after Administration of TMC278 after a Standard Breakfast, Under Fasting Conditions, after a High-fat Breakfast and after a Nutritional Drink</b></p>																																		
	<table border="1"> <thead> <tr> <th>Pharmacokinetics of TMC278 (mean ± SD, t<sub>max</sub>, median [range])</th> <th>Standard breakfast (reference)<sup>b</sup></th> <th>Fasting conditions (Test 1)</th> <th>High-fat breakfast (Test 2)</th> <th>Nutritional drink Ensure<sup>®</sup> HP (Test 3)</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>19</td> <td>19</td> <td>19<sup>a</sup></td> <td>18</td> </tr> <tr> <td>t<sub>max</sub>, h</td> <td>5.0 (2.0 - 9.0)</td> <td>4.0 (2.0 - 24.0)</td> <td>5.0 (3.0 - 9.0)</td> <td>5.0 (4.0 - 9.0)</td> </tr> <tr> <td>C<sub>max</sub>, ng/mL</td> <td>296.4 ± 117.6</td> <td>170.2 ± 65.61</td> <td>279.8 ± 102.6</td> <td>156.0 ± 59.66</td> </tr> <tr> <td>AUC<sub>last</sub>, ng.h/mL</td> <td>10340 ± 3894</td> <td>6230 ± 2339</td> <td>9717 ± 3535</td> <td>5437 ± 2421</td> </tr> <tr> <td>AUC<sub>∞</sub>, ng.h/mL</td> <td>11450 ± 4431</td> <td>7202 ± 3024</td> <td>10670 ± 4331</td> <td>6094 ± 3047</td> </tr> <tr> <td>t<sub>1/2αem</sub>, h</td> <td>47.98 ± 22.08</td> <td>54.84 ± 28.25</td> <td>43.05 ± 17.28</td> <td>47.29 ± 22.89</td> </tr> </tbody> </table> <p><sup>a</sup>n=18 for AUC<sub>last</sub>, AUC<sub>∞</sub> and t<sub>1/2αem</sub>  <sup>b</sup>The standardized breakfast consisted of 4 slices of bread, 2 slices of ham or cheese, butter, jam, and two cups of decaffeinated coffee or tea with milk and/or sugar.</p> <p>The exposure expressed as C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>∞</sub> of TMC278 was 40-50% lower when TMC278 was administered under fasting conditions or after a protein rich nutritional drink (Ensure<sup>®</sup> HP), compared to TMC278 administered after a standard breakfast. Administration of TMC278 after a high-fat breakfast or after a standard breakfast resulted in similar exposures. TMC278 should therefore always be administered with a meal for optimal absorption.</p>	Pharmacokinetics of TMC278 (mean ± SD, t <sub>max</sub> , median [range])	Standard breakfast (reference) <sup>b</sup>	Fasting conditions (Test 1)	High-fat breakfast (Test 2)	Nutritional drink Ensure <sup>®</sup> HP (Test 3)	N	19	19	19 <sup>a</sup>	18	t <sub>max</sub> , h	5.0 (2.0 - 9.0)	4.0 (2.0 - 24.0)	5.0 (3.0 - 9.0)	5.0 (4.0 - 9.0)	C <sub>max</sub> , ng/mL	296.4 ± 117.6	170.2 ± 65.61	279.8 ± 102.6	156.0 ± 59.66	AUC <sub>last</sub> , ng.h/mL	10340 ± 3894	6230 ± 2339	9717 ± 3535	5437 ± 2421	AUC <sub>∞</sub> , ng.h/mL	11450 ± 4431	7202 ± 3024	10670 ± 4331	6094 ± 3047	t <sub>1/2αem</sub> , h	47.98 ± 22.08	54.84 ± 28.25	43.05 ± 17.28
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Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>TMC278 is primarily metabolized by CYP3A4. It is therefore anticipated that high exposure to TMC278 may occur during co-administration of potent inhibitors of CYP3A4. In a drug-drug interaction study with the established CYP3A4 inhibitor ketoconazole at a dose of 400 mg q.d., the TMC278 AUC<sub>24h</sub> increased by 1.49-fold (90% CI 1.31-1.70) and the C<sub>max</sub> increased by 1.3-fold (90% CI 1.13-1.48). In combination with darunavir/ritonavir 800/100 mg q.d., the TMC278 AUC<sub>24h</sub> increased by 2.3-fold (90% CI 1.98-2.67) and the C<sub>max</sub> increased by 1.8-fold (90% CI 1.56-2.06), which is the most pronounced effect observed in drug-drug interaction studies conducted to date.</p> <p>A TMC278 dose of 25 mg q.d. has been selected for further clinical development. The mean steady-state TMC278 exposure in HIV-1- infected patients (pooled Phase III) at this dose was 2397 h*ng/mL (AUC<sub>24h</sub>, all subjects) and 134 ng/mL (C<sub>max</sub>, PK substudy Phase III).</p>
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The effect of TMC278 on the QT interval corrected by Fridericia's formula (QTcF) was evaluated in 2 thorough QT trials in healthy subjects. TMC278 at the recommended dose of 25 mg q.d. (TMC278-C152) did not demonstrate any clinically relevant effect on the QTcF interval: the mean maximum time-matched difference in QTcF versus placebo was +2.0 msec (90%CI: -1.0-5.0). The mean steady-state TMC278 exposure in this trial in healthy subjects was 3324 h\*ng/mL ( $AUC_{24h}$ ) and 247 ng/mL ( $C_{max}$ ). In a previous TQT study (TMC278-C131), supratherapeutic doses of TMC278 up to 12 times the selected dose of 25 mg q.d. (i.e., 75 and 300 mg q.d.) were used. A mean maximum time-matched difference from placebo in QTcF interval of +10.7 msec (90%CI: 6.1-15.3) was shown for 75 mg q.d. and +23.3 msec (90%CI: 18.1-28.4) for 300 mg q.d. Within the range of exposures observed with the TMC278 25 mg q.d. dose (TMC278-C152), there was no apparent relationship between TMC278 plasma concentration and change in QTcF interval. A positive TMC278 plasma concentration-relationship with changes in the QTcF interval was seen with the higher TMC278 doses of 75 mg q.d. and 300 mg q.d. (TMC278-C131), indicating that the potential for prolongation of the QTcF interval is dose- and plasma concentration-dependent.

In order to explore the increase in TMC278 exposure (based on  $C_{max}$ ) compared to the exposure obtained with TMC278 25 mg q.d. that can still be assumed to have no discernable effect on the QTcF interval (i.e., upper limit of the 90% CI of the mean QTcF interval prolongation < 10 ms), simulations were performed to assess the effect of increases in TMC278 exposure on the upper limit of the 2-sided 90% CI of the mean QTcF interval prolongation. The basis for this analysis were the combined plasma concentration and QTcF interval data obtained from the thorough QT trials C131 and C152 in healthy subjects, and a linear mixed effects model for the time-matched and placebo-corrected (double delta) QTcF interval. With these analyses, it was determined that there is a probability of 80% that the upper limit of the 2-sided 90% CI of the mean change in QTcF interval remains below 10 ms at an increase in exposure ( $C_{max}$ ) of 85% (1.85-fold) compared to the  $C_{max}$  at the 25 mg q.d. dose in healthy subjects, taking into account the variability in the pharmacokinetics. The impact of possible factors (e.g., drug-drug interactions) that would increase the exposure to TMC278 (based on  $C_{max}$ ) by no more than 85% (1.85-fold) is not expected to be of clinical relevance or cause safety concerns, and would therefore not result in the need for dose adjustment.

In addition, no obvious relationship was seen between the exposure to TMC278 and the occurrence of AEs or clinically relevant changes in laboratory parameters of interest in the Phase III trials in HIV-1 infected patients.

Table 6.2: ECG/PK Sampling Table for Study 131 (A) and Study 151 (B)

Day	Time	Blood sample		Urine sample	ECG <sup>c</sup>	Vital signs <sup>d</sup>	Other <sup>e</sup>
		Drug <sup>a</sup>	Safety <sup>b</sup>				
<b>Treatments A, B, and C (Sessions I, II, or III)</b>							
-2							Admission to the unit in the evening
-1	0 h	X <sup>gh</sup>	X <sup>g</sup>	X <sup>j</sup>	X <sup>k</sup>	X <sup>l</sup>	Physical examination <sup>f</sup> Urine pregnancy test Standard breakfast Start of 24-hour urine collection
	1 h				X		
	2 h				X		Resume water intake
	3 h				X		
	3.5 h				X		
	4 h				X		
	4.5 h				X		
	5 h				X		Standard lunch <sup>m</sup>
	6 h				X		
	9 h				X		Resume normal diet
	12 h				X		
	16 h				X		
	1	24 h / predose	X <sup>ga</sup>	X <sup>g</sup>		X <sup>k</sup>	X <sup>l</sup>
0 h							Trial medication intake
0.5 h		X <sup>i</sup>					
1 h		X <sup>i</sup>			X		
2 h		X <sup>i</sup>			X		Resume water intake
3 h		X <sup>i</sup>			X		
3.5 h		X <sup>i</sup>			X		
4 h		X <sup>i</sup>			X		
4.5 h		X <sup>i</sup>			X		
5 h		X <sup>i</sup>			X		Standard lunch <sup>m</sup>
6 h		X <sup>i</sup>			X		
9 h		X <sup>i</sup>			X		Resume normal diet
12 h		X <sup>i</sup>			X		
16 h	X <sup>i</sup>			X			
<b>Treatments A, B, and C (Sessions I, II, or III)</b>							
Day	Time	Blood sample Drug <sup>a</sup>	Blood sample Safety <sup>b</sup>	Urine sample	ECG <sup>c</sup>	Vital signs <sup>d</sup>	Other <sup>e</sup>
2	24 h	X <sup>fg</sup>	X <sup>f</sup>	X <sup>h</sup>	X <sup>i</sup>		Standard breakfast Trial medication intake Discharge from unit
3-8							Trial medication intake at home in the morning
9	predose	X <sup>fg</sup>			X <sup>i</sup>		Skin examination Standard breakfast
	0 h						Trial medication intake
10	predose	X <sup>fg</sup>			X <sup>i</sup>		Skin examination Standard breakfast
	0 h						Trial medication intake
11	predose	X <sup>fg</sup>	X <sup>f</sup>	X <sup>h</sup>	X <sup>i</sup>	X <sup>j</sup>	Admission to the unit in the evening Standard breakfast Start of 24 h urine collection
	0 h						Trial medication intake
	0.5 h	X <sup>g</sup>					
	1 h	X <sup>g</sup>			X		
	2 h	X <sup>g</sup>			X		Resume water intake
	3 h	X <sup>g</sup>			X		
	3.5 h	X <sup>g</sup>			X		
	4 h	X <sup>g</sup>			X		
	4.5 h	X <sup>g</sup>			X		
	5 h	X <sup>g</sup>			X		Standard lunch <sup>k</sup>
	6 h	X <sup>g</sup>			X		
	9 h	X <sup>g</sup>			X		Resume normal diet
	12 h	X <sup>g</sup>			X		
16 h	X <sup>g</sup>			X			

(A)

Treatments A and B:

Day	Time	Blood sample		Urine sample <sup>e</sup>	ECG <sup>c</sup>	Vital signs <sup>d</sup>	Other <sup>e</sup>
		Drug <sup>a</sup>	Safety <sup>b</sup>				
-2							Admission to the unit in the evening Start overnight fast
-1		X <sup>g</sup>	X <sup>g</sup>	X	X	X	Physical examination <sup>f</sup> Urine pregnancy test (if applicable) Standard breakfast
	0 h						
	0.5 h	X					
	1 h	X			X		
	2 h	X			X		Resume water intake
	3 h	X			X		
	3.5 h	X			X		
	4 h	X			X		
	4.5 h	X			X		
	5 h	X			X		Standard lunch <sup>l</sup>
	6 h	X			X		
	9 h	X			X		Resume normal diet
	12 h	X			X		
	14 h						Start overnight fast
	16 h	X			X		
1	24 h/ Predose	X <sup>g,h</sup>	X <sup>g</sup>	X	X <sup>k</sup>	X	Standard breakfast
	0 h						Trial medication intake in unit Discharge from unit
2-8							Trial medication intake at home in the morning after breakfast
9	predose	X <sup>g,h</sup>			X <sup>k</sup>		Skin examination Standard breakfast
	0 h						Trial medication intake in unit
10	predose	X <sup>g,h</sup>			X <sup>k</sup>		Skin examination <sup>m</sup> Standard breakfast
	0 h						Trial medication intake in unit
							Admission to the unit in the evening Urine drug screen Start overnight fast
Day	Time	Blood sample		Urine sample <sup>e</sup>	ECG <sup>c</sup>	Vital signs <sup>d</sup>	Other <sup>e</sup>
		Drug <sup>a</sup>	Safety <sup>b</sup>				
11	predose	X <sup>g,h</sup>	X <sup>g</sup>	X	X <sup>k</sup>	X	Standard breakfast
	0 h						Trial medication intake in unit
	0.5 h	X <sup>h</sup>					
	1 h	X <sup>h</sup>			X		
	2 h	X <sup>h</sup>			X		Resume water intake
	3 h	X <sup>h</sup>			X		
	3.5 h	X <sup>h</sup>			X		
	4 h	X <sup>h</sup>			X		
	4.5 h	X <sup>h</sup>			X		
	5 h	X <sup>h</sup>			X		Standard lunch <sup>l</sup>
	6 h	X <sup>h</sup>			X		
	9 h	X <sup>h</sup>			X		Resume normal diet
	12 h	X <sup>h</sup>			X		
	14 h						Start overnight fast
	16 h	X <sup>h</sup>			X		
12	24 h/ Predose	X <sup>g,h</sup>	X <sup>g</sup>	X	X <sup>k</sup>	X	Urine pregnancy test (if applicable) Standard breakfast
	0 h						Trial medication intake in unit
	2 h				X		Resume water intake
	3 h				X		
	4 h	X <sup>i</sup>			X		
	5 h				X		Standard lunch <sup>l</sup> Discharge from Unit

(B)

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/s/  
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HAO ZHU

02/24/2011

Dr. Hui Zheng is the primary clinical pharmacology reviewer

JANICE BRODSKY

02/25/2011

JOANNE ZHANG

02/25/2011

JOHN E KOERNER

02/25/2011

SUCHITRA M BALAKRISHNAN

02/25/2011

NORMAN L STOCKBRIDGE

02/25/2011



NDA 202-022

**INFORMATION REQUEST**

Tibotec, Inc.  
Attention: Debora Monshizadegan  
Associate Director  
1125 Trenton-Harbourton Road  
Titusville, NJ 08560

Dear Ms. Monshizadegan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rilpivirine (TMC278).

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request your written response to the NDA by February 25, 2011.

1. With regards to the 18-month stability data update of October 2010, please update the statistical analysis presented in 3.2.P.5.6.1.5. Specifically, please update Tables 3 and 4, where the probability of Stage 2 testing and the batch failure rate are predicted for  $Q = \text{(b) (4)}$  at 45 minutes vs.  $Q = \text{(b) (4)}$  at 45 minutes. Please include predictions for 24 and 36 months, based on most current information.
2. Please submit 24-month stability data for 25 °C/60% RH and 30 °C/ 75% RH, if available. If not available, please provide timing for the data and updated analysis to be submitted.
3. Please provide the individual dissolution data of the three primary stability batches at initial time points (t=0) which were used to construct the Figure 1 (page 5) in the section 3.2.P.5.6.1.5.2 of the original submission.
4. You provided on December 22, 2010, the comparative dissolution testing between the clinical (non-debossed) IR tablets and the to-be-marketed (debossed) IR tablets. However, you only provided the means and the ranges (in parenthesis). The individual dissolution data could not be located.

Please provide the needed individual dissolution data of the lots used to construct Table 8 (page 10). Please also provide the manufacturing information (the manufacturing date, site, and batch size) on the lot Nos. AJL2K, AJL2L and AJL2M.

If you have already submitted the needed information, please provide the Module, Section, Volume, and Page Nos. in the NDA.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Robert Kosko, Regulatory Project Manager the Office of New Drugs (Robert.Kosko@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Stephen P. Miller, Ph.D.  
Acting Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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STEPHEN P MILLER  
02/17/2011

# DSI CONSULT: Request for Clinical Inspections

**Date:** September 21, 2010

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Antoine El Hage, Ph.D., Pharmacologist, GCP2  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Yodit Belew, M.D., Clinical Reviewer, DAVP  
Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP  
Debra Birnkrant, M.D., Director, DAVP

**From:** Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager, DAVP

**Subject:** **Request for Clinical Site Inspections**

## I. General Information

Application#: NDA 202022

Applicant/ Applicant contact information (to include phone/email):

Debbie Monshizadegan  
Assoc. Director, Global Regulatory Affairs

Tibotec Inc.  
1125 Trenton-Harbourton Rd  
Rm K21410

Titusville, NJ 08560  
[dmonshiz@its.jnj.com](mailto:dmonshiz@its.jnj.com)

Phone: (609) 730-7504  
Cell: (215) 666-1371  
Fax: (609) 730-7501

Drug Proprietary Name: Pending

NME or Original BLA (Yes/No): Yes

DSI Consult  
version: 5/08/2008

Page 2-Request for Clinical Inspections

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of HIV-1 infection

PDUFA: May 23, 2010

Action Goal Date: Same as PDUFA

Inspection Summary Goal Date:

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects Enrolled</b>	<b>Indication</b>
<b>BR00014</b> RANGEL, Frederico RANGEL E GUIMARÃES ASSESSORIA EM PESQUISA CLINICA LTDA R Da Hora 559 Recife PE 52020-010 Brazil Phone: +55 81 3423.3131/3423.2611 Fax: +55 81 32217324 Email: frederico-rangel@uol.com.br	C215	33	Treatment of HIV-1 infection
<b>CR00004</b> HERRERA-MARTINEZ, Gisela CORPORACION GIHEMA S.A Barrio Aranjuez - De La Iglesia De Santa Teresita 200 Metros Al Norte Y 25 Metros Oeste Barrio Aranjuez, San Jose 00000 Costa Rica Phone: (506) 2223-6923 Fax: (506) 2221-0065 Email: N/A	C215	27	Treatment of HIV-1 infection
<b>ZA00028</b> FOURIE, Jan JAN FOURIE MEDICAL PRACTICE 58 Ann Street Dundee 3000 South Africa Phone: 034.2182092/3 Fax: 034.2182095 Email: plankics@trustnet.co.sa	C215	35	Treatment of HIV-1 infection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Indication
<b>US00258</b> LALEZARI,Jacob QUEST CLINICAL RESEARCH 2300 Sutter Street Suite 202 San Francisco CA 94115 Phone: (415) 353-0800 Fax: (415) 353-0801 Email: drjay@questclinical.com	C215	18	Treatment of HIV-1 infection

**III. Site Selection/Rationale**

*The study is a multi-center, international study. There were over 90 investigators and sites used for enrollment of subjects into protocol c215. The rationales for site selection for DSI audit include the number of subjects enrolled by a specific investigator or site as well as the reported virologic success rate. Overall, the non-U.S. sites enrolled the most number of subjects. Amongst these sites, those who reported the highest number of subjects with virologic success were selected for DSI Audit. In addition to the foreign sites, one U.S. site has been included for audit. The number of subjects enrolled into the selected U.S. site, although smaller than the foreign sites, was among the U.S. sites that enrolled a large number of subjects.*

***Rationale for DSI Audits***

*This NDA application is for an NME. As such, a DSI audit is warranted.*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): The Division would like to have at least 1 domestic site inspected.

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):  
Enrollment of large numbers of study subjects;  
This would be the first approval of this new drug and most of the limited experience with this drug has been from foreign sites; it would be desirable to include foreign sites in the DSI audits to verify the quality of conducted study.

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Robert G. Kosko, Jr., Pharm.D., M.P.H. (RPM) at 301-796-3979 or Yodit Belew, M.D. (Clinical Reviewer) at 301-796-0705.

Concurrence: (as needed)

<input checked="" type="checkbox"/>	Medical Team Leader
<input checked="" type="checkbox"/>	Medical Reviewer
<input checked="" type="checkbox"/>	Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/  
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Robert G Kosko  
09/21/2010

YODIT BELEW  
09/21/2010

KIMBERLY A STRUBLE  
09/21/2010

DEBRA B BIRNKRANT  
09/21/2010

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

<b>Application Information</b>		
NDA # 202022	NDA Supplement #: N/A	Efficacy Supplement Type: N/A
Proprietary Name: (b) (4) (pending) Established/Proper Name: rilpivirine Dosage Form: Tablet Strengths: 25mg		
Applicant: Tibotec, Inc. Agent for Applicant (if applicable): Debora Monshizadegan		
Date of Application: July 23, 2010 Date of Receipt: July 23, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: May 23, 2011	Action Goal Date (if different):	
Filing Date: September 21, 2010	Date of Filing Meeting: August 31, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only): Type 1		
Proposed indication(s)/Proposed change(s): Treatment of human immunodeficiency virus (HIV) infection		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>            and refer to Appendix A for further information.</i></b>		
Review Classification:	<input checked="" type="checkbox"/> Standard	<input type="checkbox"/> Priority
<b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>		
<b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	
Collaborative Review Division (if OTC product): N/A		

List referenced IND Number(s): IND 67,699				
<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>		X		
<b>If yes</b> , explain in comment column.			X	
<b>If affected by AIP</b> , has OC/DMPQ been notified of the submission? <b>If yes</b> , date notified:			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application:  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
  <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		X																		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, please list below:</b>		X																		
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X																		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			5 Years																

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 ( <i>BLA</i> s/ <i>BLA</i> efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X			
<b>Controlled substance/Product with abuse potential:</b> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #				

<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p>	X			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is patent information submitted on form FDA 3542a?</p>	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			

<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		Requested 8-23-10
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>		X		Requested 8-23-10
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>		X		Requested 8-23-10
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Submitted and received 8-25-10. Sent to OSE/DMEPA for review 8-26-10.
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			X	

Are annotated specifications submitted for all stock keeping units (SKUs)?			X	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?			X	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			ECG files uploaded to E-Scribe ECG Warehouse
<i>If yes, specify consult(s) and date(s) sent:</i>				

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> July 18, 2007	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> June 3, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 31, 2010

**BLA/NDA/Supp #:** 202022

**PROPRIETARY NAME:** (b) (4) (pending)

**ESTABLISHED/PROPER NAME:** rilpivirine

**DOSAGE FORM/STRENGTH:** 25mg Tablets

**APPLICANT:** Tibotec, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of human immunodeficiency virus (HIV) infection

**BACKGROUND:** Tibotec, Inc. (Tibotec) is developing a non-nucleoside reverse transcriptase inhibitor (NNRTI), TMC278 (rilpivirine, RPV), and is seeking an indication for the treatment of HIV-1 infection in treatment naïve patients. The NDA application was submitted on July 23, 2010 and was given a standard review. The goal date for action on this NDA is May 23, 2010.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Robert G. Kosko, Jr., Pharm.D., M.P.H.	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kimberly Struble, Pharm.D.		Y
Clinical	Reviewer:	Yodit Belew, M.D.	Y
	TL:	Kimberly Struble, Pharm.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Virology ( <i>for antimicrobial products</i> )	Reviewer:	Lisa Naeger, Ph.D.	Y

	TL:	Jules O'Rear, Ph.D.	Y
Clinical Pharmacology	Reviewer:	Stanley Au, Pharm.D.	Y
	TL:	Sarah Robertson, Pharm.D.	Y
Biostatistics	Reviewer:	Thomas Hammerstrom, Ph.D.	Y
	TL:	Greg Soon, Ph.D.	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton, Ph.D.	Y
	TL:	Hanan Ghantous, Ph.D., DABT	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman, Ph.D.	N
	TL:	Karl Lin, Ph.D.	N
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Maotang Zhou, Ph.D. Celia Cruz, Ph.D.	N Y
	TL:	Dorota Matecka, Ph.D.	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Antoine El-Hage, Ph.D.	Y
	TL:	Tejashri Purohit-Sheth, M.D.	N

Other reviewers	Tien-Mien (Albert) Chen-BioPharm	Y
Other attendees		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	
<p><b>Comments:</b> Requested dataset in a different format. Requested pediatric waiver and/or deferral.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>VIROLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Ed Cox, M.D., M.P.H.	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-202022	----- ORIG-1	----- TIBOTEC INC	----- TMC278

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

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/s/

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Robert G Kosko  
09/03/2010



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20993

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA: 202022**

**Drug: TMC278**

**Date: September 3, 2010**

**To: Debbie Monshizadegan  
Manager, Global Regulatory Affairs**

**Sponsor: Tibotec, Inc.**

**From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager**

**Concur: Kimberly Struble, Pharm.D., Clinical Team Leader  
Pravin Jadhav, Ph.D., Pharmacometrics Team Leader  
Jeff Florian, Ph.D., Pharmacometrics Reviewer**

**Subject: Population PK Data Request**

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Please reference your submission dated July 23, 2010. The following comments are being conveyed on behalf of the review team for your application:

Please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:

- All datasets used for model development and validation should be submitted as SAS transport files (\*.xpt). Specifically, please provide data sets 'tmc278richdb2.csv', 'tmc278phase3dfduplicorr.csv', and 'tmc278phase3cov2.csv' described on pages 73-75 of tmc278-0016435-w48-poppk.pdf as SAS transport files. In addition, please provide NONMEM data sets for the population pharmacokinetic analysis performed for study TMC278-C204 presented in tmc278-c204-crr-poppk-w96.pdf. A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension

(e.g.: myfile\_ctl.txt, myfile\_out.txt). Specifically, please provide the NONMEM control streams and output listings for the basic (run091) and final model (COV062final) described on page 80 and 109 of tmc278-0016435-w48-poppk.pdf, respectively. In addition, please provide NONMEM control streams and output listings for the population pharmacokinetic analysis performed for study TMC278-C204 presented in tmc278-c204-crr-poppk-w96.pdf.

Please submit the requested information by **September 10, 2010**.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE**. Please feel free to contact me at 301-796-3979 if you have any questions regarding the contents of this transmission.

---

Robert G. Kosko, Jr., Pharm.D., M.P.H.  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-202022	----- ORIG-1	----- TIBOTEC INC	----- TMC278

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

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/s/

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Robert G Kosko  
09/03/2010