CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202022Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202022 SUPPL # N/A HFD # 530

Trade Name EDURANT

Generic Name rilpivirine

Applicant Name Tibotec, Inc.

Approval Date, If Known 5/20/11

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

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YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

Reference ID: 2949706

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

Reference ID: 2949706

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Robert G. Kosko, Jr., Pharm.D., M.P.H.
Title: Regulatory Project Manager, Division of Antiviral Products
Date: May 20, 2011

Name of Office/Division Director signing form: Debra Birnkrant, M.D.
Title: Director, Division of Antiviral Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Robert G Kosko
05/20/2011

DEBRA B BIRNKRANT
05/20/2011

DEBARMENT CERTIFICATION

Tibotec, Inc. certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food and Drug Cosmetic Act in connection with this application.

Robin A. Keen 16 June 2010

Robin Keen
Vice President, Global Regulatory Affairs
Infectious Diseases

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202022 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: EDURANT Established/Proper Name: rilpivirine Dosage Form: Tablet		Applicant: Tibotec, Inc. Agent for Applicant (if applicable): N/A
RPM: Robert G. Kosko, Jr., Pharm.D., M.P.H.		Division: Antiviral Products (DAVP)

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

N/A

Provide a brief explanation of how this product is different from the listed drug.

N/A

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is May 23, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	N/A

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

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❖ Application Characteristics [2]

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1

☒ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	N/A
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Information Advisory

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	N/A ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A ☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	**N/A**
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	**N/A**
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	**N/A**
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	**N/A**
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

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(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	**N/A**

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 5/20/11
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5/18/11
• Original applicant-proposed labeling	7/23/10
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

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❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5/18/11
• Original applicant-proposed labeling	7/23/10
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	5/18/11
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	Letter -5/18/11, 3/25/11, and 11/19/10 Reviews -5/18/11, 3/25/11, and 11/19/10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 5/5/11 and 5/18/11 ☒ DMEPA 3/16/11 ☒ DRISK 4/8/11 ☒ DDMAC 4/14/11 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review 9/3/10 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 2/2/11 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Version: 3/15/11

❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 6/21/10
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 8/27/07
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 5/20/11
Division Director Summary Review *(indicate date for each review)*	☐ None 5/2/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/6/11
PMR/PMC Development Templates *(indicate total number)*	☐ None 4
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	3/28/11
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	3/28/11 Clinical Review- See page 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Cardio-Renal 3/14/11 DMEP 3/15/11 QT-IRT 2/25/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Review-4/13/11 Letters- 4/26/11, 4/22/11, 3/25/11, and 1/14/11

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 3/29/11
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 3/28/11
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3/28/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
0A DP/T Review(s) *(indicate date for each review)*	☐ None 3/10/11
• Supervisory Review(s) *(indicate date for each review)*	☐ None 3/23/11
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/23/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 2/15/11
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review: See Appendix 3
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 4/1/11
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 3/28/11
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Reference ID: 2949836

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3/28/11 (ONDQA Review- See page 76)
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 1/25/11 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	N/A ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Reference ID: 2949836

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/s/

Robert G Kosko
05/20/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202022

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Tibotec, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

ATTENTION: Debora Monshizadegan
Associate Director, Global Regulatory Affairs

Dear Ms. Monshizadegan:

Please refer to your New Drug Application (NDA) dated July 23, 2010, received July 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilpivirine Tablets, 25 mg.

We also refer to your May 5, 2011, correspondence, received May 5, 2011, requesting review of your proposed proprietary name, Edurant. We have completed our review of the proposed proprietary name, Edurant and have concluded that it is acceptable.

The proposed proprietary name, Edurant, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 5, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Robert Kosko at (301) 796-3979.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/18/2011

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: April 15, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #7

The attached Microsoft WORD document was sent to the Sponsor on April 29, 2011 and incorporated labeling comments for NDA 202022 (TMC278). The submission date of the revised labeling was April 21, 2011.

Additionally, the following was conveyed to the Sponsor:

With regards to the revision date at the end of the Highlights of Prescribing Information, it is a requirement for all new NDAs and BLAs and cannot be deleted.

With regards to section 17 Patient Counseling Information, please add Patient Information in parentheses after "See FDA-approved patient labeling".

As for the Country of Origin, ONDQA has no recommendation on how to add the country of origin marking to the labeling; please refer all questions regarding country of origin to US Customs. Please be advised that you are required to maintain information on the drug product manufacturers in the label, as per 21 CFR 201.1. The label you have proposed meets this requirement. Please provide an updated mock bottle label including and reflecting the following prior commitments:

1. Removal of "hydrochloride" text from the drug substance established name.

2. Removal of the asterisks at the end of the dose, "25 mg*", and at the beginning of the salt equivalency statement "*Each tablet contains…".

3. Inclusion of the drug product manufacturer information as submitted below:

"Finished Product Mfg. by: Janssen-/Cilag S.p.A., Latina, Italy

Mfg. for: Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, LP., Raritan, NJ 08869"

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

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

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/s/

Robert G Kosko
04/29/2011

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: April 15, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #6

The attached Microsoft WORD documents were sent to the Sponsor on April 15, 2011 and incorporated format labeling comments for NDA 202022 (TMC278). The submission date of the revised labeling was April 8, 2011.

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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

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/s/

Robert G Kosko
04/15/2011

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: March 31, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #4

The attached Microsoft WORD documents were sent to the Sponsor on March 31, 2011 and incorporated labeling comments for NDA 202022 (TMC278). The submission date of the revised labeling was March 25, 2011.

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

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/s/

Robert G Kosko
04/01/2011

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: March 31, 2011

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

Subject: Proposed PMRs and PMC for NDA 202022

Please reference your original NDA dated July 23, 2010. The following are proposed Post Marketing Requirements (PMRs) and a Post Marketing Commitment (PMC) for your application:

PMRs

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

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

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

Study completion by: September 2013
Final report submission by: January 2014

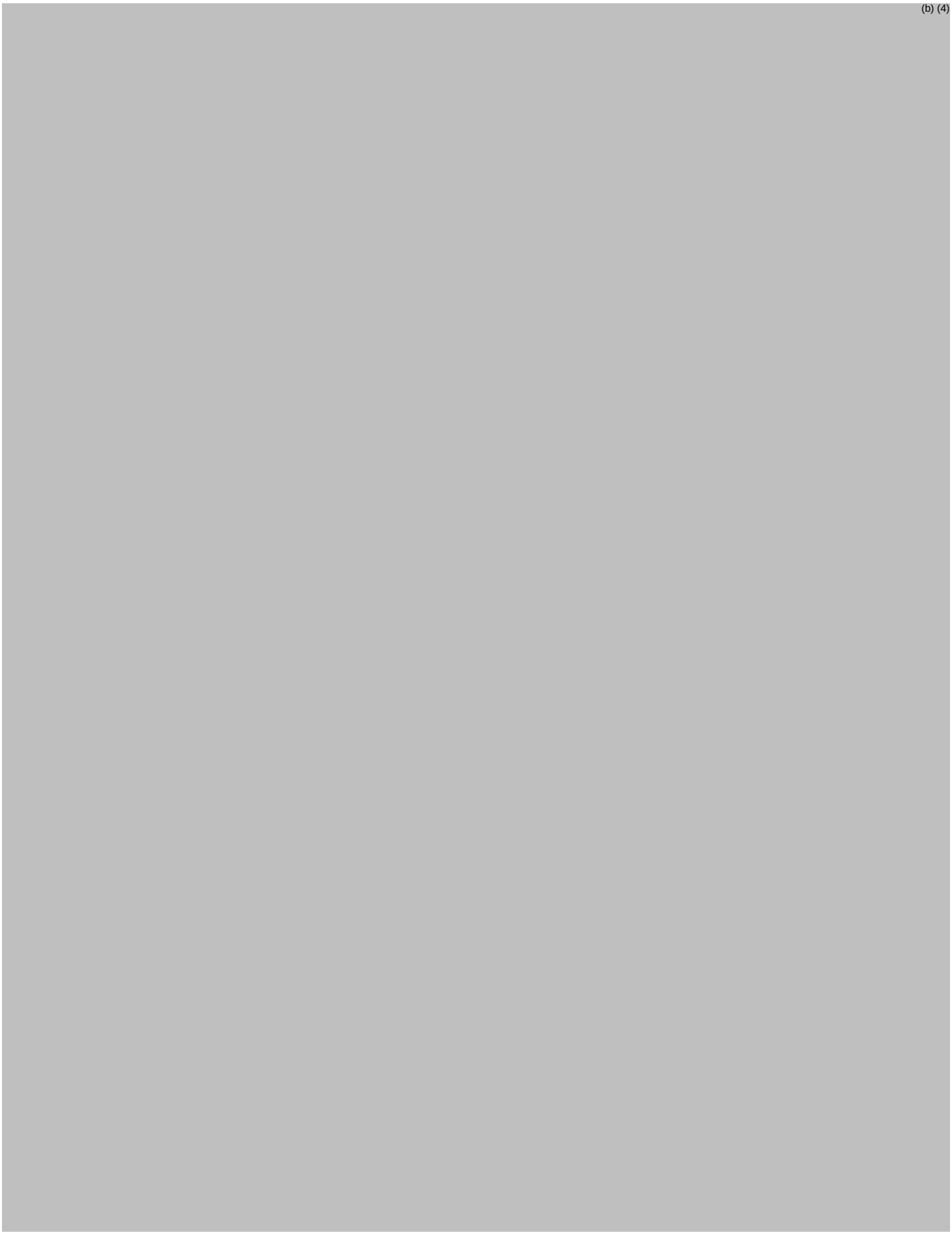
3. Submit final study reports for Week 96 data analyses (safety, efficacy and resistance evaluation) from the ongoing Phase 3 studies TMC278-C209 and TMC278-C215.

   Please propose a timeline for submission.

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

   Please propose a timeline for submission.

(b) (4)


(b) (4)

(b) (4)

These PMRs and PMC will be discussed during the April 7, 2011 teleconference.

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_____

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

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/s/

Robert G Kosko
03/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DRISK-Sharon Mills

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Robert G. Kosko, Jr., Pharm.D., M.P.H.
OND/OAP/DAVP 301-796-3979

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/28/11	N/A	202022	Original NDA	3/25/11

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TMC278	Standard	7030202	4/6/11

NAME OF FIRM: Tibotec, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
EDR link to submission:

\\CDSESUB1\EVSPROD\NDA202022\202022.enx

SIGNATURE OF REQUESTOR
Robert G. Kosko, Jr.

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Robert G Kosko
03/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM Lynn Panholzer/Michelle Safarik	Robert G. Kosko, Jr., Pharm.D., M.P.H. OND/OAP/DAVP 301-796-3979

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
3/28/11	N/A	202022	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
TMC278	Standard	7030202	4/6/11

NAME OF FIRM:	PDUFA Date: 5/23/11
Tibotec, Inc.	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☑ PACKAGE INSERT (PI)
☑PATIENT PACKAGE INSERT (PPI)
☑ CARTON/CONTAINER LABELING
☑MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☑ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☑ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

\\CDSESUB1\EVSPROD\NDA202022\202022.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER
Robert G. Kosko, Jr.

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☑ eMAIL ☐ HAND

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/s/

Robert G Kosko
03/28/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202022

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Tibotec, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

ATTENTION: Debora Monshizadegan
Associate Director, Global Regulatory Affairs

Dear Ms. Monshizadegan:

Please refer to your New Drug Application (NDA) dated July 23, 2010, received July 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilpivirine Tablets, 25 mg.

We also refer to your December 27, 2010, correspondence, received December 27, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Robert Kosko, at (301) 796-3979.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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 also refer to your March 17, 2011, submission and have the following comments and information requests. We kindly request your written response to the NDA by March 25, 2011.

1. The proposed inclusion of microbiological purity testing into the marketed stability protocol (Section 3.2.P.8.2) for commitment batches and annual monitoring already appropriately captures the reduced testing justified by the microbiological purity assessment and the data provided. Specifications listed in Section 3.2.P.5.1 should be tested for every batch upon release and should not include reduced frequency testing plans.

   Please keep microbiological purity testing in Section 3.2.P.5.1, only if it will be tested on every batch upon release. Otherwise, update NDA Section 3.2.P.5.1 accordingly.

2. In addition, please update the drug product dissolution specification, as communicated on March 18, 2011.

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/

STEPHEN P MILLER
03/23/2011

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: March 18, 2011

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
Yodit Belew, M.D., Clinical Reviewer
Stephen Miller, Ph.D., Acting ONDQA Branch Chief
Celia Cruz, Ph.D., CMC Reviewer

Subject: Comments Regarding Bottle Label and Labeling

Please reference your submission dated February 23, 2011. The following additional label comments are being conveyed on behalf of the review team for your application:

After obtaining input from multiple groups within CDER, we find that your original proposed name, "rilpivirine" is preferred over "rilpivirine hydrochloride." As a result, we have the following recommendations for the bottle label and the labeling. If these revisions would adversely impact packaging timelines we would be willing to discuss alternative schedules for implementation.

1. On the bottle label, please change the established name from "(rilpivirine hydrochloride)" to "(rilpivirine)" and change from "25 mg*" to "25 mg", by removing the asterisk following the dose. Please submit a revised bottle label that reflects the following language:

TRADE NAME™ (rilpivirine) Tablets

25 mg

Each tablet contains 27.5 mg of rilpivirine hydrochloride which is equivalent to 25 mg of rilpivirine.

2. In the label text and package inserts please change the established name from "rilpivirine hydrochloride" to "rilpivirine" as it appears in
   - the prescribing information heading,
   - the initial sentence of section 11 "Description",
   - the initial sentence of section 16 "How Supplied and Handling"
   - the patient information heading.

The equivalency statement, "Each tablet contains 27.5 mg of rilpivirine hydrochloride which is equivalent to 25 mg of rilpivirine", should remain in the text as indicated in the annotated label version communicated on March 09, 2011.

3. The empirical formula in section 11 "Description" appears to have spaces and a non-superscripted period. Please ensure that the final form is appropriate.

Please submit revised labeling by ***March 23, 2011***.

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

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/s/

Robert G Kosko
03/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-022

GENERAL ADVICE

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 also refer to our Information Request letter dated March 11, 2011, our teleconference with Tibotec, Inc. on March 14, 2011, and to your amendment dated March 17, 2011, containing 24-month stability data and dissolution data for clinical batch 8BL2H.

We have reviewed the referenced material and have the following recommendation.

The data show that:

- The clinically tested batch (No. 8BL2H) that started at (b) (4) at 45 min in dissolution at the time of initial manufacturing (t=0) still maintained (b) (4) dissolved under 25ºC/60% RH, and 85% under 30ºC/75% RH conditions after 33 months.

- One of the three stability batches (No. 8JL3S) that started with low dissolution (b) (4) at 45 min) at the time of initial manufacturing (t=0) still maintained (b) (4) dissolved under 25ºC/60% RH, and 83% under 30ºC/75% RH conditions after 24 months.

Based on the above findings, and the need to maintain similar exposure levels as was tested clinically, a dissolution specification of Q= (b) (4) at 45 minutes is still recommended, as indicated earlier in our May 20, 2010, comments to IND 67,699, and March 11, 2011, Information Request letter to NDA 202-022.

We recommend that you revise your proposed specification as follows:

From **Q= (b) (4) at 45 minutes**
To **Q= (b) (4) at 45 minutes**

Please update Section 3.2.P.5.1 to reflect this change in the dissolution specification.

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/

STEPHEN P MILLER
03/18/2011

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: March 17, 2011

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
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding USPI

Please reference your submission dated February 23, 2011 and our labeling comments sent March 9, 2011. The following additional label comments are being conveyed on behalf of the review team for your application:

Renal Adverse Events- glomerulonephritis and nephrolithiasis

Glomerulonephritis

1. Membrenous glomerulonephritis

Subject ID 209-0387: This 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 Tibotec decided that the relationship was doubtful at this later point, a relationship between TMC278 and this patient's glomerulonephritis cannot be ruled out.

2. Mesangioproliferative glomerulonephritis

Subject ID 209-0142: This is a 45 year old white male with past medical history of hypertension (HTN) (on carvedilol) who was randomized to TMC278 treatment group with tenofovir/emtricitabine background therapy. He developed mesangioproliferative glomerulonephritis on Day 174 of treatment. 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) and lasted 342 days (the entire time that the patient stayed on drug after AE occurrence). The patient continued on treatment and the causal relationship between TMC278 and the event was considered by the investigator to be doubtful. Of note, the subject had proteinuria (grade 3) approximately 12 days prior to the event. A right sided renal colic (grade 3) was also diagnosed approximately 2 months after the diagnosis of glomerulonephritis. Although the subject has history of HTN, there is no reported past medical history of renal disease. In addition, since this event occurred during treatment, it is reasonable to conclude that the event may possibly have been related to TMC278.

In conclusion, the total number of cases of 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 and because the association of the events with TMC278 could not be ruled out in either case, this AE should be noted in the label.

Nephrolithiasis:

There were more cases of nephrolithiasis and colic in the TMC278 group compared to the efavirenz group (8 vs. 4, respectively, RR=2). To further address the observed imbalance between treatment groups in events of nephrolithiasis and colic, the number and percent of patients that had urinary crystals on urinalysis was analyzed (using LBAD.15 from the September 24, 2010 submission). In summary, 80/686 (12%) patients in the TMC278 treatment arm had urinary crystals (amorphous, oxalate, or uric acid) while 64/682 (9%) 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.

Serum Creatinine

In addition to displaying the graded increase in serum creatinine in Table 3, the following text should be included in the label:

(b) (4)

Proposed revision to the Package Insert (only highlighting sections where new renal AEs - as discussed above, are added):

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Less Common Adverse Drug Reactions

(b) (4)

Laboratory Abnormalities in Treatment-Naïve Subjects

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

[Insert the following text after Adrenal Function]

(b) (4)

Please submit revised labeling by ***March 23, 2011***.

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

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/s/

Robert G Kosko
03/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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.

In order to provide an opportunity to obtain your input, we would like to arrange for a teleconference to discuss these issues.

1. Based on the overall dissolution data at the initial stability time (t=0) showing that the mean dissolution value for rilpivirine is (b) (4) at 45 minutes (*mean values ranged from* (b) (4) we recommend that you revise your proposed specification as follows:

   From **Q=** (b) (4) **at 45 minutes**
   To **Q=** (b) (4) **at 45 minutes**

   Please update Section 3.2.P.5.1 to reflect this change in the dissolution specification.

2. In Sections 3.2.P.5.6.1.5 "Justification of Specifications: Dissolution" and 3.2.P.8.4 "Stability: Evaluation", and in your "Response to FDA Communication of 17 February 2011", you discussed the impact of the observed dissolution decrease on product shelf life and on the probability of batch failures, while assuming different dissolution specifications. Section 3.2.P.8.4 also identifies that there is a statistically significant decrease in dissolution observed at 30ºC/75% RH and not at 25ºC/60% RH. It appears that dissolution is the one attribute with an apparent downward trend on stability, which can have a meaningful impact on the expiration dating period.

   Given that we are recommending a Q= (b) (4) at 45 minutes dissolution specification, we have concluded that the stability data supports the approval of a 30 month shelf life for

Climatic Zones I and II (as supported by the 25ºC/60% RH data) [redacted] (b) (4)

Please update shelf life proposals in Sections 3.2.P.8.6 and 2.3.P.8.1.5 to reflect 30 months for Climatic Zones I [redacted] (b) (4).

3. In order to propose an extension of shelf life post-approval, we have the following recommendation for the stability analysis updates at 24 and/or 36 months, as discussed in Section 3.2.P.8.2 and Section 3.2.P.8.4:

    a. If 24 month data are used to justify extension of shelf life to 36 months, please provide, along with the stability data updates, a statistical analysis of dissolution data on storage for the primary stability batches following recommendations from ICH Q1E. This evaluation should include:

        i. A discussion of the observed trends and any valid regression used to project dissolution at 36 months.

        ii. A discussion of how the observed data at 24 months has been used to extrapolate dissolution values at 36 months.

        iii. An assessment of whether the dissolution mean at 45 minutes would pass S3 level of testing, within a 95% confidence interval level. Please include any major assumptions used for the prediction or simulation of the 36 month data. A specification of Q= [redacted] (b) (4) at 45 minutes should be assumed.

    b. Alternatively, please provide 36 month stability data and an updated stability evaluation to justify extension of shelf life.

    We will use this information to assess the expiration that is supported under both the 25°C/60% RH and 30°C/75% RH conditions. This information can be submitted in an Annual Report.

4. We have issued a DMF Deficiency Letter, dated March 9, 2011, to Janssen Pharmaceutica, N.V. for DMF 23824. We have requested Janssen's response by Wednesday, March 16, 2011.

SUGGESTED TELECONFERENCE DATES/TIMES

Monday, March 14, 2011, 9:30 am – 10:30 am US EST

We would appreciate if you can provide the call-in number for the teleconference.

After our teleconference discussion, or if you decide to agree to the points above and a teleconference is not necessary, please submit your official response to this information request letter, by Friday, March 18, 2011.

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/

STEPHEN P MILLER
03/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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 March 11, 2011.

1. Regarding the proposed Rilpivirine Hydrochloride Tablets 25-mg Marketed Product Stability Protocol in Table 1 of Section 3.2.P.8.2:

    a. Please include testing for (b) (4) assay in testing group "A", for the first three commercial batches of drug product placed on stability. This testing can be limited to the first three commercial batches and does not need to be included in the annual stability monitoring program.

    b. Please propose and include a protocol for microbial purity testing for the first three commercial batches of TMC278-25 mg tablets placed on stability and for the annual stability monitoring protocol. The proposed frequency of testing should be based on the level of risk of microbial contamination and growth, as described in USP <1112> and ICH Q6A Decision Tree #8. This analysis should include consideration of (b) (4) of the tablets upon storage, risk of microbial contamination during processing and from incoming materials, and current available data on microbial purity at release and from primary stability studies.

2. In Section 3.2.P.5.6.1.2 for the "Justification of Specifications: Microbiological Purity", please provide representative data on the (b) (4) for Rilpivirine Hydrochloride Tablets 25-mg in the primary packaging container. Please discuss the (b) (4) results with regards to risk for microbial growth and the overall

proposed testing strategy for microbial purity, as described in USP <1112> and ICHQ6A Decision Tree # 8. Please refer to Question 1b.

3. The protection against growth of (b) (4) in Rilpivirine Hydrochloride Tablets 25-mg exposed to light is based on (1) maintaining the tablets inside the primary container until time of use and on (2) the specifications and adequacy of the primary container. Currently, based on Section 3.2.P.7.3, packaging suitability requirements state that the 75-ml HDPE bottle must pass light transmission acceptance criterion of (b) (4) which is adequate for the intended use. Also, users handling Rilpivirine Hydrochloride Tablets 25 mg are instructed to "Store in original bottle in order to protect from light".

   In order to assure that the risk of (b) (4) formation in the drug product due to light exposure is adequately controlled, please consider implementing the following recommendation as part of future commitments in Section 3.2.P.8.2:

   For any future changes to primary packaging which could significantly reduce the protection from light, please include testing for (b) (4) levels in photo stability studies following ICH Q2B.

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/

STEPHEN P MILLER
03/04/2011

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: March 9, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #3

The attached Microsoft WORD documents were sent to the Sponsor on March 9, 2011 and incorporated labeling comments for NDA 202022 (TMC278). The submission date of the revised labeling was February 23, 2011.

Additionally, a rational for these changes and virologic comments were also relayed to the Sponsor (see attached). The Sponson was also asked to change the established name in the bottle label from "rilpivirine HCl" to "rilpivirine hydrochloride", in order to make the product name on the bottle label consistent with the package insert.

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

Please refer to the current FDA-revised label, Sections 1, 5, 6 and 14. Specifically, below is our rationale for the labeling revisions we have made with regards to Indications and Usage, and inclusion of the following safety information: Depressive Disorders, Less Common ADRs, and Adrenal Function.

INDICATIONS AND USAGE and Description of Clinical Studies:

Based on our analyses of virologic failure (as defined in the snapshot algorithm), the virological failure rates increased from 5% in patients with baseline HIV RNA < 100,000 copies/mL, to 20% and 29% in patients with baseline HIV RAN > 100,000 to < 500,000 copies/mL and > 500,000 copies/mL, respectively. As a consequence a higher rate of overall treatment resistance, including a higher rate of cross-resistance to the NNRTI class and more lamivudine/emtricitabine associated resistance was observed with rilpivirine compared to efavirenz. These data are important to put the overall trial results into perspective. In this case, only displaying the virologic response rates (< 50 copies/mL) can be misleading because virologic response rate is based on a composite endpoint that takes efficacy and discontinuations for safety, into account. While the virologic response rates appear similar between rilpivirine and efavirenz for the baseline viral load strata, in fact the important differences are due to virologic failure. As a result the Indications and Usage and Description of Clinical Studies section must include these points. The data are critical for the risk/benefit assessment when choosing rilpivirine for treatment-naïve patients.

WARNING AND PRECAUTION: Depressive Disorders

A WARNING AND PRECAUTION for depressive disorders is warranted based on the following rationale:

- Pooled terms- Reference is made to the definition of Depressive Disorders, as outlined in DSM-IV-TR, 2000. In summary, Major Depressive Disorder and Depressive Disorder Not Otherwise Specified are included under the umbrella "Depressive Disorders". In addition, the DSM-IV-TR makes reference to suicide as being among the associated descriptive features and mental disorders for Depressive Disorders (e.g. Major Depression). For these reasons, we believe major depression, suicide ideation or attempt should be included when discussing depression.

- Rate calculation- We appreciate your due diligence in conducting analysis for ADR based on your ADR algorithm. As previously mentioned, we are in general agreement with the overall results generated with your ADR algorithm. In most cases, your analysis is very similar or the same as the FDA's analysis which considers all events at least possibly related.

In our Phase 3 trials analysis, depressive disorder events occurred -at minimum, in similar incidence between the two groups. In fact some of the events were also considered related by the investigator. Please refer to Attachment 1 to view our analysis.

The *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products- Content and Format*. states, "rate of an identified adverse reaction is ordinarily derived from all reported adverse events of that type in the database used. Determining a rate based on a subset of reported events that individual investigators believe to be causally related to drug exposure is discouraged. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations".

We acknowledge decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and based on factors such as (1) frequency of reporting, (2), whether the rate for the drug exceeds the placebo rate, (3) extent of dose-repose, (4) extent to which the event is consistent with the pharmacology of the drug, (5) timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience and (7) whether the event is known to be caused by related drugs.

We therefore believe that the text discussing identified adverse reactions (e.g. 'depression') should include '*all reported adverse events of that type in the database'.* We have thus included all grades, regardless of causality when describing depressive disorders.

Of note, efavirenz label contains Psychiatric Disorders section under the Warnings and Precautious Section. Based on the above considerations, the Division believes the label should contain 'Depressive Disorders' in the Warnings and Precautious Section (refer to the label).

ADR Table:
When constructing ADR tables, the Division has generally included ADRs with Grade 2 and above in severity and at least possibly treatment-related by the investigator. In order to maintain consistency across other HIV drug labeling, similar approach was taken with rilpivirine labeling. Overall, the rate generated with your algorithm is similar to the Division's calculated rate. However, your algorithm includes several other criteria as outlined in your lengthy appendix and without these criteria one is not able to reproduce your table with exact certainty.

Less Common Adverse Drug Reactions
As not all treatment-emergent ADRs of at least moderate intensity (≥ Grade 2) occurring in < 2% of subjects receiving rilpivirine are listed in this section, a qualifying statement on how these terms were selected is necessary. Again, we have included these events because of investigator's assessment of potential causal relationship and were considered serious or have been reported in more than 1 subject treated with rilpivirine. We do not

favor your approach of excluding events when the individual investigator determines the event was possibly related. We do not have access to all patient narratives for every event nor the safety team's adjudication comments about whether or not to include the event in the label. Please note, the Agency may also consider an adverse event to be related to treatment even if the Sponsor or the investigator did not believe there was causal relationship. Refer to the discussion above with regards to our rationale for including suicide ideation and attempt.

Adrenal Function

The Division had sought a consultation from FDA's Division of Metabolic and Endocrinology Products. Based on their review of the Phase 3 data, the following paragraph should be included in Section 6, Adverse Reactions:

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

ATTACHMENT 1

I) Depressive Disorders, regardless of causality

1. Depression Disorders regardless of causality, severity

Table 1 Depressive Disorders Regardless of Causality, Severity

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

2. Grade 3 and 4 Depression Disorders regardless of causality

Table 2 Grade 3 or 4 Depression Disorders (regardless of causality)

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Grade 3-4 Depressive Disorders, n(%)						
Any subject with grade 3-4 depressive disorders	3(0.9)	4(1.2)	2(0.6)	2(0.6)	5(0.7)	6(0.9)
Grade 3	2(0.6)	4(1.2)	1(0.3)	2(0.6)	3(0.4)	6(0.9)
Major depression	0	0	0	1(0.3)	0	1(0.1)
Depression	1(0.3)	3(0.9)	1(0.3)	1(0.3)	2(0.3)	4(0.6)
Suicide attempt	1(0.3)	0	0	0	1(0.1)	0
Suicide ideation	0	1(0.3)	1(0.3)	0	1(0.1)	1(0.1)
Grade 4	1(0.3)	0	1(0.3)	0	2(0.3)	0
Major depression	1(0.3)	0	0	0	1(0.1)	0
Suicide attempt	0	0	1(0.3)	0	1(0.1)	0

3. Discontinuations due to Depressive Disorders

Table 3 Discontinuations due to Depressive Disorders

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any discontinuation due to Depressive disorders	1(0.3)	3(0.9)	5(1.5)	2(0.6)	6(0.9)	5(0.7)
Depression						
Depression	0	3(0.9)	2(0.6)	1(0.3)	2(0.3)	4(0.6)
Depressed mood						
Depressed mood	0	0	2(0.6)	0	2(0.3)	0
Suicide ideation	0	1(0.3)	1(0.3)	1(0.3)	1(0.1)	2(0.3)
Suicide attempt	1(0.3)	0	1(0.3)	0	2(0.3)	0

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

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

II) Treatment Related Depressive Disorders

4. Depressive Disorders considered treatment related by the investigator, regardless of severity

Table 4 Depression, Depressed Mood, Suicidal Ideation, Suicidal Attempt, Considered Treatment Related by the Investigator, Regardless of Severity

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any subject with depressive disorders	8(2.3)	13(3.8)	9(2.6)	11(3.3)	17(2.5)	24(3.5)
Depression	6(1.8)	9(2.6)	6(1.8)	8(2.4)	12 (1.7)	17(2.5)
Depressed mood	1(0.3)	4(1.2)	3(0.9)	2(0.6)	4(0.6)	6(0.9)
Suicide attempt	1(0.3)	0	1(0.3)	0	2(0.3)	0
Suicide ideation	0	1(0.3)	1(0.3)	1(0.3)	1(0.1)	2(0.3)

5. Treatment Related Depression Disorders of at least moderate intensity (≥ Grade 2) reported in at least 2% of adult subjects

Table 5 Treatment Related Depression Disorders of at least moderate intensity (≥ Grade 2) reported in at least 2% of adult subjects

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

6. Grade 3 and 4 treatment related Depressive Disorders

Table 6 Grade 3 and 4 Treatment Related Depressive Disorders

	C209		C215		Pooled	
	rilpivirine N=346	EFV N=344	rilpivirine N=340	EFV N=338	rilpivirine N=686	EFV N=682
Any subj with Grade 3 or 4 AE	1	2	2	2	3(0.4)	4(0.6)
Depression	0	2	1	2	1(0.1)	4(0.6)
Suicide attempt	1	0	1	0	2(0.3)	0
Suicide ideation	0	1	1	0	1(0.1)	1(0.1)

7. Treatment related adverse events leading to discontinuation

Table 7 Treatment Related Adverse Events Leading to Discontinuation

	Pooled	
System Organ Class Preferred term, n (%)	Rilpivirine N=686	EFV N=682
Any discontinuation due to treatment related adverse events	17(2.5)	34(5)
Psychiatric events		
Any sub w/ psychiatric events	10(1.5)	14(2.1)
depression	2(0.3)	4(0.6)
Depressed mood	2(0.3)	0
Mood swing	1(0.1)	0
Suicidal ideation	1(0.1)	2(0.3)
Suicide attempt	2(0.3)	0

Comments to Applicant:

- There were 40 TMC278 virologic failures with >2.5 FC TMC278 susceptibility and genotypic changes (See Table A). However, we agree to remove C209-0629 and C215-0783, because C209-0629 had 3.4 FC at baseline and did not develop any of the frequently emerging TMC278 substitutions and C215-0783 did not develop any of the frequently emerging TMC278 substitutions. Therefore, "38 rilpivirine virologic failures with evidence of rilpivirine resistance emergence" was used.

- We have removed phenotypic cutoff references (i.e. >2.5 fold or 3.7 BCO) because we are unable to establish a clear clinical phenotypic cutoff and the BCO is not clinically relevant. Clearly, there is evidence of TMC278 genotypic resistance in rilpivirine virologic failures with phenotypic fold changes >2.5 and <3.7 (See Table A). In addition, text and data using the BCO were removed, because they are not clinically helpful or relevant.

- We have provided the list of as-treated TMC278 virologic failures (n=92) and EFV virologic failures (n=60) and maintain that this is the appropriate denominator for Table 8 and text in the *In Treatment-Naïve Subjects* section.

- We removed E138A because it was present at baseline, but kept V179I/L, F227C and M230L/I because these substitutions emerged in cell culture and on treatment in virologic failures and were associated with decreased TMC278 susceptibility.

Listing of TMC278 Virologic Failures As-treated (censored) n=92
TMC278-C209-0009
TMC278-C209-0011
TMC278-C209-0023
TMC278-C209-0046
TMC278-C209-0066
TMC278-C209-0079
TMC278-C209-0119
TMC278-C209-0129
TMC278-C209-0146
TMC278-C209-0161
TMC278-C209-0163
TMC278-C209-0199
TMC278-C209-0226
TMC278-C209-0231
TMC278-C209-0256
TMC278-C209-0297
TMC278-C209-0361
TMC278-C209-0371
TMC278-C209-0378
TMC278-C209-0383
TMC278-C209-0389
TMC278-C209-0405
TMC278-C209-0419

TMC278-C209-0495
TMC278-C209-0512
TMC278-C209-0538
TMC278-C209-0548
TMC278-C209-0555
TMC278-C209-0573
TMC278-C209-0574
TMC278-C209-0594
TMC278-C209-0612
TMC278-C209-0629
TMC278-C209-0636
TMC278-C209-0667
TMC278-C209-0679
TMC278-C209-0683
TMC278-C209-0703
TMC278-C209-0724
TMC278-C209-0745
TMC278-C209-0750
TMC278-C209-0760
TMC278-C209-0768
TMC278-C209-0779
TMC278-C209-0784
TMC278-C209-0787
TMC278-C209-0807
TMC278-C209-0835
TMC278-C209-0857
TMC278-C209-0871
TMC278-C209-0887
TMC278-C209-0915
TMC278-C209-0935
TMC278-C215-0001
TMC278-C215-0028
TMC278-C215-0032
TMC278-C215-0065
TMC278-C215-0080
TMC278-C215-0089
TMC278-C215-0095
TMC278-C215-0110
TMC278-C215-0130
TMC278-C215-0135
TMC278-C215-0181
TMC278-C215-0208
TMC278-C215-0222
TMC278-C215-0227
TMC278-C215-0264
TMC278-C215-0313
TMC278-C215-0330
TMC278-C215-0339
TMC278-C215-0344
TMC278-C215-0387
TMC278-C215-0416

TMC278-C215-0426
TMC278-C215-0439
TMC278-C215-0446
TMC278-C215-0454
TMC278-C215-0466
TMC278-C215-0494
TMC278-C215-0515
TMC278-C215-0534
TMC278-C215-0551
TMC278-C215-0565
TMC278-C215-0592
TMC278-C215-0646
TMC278-C215-0656
TMC278-C215-0707
TMC278-C215-0783
TMC278-C215-0793
TMC278-C215-0914
TMC278-C215-0955

Listing of EFV Virologic Failures As-treated censored n=60
TMC278-C209-0007
TMC278-C209-0054
TMC278-C209-0076
TMC278-C209-0085
TMC278-C209-0092
TMC278-C209-0118
TMC278-C209-0176
TMC278-C209-0285
TMC278-C209-0294
TMC278-C209-0330
TMC278-C209-0333
TMC278-C209-0421
TMC278-C209-0506
TMC278-C209-0542
TMC278-C209-0564
TMC278-C209-0583
TMC278-C209-0648
TMC278-C209-0709
TMC278-C209-0711
TMC278-C209-0726
TMC278-C209-0755
TMC278-C209-0758
TMC278-C209-0908
TMC278-C209-0909
TMC278-C215-0049
TMC278-C215-0066
TMC278-C215-0088
TMC278-C215-0109
TMC278-C215-0134
TMC278-C215-0143
TMC278-C215-0147

TMC278-C215-0164
TMC278-C215-0165
TMC278-C215-0172
TMC278-C215-0228
TMC278-C215-0251
TMC278-C215-0266
TMC278-C215-0281
TMC278-C215-0287
TMC278-C215-0289
TMC278-C215-0317
TMC278-C215-0319
TMC278-C215-0419
TMC278-C215-0472
TMC278-C215-0490
TMC278-C215-0540
TMC278-C215-0591
TMC278-C215-0594
TMC278-C215-0596
TMC278-C215-0621
TMC278-C215-0625
TMC278-C215-0702
TMC278-C215-0773
TMC278-C215-0779
TMC278-C215-0806
TMC278-C215-0835
TMC278-C215-0860
TMC278-C215-0867
TMC278-C215-0871
TMC278-C215-0879

Listing of PIDs from TMC278 arm with Phenotypic Resistance Emergence to a Background Drug n=44

TMC278-C209-0009
TMC278-C209-0011
TMC278-C209-0023
TMC278-C209-0066
TMC278-C209-0079
TMC278-C209-0119
TMC278-C209-0129
TMC278-C209-0146
TMC278-C209-0161
TMC278-C209-0163
TMC278-C209-0226
TMC278-C209-0231
TMC278-C209-0297
TMC278-C209-0361
TMC278-C209-0389
TMC278-C209-0495
TMC278-C209-0512
TMC278-C209-0573

TMC278-C209-0594
TMC278-C209-0636
TMC278-C209-0745
TMC278-C209-0768
TMC278-C209-0779
TMC278-C209-0787
TMC278-C209-0807
TMC278-C209-0835
TMC278-C209-0871
TMC278-C209-0887
TMC278-C215-0001
TMC278-C215-0032
TMC278-C215-0065
TMC278-C215-0080
TMC278-C215-0110
TMC278-C215-0135
TMC278-C215-0181
TMC278-C215-0208
TMC278-C215-0330
TMC278-C215-0339
TMC278-C215-0344
TMC278-C215-0416
TMC278-C215-0466
TMC278-C215-0515
TMC278-C215-0534
TMC278-C215-0592

Listing of PIDs from EFV arm with Resistance Emergence to a Background Drug n=9

TMC278-C209-0007
TMC278-C209-0176
TMC278-C209-0333
TMC278-C209-0711
TMC278-C215-0109
TMC278-C215-0289
TMC278-C215-0540
TMC278-C215-0702
TMC278-C215-0773

Table A. Virologic Failures with Evidence of Emerging TMC278 Resistance (n=40)

PID	Bgrd TRT	Reason for Failure	Baseline RT Substitutions	RT Substitutions Emerging	Baseline Phenotype	Failure Phenotype
C209-0009	FTC TDF	Never suppressed		E28K **V90I/V E138K M184I** M357I		13 TMC278 EFV-R ETR-R FTC-R
C209-0011	FTC TDF	Never suppressed	E138A R211K	E6E/K **V90I Y181I M184I** R211Q		621 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0066	FTC TDF	Never suppressed		**K65K/R D67D/G K70E/K K101E Y181C M184V H221H/Y**	3.2 TMC278 TDF 2.2	17 TMC278 NVP-R EFV-R, ETR-R FTC-R
C209-0079	FTC TDF	Rebounder	D67D/N A98S Q207E T215I/T K219E/K	A158T **M184I** Q207A K219E P313T		8.6 TMC278 ETR-R FTC-R
C209-0119	FTC TDF	Rebounder	A98S	**E138K M184I** R356K		5.1 TMC278 EFV-R ETR-R FTC-R
C209-0129	FTC TDF	Never suppressed		P4S **L100I** I135I/T **E138K** T139K **M184I** K219E		64 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0146	FTC TDF	Never suppressed	V90I	**E138K M184I** L214F **H221H/Y**		7 TMC278 ETR-R FTC-R
C209-0161	FTC TDF	DC	A98A/S	**L74I E138K M184V** E358K/R		6.5 TMC278 NVP-R ETR-R FTC-R
C209-0163	FTC TDF	Rebounder		**K101E M184I** I293I/V		4.6 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0231	FTC TDF	Never suppressed	V179I/V	**E138K V179I M184I/V** K219E/K		32 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0297	FTC TDF	Never suppressed	A98S V106I	**Y181C M184I H221H/Y**		5.1 TMC278 NVP-R EFV-R ETR-R FTC-R

C209-0361	FTC TDF	Never suppressed		A62V **K65R V90I/V E138E/K Y181C M184I H221H/Y**		14 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0389	FTC TDF	Rebounder		**K65N** Y115F **E138K** G282G/R		3.6 TMC278 DTR-R FTC-R TDF-R
C209-0495	FTC TDF	Never suppressed		K32E/K K70E/K **V90I/V E138K M184I**	6.1 TDF-R	7.8 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0512	FTC TDF	Rebounder But <50 copies/mL at Week 48	A98S	E40K **K65R K101E Y181C V189I** K219E		10 TMC278 NVP-R EFV-R ETR-R FTC-R TDF-R
C209-0573	FTC TDF	Never suppressed	V179I	**V108I** E122K **Y181C M184V** K219E		28 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0594	FTC TDF	Never suppressed		E28E/K D67N K70E/K **V90I E138K M184I** K219R D256D/E Y354H/Y	NVP-R TDF-R	8 TMC278 NVP-R EFV-R ETR-R FTC-R
*C209-0629**	FTC TDF	Rebounder		L109L/Q I178I/L	3.4 TMC278	3.5 TMC278 NVP-R EFV-R ETR-R
C209-0636	FTC TDF	Rebounder		W88G/W **K101E/K E138K M184I** L214F		5.9 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0745	FTC TDF	DC		**K65K/R E138K M184I**		8.8 TMC278 EFV-R ETR-R FTC-R
C209-0768	FTC TDF	Never suppressed		**K101E M184I** E204K		4.6 TMC278 EFV-R FTC-R
C209-0779	FTC TDF	Never suppressed		I31I/L **K65K/R E138K M184I** I257L		8.7 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0787	FTC TDF	DC		**K101E** T165K/T **M184I** T240A/T R277K/R		3.5 TMC278 NVP-R EFV-R ETR-R FTC-R
C209-0807	FTC TDF	Never suppressed		**K101E/K** Y115F **E138K M184V V189I/V** M357L/M		7.5 TMC278 NVP-R EFV-R ETR-R

				T376A/T		FTC-R
C209-0871	FTC TDF	Never suppressed		K64Q **E138K** S162C **M184I** S332T A360T K390R T400A		4.9 TMC278 EFV-R ETR-R FTC-R
C209-0887	FTC TDF	Never suppressed	T215N	**V90I E138K/Q V179I/V M184I V189I/V** L228I/L		7.9 TMC278 NVP-R EFV-R ETR-R FTC-R
C215-0001	FTC TDF	DC	V35I A98S	V35T **K65N D67N** S68G **V106A** E122K **E138K V179I F227L** K281R		29 TMC278 NVP-R EFV-R FTC-R TDF-R
C215-0032	FTC TDF	Never suppressed		E6E/K **K101E E138E/K M184I** K219E E297K		6.9 TMC278 NVP-R EFV-R ETR-R FTC-R
C215-0110	FTC TDF	Never suppressed		**E138K M184I/V/M** T200A/T		8.3 TMC278 EFV-R ETR-R FTC-R
C215-0135	AZT LAM	Rebounder		I31I/L L100I/L **K101E/K E138K M184V** T338S		2.6 TMC278 NVP-R EFV-R ETR-R LAM-R
C215-0181	ABC LAM	Never suppressed	E122K	**L100I K101E/K E138K M184I** K219E/K R356G/R		19.9 TMC278 NVP-R EFV-R ETR-R LAM-R
C215-0208	AZT LAM	Never suppressed	E122K	E28K A62A/V S68G **V90I V108I E138K V179L M184V** G196G/R N348I T377I		64 TMC278 NVP-R EFV-R ETR-R LAM-R
C215-0330	FTC TDF	DC		**V90I/V Y181C M184I** D324D/E		16 TMC278 NVP-R EFV-R ETR-R LAM-R
C215-0339	FTC TDF	Never suppressed	K103R	I135T **M184V F227C M230L**		17 TMC278 NVP-R EFV-R ETR-R FTC-R
C215-0344	FTC TDF	Never suppressed	A98S	**V90I E138K M184I** G285R M357T		6.3 TMC278 EFV-R ETR-R FTC-R
C215-0416	FTC TDF	Never suppressed		**E138K M184I/V/M V189I/V H221H/Y**		9.6 TMC278 NVP-R EFV-R ETR-R

						FTC-R
C215-0466	AZT LAM	Never suppressed	D123S M184M/V L210F/L	I47L V75I/V **K101P/T** D123N I132L S163T **M184V** L210F		138 TMC278 NVP-R EFV-R ETR-R LAM-R
C215-0515	FTC TDF	Never suppressed	V106I	**K101E/K V118I/V E138E/K M184I/M/V** E204E/K **H221H/Y**		5.9 TMC278 NVP-R EFV-R ETR-R FTC-R
C215-0534	FTC TDF	Never suppressed		**K101E/K** E122K D123N **M184I V189I/V** T200A Q207A R307K		**3.1 TMC278** NVP-R EFV-R FTC-R
*C215-0783**	FTC TDF	DC	E122K	K11K/T		2.6 TMC278

*Removed C209-0629 and C215-0783 from original 40 TMC278 virologic failures with >2.5 FC TMC278 susceptibility and genotypic changes, because C209-0629 had 3.4 FC at baseline and did not develop any of the frequently emerging TMC278 substitutions and C215-0783 did not develop any of the frequently emerging TMC278 substitutions. Therefore, total =38 rilpivirine virologic failures with evidence of rilpivirine resistance emergence.

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/s/

Robert G Kosko
03/09/2011

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: February 8, 2011

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
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer

Subject: Comments Regarding January 31, 2011 Submission

Please reference your submission dated January 31, 2011. The following comments are being conveyed on behalf of the review team for your application:

1. For the didanosine long term stability experiments, please clarify the following:

a) In the response to the Request for Information dated October 1, 2010, it was stated that data for QC samples stored for 11 months and evaluated using a fresh calibration curve would be submitted. Please confirm that rather than conducting a dedicated long term stability experiment, data from the didanosine QC samples that were analyzed for the C106 trial was used instead.

b) Please confirm that the QC samples from the C106 trial (30 ng/mL [Q1120], 400 ng/mL [1121], and 4000 ng/ml [Q1122]), were stored for approximately 11 months at -20°C.

c) Please clarify whether the didanosine calibration curve concentrations that were analyzed for the C106 trial were prepared using the new didanosine stock solution (S-0630).

2. For the chlorzoxazone and 6-hydroxychlorzoxazone long term stability experiments, please clarify the following:

a) In the response to the Request for Information dated October 1, 2010, it was stated that 6-hydroxychlorzoxazone concentrations were analyzed using a qualified method and no long term stability experiments were conducted. However, data for 6-hydroxychlorzoxazone long term stability was submitted. Please clarify the differences between a qualified and a validated method for 6-hydroxychlorzoxazone and specify whether the (b) (4) chlorzoxazone and 6-hydroxychlorzoxazone analytical method (LCMSC 209) that was used to analyze concentrations of both analytes in the C139 trial and for the stability experiments was a qualified or a validated method.

b) In the response to the Request for Information dated October 1, 2010, it was stated that the plasma samples for coadministered drugs at the bioanalytical laboratory and at the clinical trial site were stored at -20°C. However, please clarify whether the chlorzoxazone and 6-hydroxychlorzoxazone plasma samples for the C139 trial were exceptions to the above statement and were stored at -70°C throughout the lifecycle of the samples (e.g. at the bioanalytical laboratory, any biological sample storage facility, and at the clinical trial site).

3. Please clarify whether both the sildenafil and atorvastatin plasma samples for the C123 and C116 trials, respectively, were stored at -70°C throughout the lifecycle of the samples (e.g. at the bioanalytical laboratory, any biological sample storage facility, and at the clinical trial site).

4. Please clarify whether the sildenafil and desmethysildenafil samples from the C123 trial were analyzed within 47 hours (the limit of post-preparative extract stability for desmethysildenafil).

5. Please confirm that the plasma samples both for rilpivirine and the coadminstered drugs evaluated in the drug-drug interaction trials were only stored at either the clinical trial site or the bioanalytical laboratory.

6. Please provide responses for the following comments that were sent with the rilpivirine labeling comments:

a) Please confirm that (a) long term stability for atorvastatin (and metabolites), tenofovir, acetaminophen (and acetaminophen metabolites) was evaluated at -20 C (-20C and -70C for atorvastatin) and (b) only the t=0 samples were stored at -196C.

b) In the C104 trial, for tenofovir, please confirm that the time between when the first sample was collected and the date the last sample was analyzed was 60 days or less (the duration of documented long term sample stability at -20C as indicated in the tenofovir method validation report)

c) In the C123 (sildenafil DDI trial), please provide information regarding the number of days between when the first sample was collected and the date the last sample was analyzed.

Please submit the requested information by ***February 25, 2011***.

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

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/s/

Robert G Kosko
02/08/2011

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: February 1, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #2

The attached Microsoft WORD documents were sent to the Sponsor on February 1, 2011 and incorporated labeling comments for NDA 202022 (TMC278). The submission date of this original NDA was July 23, 2010.

Additionally, the following comments from DMEPA were relayed to the Sponsor:

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 [redacted] (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.

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

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/s/

Robert G Kosko
02/01/2011

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: January 13, 2011

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

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

Subject: Labeling Comments #1

The attached Microsoft WORD document was sent to the Sponsor on January 13, 2011 and incorporated labeling comments for NDA 202022 (TMC278). The submission date of this original NDA was July 23, 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

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

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/s/

Robert G Kosko
01/13/2011

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: January 4, 2011

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
Jules O'Rear, Ph.D., Virology Team Leader
Lisa Naeger, Ph.D., Virology Reviewer

Subject: Information Request Regarding July 23, 2010 Submission

---

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

1. Please submit the report describing the assessment of the activity of TMC278 against cellular DNA polymerases α, β, and γ.

Please submit the requested information as soon as possible, but no later than ***January 21, 2011***.

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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

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/s/

Robert G Kosko
01/04/2011

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: December 28, 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
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

1. Identify all individual patients in the TMC278 treatment group with abnormal basal cortisol values at screening/baseline by trial (C209 and C215). List all individual values for basal and ACTH-stimulated cortisols at all timepoints on study for these patients.

2. Regardless of baseline/screening cortisol values, identify all individual patients in the TMC278 treatment group who developed abnormal basal and/or ACTH-stimulated cortisol values during the treatment period by trial (C209 and C215). List all individual values for basal and ACTH-stimulated cortisols at all timepoints on study for these patients.

3. Present all individual cortisol values for each patient who discontinued trials C209 and C215.

4. Identify whether any patients who discontinued trials C209 and C215 in the TMC278 arms had any symptoms or clinical features consistent with adrenal insufficiency.

Please submit the requested information by ***January 15, 2011***.

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

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/s/

Robert G Kosko
12/28/2010

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: December 22, 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
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding December 15, 2010 Submission

Please reference your submission dated December 15, 2010. The following comments are being conveyed on behalf of the review team for your application:

Reference is made to your ADRs (excluding laboratory abnormalities and Investigation Disorders) as displayed in Table 113 of Summary of Clinical Safety.

The methodology used for the identification of Adverse Drug Reactions includes

- Pooled Phase 1, Phase 2a, Phase 2b and Phase 3 data,
- Incidence of at least 1%,
- Led (in at least 1 instance) to permanent discontinuation,
- Were (in at least 1 instance) considered at least possibly related to TMC278 by the investigator,
- Were reported (in at least 1 instance) as a SAE for TMC278 (irrespective of causality),
- Were of special interest, generated using all AEs reported in the pooled Phase 3, Phase 2b, Phase 2a and Phase 1 trials, and the known association with other ARV (e.g. NNRTI)
- Were considered as typically drug-related

Our analysis identified the following treatment-emergent AEs of at least moderate intensity (Grade 2-4) and considered at least possibly related to TMC278 by the investigator:

‡**Table 1: Treatment-Emergent Adverse Events* of at least Moderate Intensity (Grades 2-4)**		
System Organ Class, Preferred Term, n	**Pooled Data from the TMC278-C209 and TMC278-C215 Trials**	
	TMC278 N=686	**EFV N=682**
Cardiac Disorders		
Incomplete R BBB	1	1
Ear and Labyrinth Disorders		
Vertigo	1	6
Endocrine Disorders		
Hyperprolactinemia	1	0
Gastrointestinal Disorders		
Abdominal Pain	3	4
Diarrhea	6	8
Nausea	4	17
Vomiting	2	9
General Disorders and Administration Site Conditions		
Fatigue	6	5
Investigation		
Abnormal ECG	1	2
Metabolism and Nutrition Disorders		
Decreased Appetite	3	2
Lipomatosis	1	0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	1	2
Nervous System Disorders		
Headache	11	15
Dizziness	4	43
Somnolence	4	9
Sleep paralysis	1	0
Carpal tunnel syndrome	1	0
lethargy	1	1
Miller Fisher	1	0
Psychiatric Disorders		
Abnormal dreams	7	16
Affect lability	1	0
anxiety	4	7
bruxism	1	0
Confusional or disoriented state	1	1
delirium	2	0
depression	9	12
Euphoric moon	1	0
Increased libido	1	1
Hallucination	1	1
insomnia	13	15

nightmare	2	9
Sleep disorder	5	4
Suicide ideation	1	0
Suicide attempt	1	0
Renal and Urinary Disorders		
Pollakiuria	1	0
Membranous glomerulonephritis	1	0
Reproductive System and Breast Disorders		
Erectile dysfunction	1	
Skin and Subcutaneous Tissue Disorders		
† Rash	13	62
Vascular Disorders		
Hypertension	1	1

N=total number of subjects per treatment group,
n= number of subjects with an adverse event
‡Table excludes laboratory events reported as Investigation Disorders or Blood and Lymphatic Disorders; Infections and Infestations Disorders; Neoplasm. Events are not included in the table if they only occurred in the control arm.
* Includes adverse events at least possibly, probably, or very likely related to the drug.
† Rash includes: maculo-, papulo-, erythematous-, pruritic- rash; drug rash, urticaria, facial swelling, pruritis, prurigo)

Although the above AEs were considered at least possibly related to TMC278 by the investigator, and/or were previously identified as AEs of Special Interest, they were not included in your ADRs list. We therefore do not entirely agree with your methodology for creating the final ADRs list. Adverse events, in particular those events within the Psychiatric and Skin and Subcutaneous Tissue Disorders, considered treatment related by investigators should be considered ADRs. Please revise Table 1 of the USPI accordingly.

Please submit the requested information by ***January 10, 2011***.

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

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/s/

Robert G Kosko
12/22/2010

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: December 14, 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

Subject: QT Data Request

Please reference your submission dated July 23, 2010. The following information is being requested on behalf of the QT team for your application:

Please submit the following for studies 131 and 151:

1. Estimated slope (b hat) of QTcTLR
2. Estimated slope (b hat) of QTcTNLR
3. Individual estimated slope of QTcILR for all subjects (b hat for each subject)
4. Individual estimated slope of QTcINLR for all subjects (b hat for each subject)

Please submit the requested information by **December 22, 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

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/s/

Robert G Kosko
12/14/2010

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: December 10, 2010

To: Debbie Monshizadegan
Manager, Global Regulatory Affairs

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Kimberly Struble, Pharm.D., Clinical Team Leader
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

Reference is made to your proposed USPI for rilpivirine (TMC278). We have not been able to verify the results displayed in Table 1: Treatment-Emergent Adverse Drug Reactions* of at least Moderate Intensity† (Grades 2-4) in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects Treated with TRADE NAME™

Please also note, data displayed on page 78 of the Summary of Clinical Safety [Table 21: Adverse Events with Severity at Least Grade 2 and at Least Possibly Related to TMC278/Control in at Least 2% of Subjects (by System Organ Class or Preferred Term) in the TMC278 or Control Group (Phase III Week 48 Pooled Analysis)] does not match with Table 1 from the USPI. The results of our analysis are in alignment with Table 21.

Please provide and explanation for the discrepancy between Table 1 of the USPI and Table 21 of the Summary of the Clinical Safety. Please provide details in regards to how the results for Table 1 of the USPI were derived.

Please submit the requested information to Robert Kosko by December 15, 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 Robert G. Kosko at 301-796-3979 if you have any questions regarding the contents of this transmission.

_____

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
12/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
QT IRT Division of Cardio-Renal Products	Robert G. Kosko, Jr., Pharm.D., M.P.H. OND/OAP/DAVP 301-796-3979

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/3/10	N/A	202022	Original NDA	7/23/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TMC278	Standard	7030202	1/17/10

NAME OF FIRM: Tibotec, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: QT IRT Consult: Please review studies TMC278-TiDP6-C131 and TMC278-TiDP6-C151 and provide assessment of agreement with the applicant's results/conclusions. Review of study TMC278-TiDP6-C152 is optional. Location is 5.3.4.1 in GlobalSubmit under 7/23/10 submission for NDA 202022. Network Location: \\CDSESUB1\EVSPROD\NDA202022\202022.ENX. An electronic copy of the Clinical Pharmacology Table will be submitted to the QT-IRT project manager via email.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Robert G. Kosko, Jr.	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Robert G Kosko
12/03/2010

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: December 2, 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
Yodit Belew, M.D., Clinical Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

1. Please clarify whether the rilpivirine Phase 2 and Phase 3 plasma samples from HIV-1 infected subjects were heated to inactivate the HIV-1 virus. If samples from HIV-1 infected subjects were heated, please submit the data (including the temperature(s) that were studied) evaluating the impact of heating the plasma samples to inactivate the HIV-1 virus.

Please submit the requested information by December 17, 2010.

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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

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/s/

Robert G Kosko
12/02/2010

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: November 23, 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
Yodit Belew, M.D., Clinical Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

1. a) For the rilpivirine-methadone drug-drug interaction trial, please confirm that the method validation was conducted with methadone spiked into K_3EDTA anticoagulated plasma and blood samples for analysis of the methadone analytes in the TMC278-C121 trial were collected in tubes containing K_2EDTA.

   b) Please submit the data demonstrating assay equivalency for methadone in K_3EDTA anticoagulated plasma compared to K_2EDTA anticoagulated plasma as indicated in the TMC278-C121 bioanalytical report for methadone.

2. For the rilpivirine-ethinyl estradiol/norethindrone drug-drug interaction trial, please confirm that the method validation was conducted with ethinyl estradiol and norethindrone spiked into K_2EDTA anticoagulated plasma and blood samples for analysis of the ethinyl estradiol and norethindrone analytes in the TMC278-C136 trial were collected in tubes containing K_2EDTA.

3. For all other drug-drug interaction trials, please confirm that the method validation was conducted with the analytes relevant for the coadministered drug spiked into heparin anticoagulated plasma and blood samples for analysis of the analytes relevant for the coadministered drug were collected in tubes containing heparin.

Please submit the requested information by December 17, 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.

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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

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/s/

Robert G Kosko
11/23/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202022

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Tibotec, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

ATTENTION: Debora Monshizadegan
Associate Director, Global Regulatory Affairs

Dear Ms. Monshizadegan:

Please refer to your New Drug Application (NDA) dated July 23, 2010, received July 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilpivirine Tablets, 25 mg.

We also refer to your August 25, 2010, correspondence, received August 25, 2010 requesting review of your proposed proprietary name, (b) (4) and proposed alternate proprietary name (b) (4). We have completed our review of these proposed proprietary names and have concluded that the names are unacceptable for the following reasons.

(b) (4)

(b) (4)

[redacted]

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience.
[21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

Since your primary and proposed alternate proprietary names are unacceptable; we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,*
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm
and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Robert Kosko, at (301) 796-3979.

Sincerely,

{See appended electronic signature page}

Denise Toyer, Pharm.D.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
11/19/2010

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: November 16, 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
Yodit Belew, M.D., Clinical Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer

Subject: Comments Regarding November 1, 2010 Submission

Please reference your submission dated November 1, 2010. The following comments are being conveyed on behalf of the review team for your application:

1. In the response to Question 1, it was stated that all rilpivirine reference standards were used prior to the retest or expiration date. However, for the BA1071 method validation report, the retest date for the rilpivirine reference standard is (b) (4) and the experimental start and end dates are (b) (4) Please clarify this discrepancy.

2. Based on the submitted long term sample stability data for atorvastatin and the atorvastatin metabolites, long term sample stability was not demonstrated at -20°C beyond 60 days for most analytes. Please confirm that the atorvastatin plasma samples were stored at -70°C instead throughout the lifecycle of the samples (e.g. at the clinical site and the bioanalytical laboratory).

3. With the exception of sildenafil (and potentially atorvastatin plasma samples), please confirm that plasma samples for coadministered drugs in the drug-drug interaction trials were stored at 20°C throughout the lifecycle of the samples (e.g. at the clinical site and the bioanalytical laboratory).

4. The submitted information for the ketoconazole method validation (version 2) did not include the long term sample stability data for 691 days at -20°C (the report states that the data is on file at (b) (4). Please submit this information.

Additional Bioanalytical Comments

5. For the mass balance trial (TMC278-C119), please clarify whether the rilpivirine samples were analyzed in April 2005 using a current certificate of analysis (the text of the report list a retest date of (b) (4) and the certificate of analysis in the bioanalytical report has a retest date of (b) (4)

6. In the TMC278-C215 trial, please clarify if the reasons for the failures of the QCs in run 4 and the calibration curve standards in run 7 to meet acceptance criteria were further investigated.

7. In the TMC278-C209 trial, please elaborate on the analytical error that was the reason for rejecting run 3 and clarify if reasons for the failures of the QCs in run 5 to meet acceptance criteria were further investigated.

8. In the TMC278-C130 trial, please elaborate on the analytical error that was the reason for rejecting run 4.

9. In the TMC278-C209 trial, please confirm that rilpivirine reference standard from batch ZR278474PFA061 was only used to prepare calibration curve standards and QC samples before the retest date of (b) (4)

Please submit the requested information by ***December 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

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/s/

Robert G Kosko
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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 section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In section, 3.2.P.2.1.1, the statement regarding polymorphism, "Only (b) (4) has been observed in drug product" should be clarified. Please clarify if this has been verified by testing of drug substance prior to formulation only, or by direct analysis of form in the drug product. Please provide summary of methods used and available results.

2. Please provide sufficient dissolution data to justify the range of hardness values (b) (4), using the accepted dissolution methodology (as the Agency agreed upon in a letter faxed to you on 05/20/10), specifically:

(a) Please provide tablet hardness and/or thickness values for profiles in Figure 8 in 3.2.P.2.2.3 for DOE (b) (4) TMC278 25 mg and explain in relation with Table 29 of 3.2.P.2.3

(b) Please provide representative dissolution data with the accepted method, for tablets from (b) (4) at high and low compression force, as shown in Figure 6 in 3.2.P.2.3, to capture the proposed range of process.

(c) Please justify, in sections 3.2.P.2.3 and 3.2.P.3.4, the proposed range for in-process hardness limits, based on impact on tablet dissolution with the accepted dissolution method and on (a) and (b) above.

3. Please provide the comparative dissolution data/profile between the clinically tested and the TBM (to-be-marketed) formulations to address the difference in de-bossing between the two formulations.

4. Please provide a detailed manufacturing description narrative and master batch record for the drug product. This should include detailed description of the critical parameters and in-process controls, as

well as, general equipment type descriptions for unit operations and other non-critical proven acceptable ranges.

5. Please align the stated proven acceptable ranges for the critical process parameters (Table 44 in 3.2.P.2.3 and Table 1 in 3.2.P.3.3) with the actual set points in pivotal experiments, and not with the "actual operating range", which includes natural process fluctuations and extreme values. Please refer to Table 20 in 3.2.P.2.3 for "setting" vs. "actual operating range". Based on this information, the proven acceptable ranges for critical process parameters for (b) (4) (b) (4) should be:

6. Please rectify the discrepancy between stated critical in-process controls for (b) (4) (Table 45 of Section 3.3.P.2.3 and Table 1 of Section 3.3.P.3.4) and the executed batch records instructions for LOD (%) acceptable limits after (b) (4). The critical in- process acceptance criterion is LOD (b) (4) while the executed batch record instructions states (b) (4) allowing values outside critical range (i.e. (b) (4)). This should be verified and reflected in the manufacturing description and the master batch record (please refer to question 4).

7. Please include a description of the (b) (4) process (b) (4), in light of presented evidence of (b) (4) impact on tablet IPC's and CQA's. Please refer to Table 21 vs. Table 24 in 3.2.P.2.3, where (b) (4) has a clear impact on (b) (4) In the detailed manufacturing description and master batch record (refer to question 4),

(a) Please indicate the process parameters (b) (4) (b) (4)

(b) Please clarify if the addition of croscarmellose sodium and silicified microcrystalline cellulose is part of same (b) (4) process (as suggested by executed batch record), or an independent screening process (as suggested by the process flow diagram). If the former, please provide processing descriptions for additional (b) (4) of excipients, if any.

8. In DOE 2, section 3.2.P.2.3 Table 37, the assay result for Run 9 (high compression speed) is (b) (4) (for 95.0 to 105.0%, experimental target), while assay is not reported for the other high compression speed experiments, Run 11 and Run 12 (Table 39). Please discuss risk to assay loss due to segregation across the batch for the high compression speed, in support of proposed compression speed ranges.

9. Please justify the lack of a (b) (4) specification upon release, specifically in 3.2.P.5.6:

(a) Please discuss impact of (b) (4) on tablet quality, based on relevant studies, and indicate if any threshold for (b) (4) impacting quality has been identified.

(b) Please address level of control of (b) (4) in the drug product by current manufacturing or packaging process, in absence of an appropriate specification.

If you have any questions please call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

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/

RAPTI D MADURAWE
11/10/2010
(for Stephen Miller, secondary reviewer)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Brantley Dorch
SRPM, OSE
301-796-0150

FROM: Robert G. Kosko, Jr., Pharm.D., M.P.H.
RPM, DAVP
301-796-3979

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/10/10	N/A	202022	Original NME	7/23/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TMC278	Standard	Antiretroviral-Systemic	1/7/11

NAME OF FIRM: Tibotec, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the submitted PPI and provide comments as needed. Labeling negotiations have not begun with the sponsor.

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Robert G. Kosko, Jr., 11/10/10	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Robert G Kosko
11/10/2010

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: October 15, 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
Yodit Belew, M.D., Clinical Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

1. The food effect trial (C137) was conducted with the 75 mg (F008) Phase 3 formulation. Please provide information to support the applicability of the results of the C137 trial to the 25 mg (F006) Phase 3/to-be-marketed formulation, including any comparative dissolution results.

2. Please clarify whether any additional in vitro CYP450 induction experiments were conducted evaluating rilpivirine at concentrations corresponding to 25 mg once daily dosing (approximately 0.5 uM).

Please submit the requested information by October 27, 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

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/s/

Robert G Kosko
10/15/2010

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: October 12, 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

Subject: Clarification Regarding September 28, 2010 Facsimile

Please reference our facsimile dated September 28, 2010. The following comments are being conveyed on behalf of the review team for clarification:

1. The table on pages 4 and 5 is inclusive of the table on pages 2 and 3. Please provide all information in the table on pages 4 and 5.

2. In reference to the DEATHDSC variable, please use the code list describing the cause of death.

As clarification of our previous comments was required, please submit the requested information by ***October 19, 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

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/s/

Robert G Kosko
10/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Metabolism and Endocrinology Products
Attention: Enid Galliers and Lina Aljuburi

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Robert G. Kosko, Jr., Pharm.D., M.P.H.
OND/OAP/DAVP 301-796-3979

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/4/10	N/A	202022	Original NDA	7/23/10 9/24/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TMC278	Standard	7030202	2/23/11

NAME OF FIRM: Tibotec, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: See Attached (location of material to be reviewed is located in appendix 1).
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Robert G. Kosko, Jr.	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Consult Request

From: Yodit Belew, M.D., Medical Officer
Division of Antiviral Products

To: Division of Metabolic and Endocrine Products

NDA: 202022

Sponsor: Tibotec Pharmaceuticals Ltd.

Subject: Effect of TMC278 on adrenal function

Date: 10/4/10

Please refer to previous consults from the Division of Antiviral Products, dated July 18, 2007 and March 5, 2010. The Division of Metabolic and Endocrine Products had reviewed previous reports from Phase 1 and 2 studies to evaluate the effect of TMC278 (rilpivirine) on adrenal function. Tibotec has completed the two pivotal Phase 3 trials and DAVP would like you to review the safety data from NDA 202022 (rilpivirine, TMC278) related to adrenal function.

Background

Rilpivirine, an NME, is an anti-retroviral drug developed for the treatment of HIV-1 infection in combination with other antiretroviral drugs. Based on the mechanism of action on the life cycle of the human immunodeficiency virus, HIV drugs are classified into 6 classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Rilpivirine belongs to the NNRTI class.

Adverse events from NNRTIs include neuropsychiatric events, liver toxicity, and rash. NNRTIs are also substrates of CYP3A4 enzymes and these agents can interact with commonly prescribed drugs. Effect on adrenal function has not been previously described for the NNRTI class.

Pre-clinical, Phase 1 and 2 trials have 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.

Based on the assessment of the available data from pre-clinical and clinical data, the following recommendations were made for the phase 3 trials:

- All subjects should be screened with a basal morning cortisol levels, using a cutoff value of 19 µg/dL as evidence of excluding primary adrenal insufficiency.
- Any subject with a value below 19 µg/dL should undergo standard 250 mcg cosyntropin stimulation testing. A cortisol value greater than 19 µg/dL would exclude adrenal insufficiency.

- It should be noted that a normal response does not adequately exclude secondary adrenal insufficiency. Therefore, a normal cortisol response in the context of a high clinical suspicion of AI warrants further testing, both at screening and during treatment.

- Subjects who have an abnormal response to the cosyntropin test may require initiation of treatment with replacement steroids and should be excluded from study participation

- Orthostatic vital signs, along with assessment of hirsutism and hyperpigmentation, should be done at every physical examination visit.

- Basal morning cortisol levels should be measured at baseline and during treatment at Weeks 12, 24, 48, 72, and 96. Criteria for diagnosis of hypocortisolemia should be identical to those used for screening (i.e., cortisol less than 19 µg/dL should prompt cosyntropin stimulation testing).

- Measurement of 17-OH progesterone at the same time points for cortisol is also highly recommended. One would postulate that 17-OH progesterone would increase if TMC278's inhibition of 21-hydroxylase is the potential mechanism of adrenal insufficiency.

- To help elucidate the mechanism of possible adrenal suppression, DMEP recommends evaluation of the following hormone levels at Baseline, Week 48 and Week 96: DHEAS, androstenedione, testosterone, progesterone, aldosterone, testosterone and LH.

- Criteria for withdrawal of subjects should be expanded to include both those who do not meet laboratory criteria of sufficient adrenal response or those with a strong clinical suspicion of AI based on physical exam and vital signs.

After the initial 48-week study period, treatment and dosing is scheduled to continue for additional 48 weeks, with 4 more scheduled visits (Weeks 60, 72, 84, and 96).

Based on the preliminary Phase 3 trial results from a Week-24 analysis the sponsor amended the protocol for the visits after Week 48 to change the ACTH testing indications and timing:

- For subjects who already presented with abnormal basal and/or stimulated cortisol results at baseline, and present with abnormal basal and/or stimulated cortisol at any time point after baseline, the need and timing of an unscheduled ACTH stimulation test should always be discussed with the sponsor.

- Except for subjects with clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency, the unscheduled ACTH stimulation test can be performed at the next scheduled visit. This implies that for subjects who have reached Week 48, there will be more than 8 weeks between consecutive ACTH stimulation tests.

NDA 202022 was submitted on July 23, 2010. Revised laboratory data were submitted on September 27, 2010. The following are the main endocrine findings presented by the Sponsor. In addition, the sponsor has provided as assessment made by an independent endocrinologist (submission 0000 Module 5.4- under Literature References).

Overall, there were no adrenal function related serious adverse events, severe adverse events or treatment discontinuation. However, 15 (2.2%) subjects in the TMC278 arm

had laboratory abnormalities “blood cortisol decreased” reported vs. 7 (1%) subjects in the control arm.

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)

	C209				C215				Pooled			
	TMC278 N = 346		Control N = 344		TMC278 N = 340		Control N = 338		TMC278 N = 686		Control N = 682	
Parameter Time point	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)	N'	Mean (95% CI)
Cortisol (nmol/L)												
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)
17-OH-progesterone (nmol/L)												
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)
Aldosterone (pmol/L)												
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.

Best Available Copy

Table 54: Treatment-emergent Abnormal Cortisol Response to ACTH Stimulation (Worst Case) (Phase III Week 48 Pooled Analysis)

	C209		C215		Pooled	
Parameter Abnormality, n (%)	TMC278 N = 346	Control N = 344	TMC278 N = 340	Control N = 338	TMC278 N = 686	Control N = 682
ACTH stimulation test at Week 48						
N'	**294**	**279**	**299**	**279**	**593**	**558**
Any abnormal ACTH test	12 (4.1)	6 (2.2)	11 (3.7)	2 (0.7)	23 (3.9)	8 (1.4)
[450, 500[nmol/L	7 (2.4)	2 (0.7)	6 (2.0)	2 (0.7)	13 (2.2)	4 (0.7)
< 450 nmol/L	5 (1.7)	4 (1.4)	5 (1.7)	0	10 (1.7)	4 (0.7)
ACTH stimulation tests in the course of the 48-week treatment period, including Week 48						
N'	**326**	**311**	**317**	**294**	**643**	**605**
Any abnormal ACTH test	22 (6.7)	10 (3.2)	16 (5.0)	3 (1.0)	38 (5.9)	13 (2.1)
[450, 500[nmol/L	9 (2.8)	4 (1.3)	9 (2.8)	3 (1.0)	18 (2.8)	7 (1.2)
< 450 nmol/L	13 (4.0)	6 (1.9)	7 (2.2)	0	20 (3.1)	6 (1.0)
At least 2 consecutive abnormal ACTH tests	6 (1.8)	0	5 (1.6)	0	11 (1.7)	0

N = overall number of subjects, N' = number of subjects per test and treatment group; n = number of observations.
A test result was defined as abnormal when none of the cortisol values at T0, T30, or T60 was ≥ 500 nmol/L.
Percentages are calculated relative to the number of subjects with data.
Source: Module 5.3.5.1/TMC278-C209-W48-Anal-Saf-Endo/Display SAF.26, Module 5.3.5.1/TMC278-C215-W48-Anal-Saf-Endo/Display SAF.27 and Module 5.3.5.3/TMC278-C904-Anal-Saf-Endo/Display SAF.41.

At Week 48, the mean change from baseline in maximum change in cortisol after ACTH stimulation 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 III studies at baseline, nor for the changes vs baseline. Small mean increases vs baseline in the maximum change in 17-OH-progesterone levels after ACTH stimulation were observed (+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) (Table 53).

Consult Question

DAVP would like to ask for your independent evaluation of the safety results of TMC278 as it relates to adrenal function.

Specifically,

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 I cortisol after ACTH stimulation be presented in labeling? What additional labeling, if any, do you propose relating to adrenal function.

Location of NDA 202022

NDA 202022 has been submitted electronically (eCTD, Global Submit). Please note, there are two submissions - 0000 and 0004. Submission 0000 contains the study reports (clinical efficacy and safety) as well as the datasets. However, the laboratory datasets were resubmitted under Submission 0004 (broken into smaller dataset .xpt files based on type of laboratory analate).

Launch GSReview for viewing eCTD documents.

0000 Original Application

- 2.7 Clinical Summary
- 5. Clinical Study Reports
  - 5.3.4.3.25.3.1 Analysis dataset (enad.xpt)
  - 5.3.5 Reports of Efficacy and Safety Studies

-5.3.5.3 Reports of analysis of Data from More than One Study

- 5.3.5.3 tmc278-c904- Pooling TMC278 Phase III Trials

-5.3.5.3.25 Individual Subject Data Listing

0004 Other

- 5. Clinical Study Reports
  - 5.3.5.3.25.3.1 Analysis Dataset (lbad01.xpt-lbad15.xpt)
  - 5.3.5.4.25.3.3 Analysis Data Definition

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/s/

Robert G Kosko
10/04/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202022 **FILING COMMUNICATION**

Tibotec, Inc.
Attention: Debora Monshizadegan
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Rd
Rm K21410
Titusville, NJ 08560

Dear Ms. Monshizadegan:

Please refer to your new drug application (NDA) dated and received July 23, 2010 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for rilpivirine 25 mg Tablets.

We also refer to your submission dated September 24, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is May 23, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 1, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

Additionally, we have the following comments:

Clinical Pharmacology

Method validation of rilpivirine

1. For the rilpivirine method that was validated in the four submitted reports (BA28, BA218, BA1071, and the (b) (4) method validation) and for the rilpivirine long term stability experiments (99, 296 1093 and 1598 days), please clarify whether the reference standards for rilpivirine and the internal standards (b) (4) were used prior to the retest or expiration dates.

2. For the rilpivirine method that was validated at (b) (4) please clarify whether any additional stability studies were conducted besides postoperative stability or whether Tibotec's stability data from BA28 were used instead as a reference.

3. Please clarify why a 5 ng/mL low QC was evaluated for rilpivirine long term stability instead of the 2.5 ng/mL low QC that was evaluated in the rilpivirine accuracy and precision experiments. Secondly, was precision and accuracy established for the 5 ng/mL low QC?

4. Please clarify the specific temperature that the rilpivirine freeze thaw and the long term stability experiments (99, 296 1093 and 1598 days) was evaluated at, and b) confirm that rilpivirine samples for all clinical trials were stored at this temperature.

5. During the rilpivirine method validation (BA28, BA218, BA1071, and the (b) (4) method validation) and bioanalysis of rilpivirine plasma samples from clinical trials, was the potential conversion of rilpivirine to the Z isomer monitored for? If yes, please describe the extent to which conversion to the Z isomer was observed.

Validation and bioanalysis of other analytes

6. Based on the submitted results, the long term stability of rifabutin and 25-O-desacetylrifabutin can not be established for approximately 12 months. Please confirm that the TMC278-C125 samples were stored at approximately -20°C for the duration of the sample lifecycle and provide long term stability data for rifabutin and 25-O-desacetylrifabutin covering approximately 5 months at the appropriate storage temperature to support the inclusion of rifabutin pharmacokinetic data from the TMC278-C125 trial in the proposed rilpivirine label.

7. For the analytes listed below, long term sample stability data was not provided. Please submit the long term sample stability data covering the specified time interval (including specifying the specific temperatures that were evaluated and confirming that the samples from the respective drug-drug interaction trials were stored at this temperature for the duration of the sample

lifecycle) and comment on whether the available data at the appropriate temperature covers the duration of the required long term stability data for the respective drug-drug interaction trials:

a. lopinavir/ritonavir (approximately 3 months)
b. didanosine (approximately 7 months)
c. atorvastatin (and atorvastatin metabolites) [approximately 3 months]
d. chlorzoxazone and 6-hydroxychlorzoxazone (approximately 5 months)

8. For the TMC278-C127 trial, please submit the validation report including the long term stability data for omeprazole and the omeprazole metabolites covering approximately 4 months at the appropriate storage temperature. For the long term stability data, please specify the specific temperature(s) that were evaluated and confirm that the samples from the TMC278-C127 trial were stored at this temperature for the duration of the sample lifecycle.

9. Please submit the 85 and 97 day long term sample stability data at -70°C for desmethylsildenafil and sildenafil, respectively and confirm that the TMC278-C123 samples were stored at this temperature for the duration of the sample lifecycle and were not stored at -20°C instead.

10. For the atorvastatin method validation, increased bench top stability for atorvasatin was observed in an ice bath (0°C). Please clarify whether the TMC278-C116 plasma samples were processed at room temperature or in an ice bath (0°C).

11. Please clarify whether the validation results (including the long term stability data using QC concentrations of 0.2 µg/mL and 15 µg/mL) from the submitted ketoconazole LC/MS/MS method (version 3) are applicable to analysis of the TMC278-C127 ketoconazole samples that used version 2 of the ketoconazole method.

Please respond to the additional bioanalytical comments by November 1, 2010.

If you have any questions, call Robert G. Kosko. Jr., Pharm.D., M.P.H., Regulatory Project Manager, at (301) 796-3979 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
10/01/2010

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 28, 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
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

Please provide the following ADSL variables to allow JMP Clinical analysis.

ADSL File Variable Requirements for Running JMP Clinical
(for more information refer to www.cdisc.org)

CDISC Standard	Data Set	Variable	Type	Label
ADaM	ADSL	AGE	N	AGE
ADaM	ADSL	AGEGR1	C	Age Group 1
ADaM	ADSL	ARM	C	Description of Planned Arm
ADaM	ADSL	DEATHDSC	C	Death Description
ADaM	ADSL	RACE	C	Race
ADaM	ADSL	SEX	C	Sex
ADaM	ADSL	STUDYID	C	Study Identifier
ADaM	ADSL	TRTEDT	N	Date of Last Exposure to Treatment
ADaM	ADSL	TRTEDTM	N	Datetime of Last Exposure to Treatment

ADaM	ADSL	TRTSDT	N	Date of First Exposure to Treatment
ADaM	ADSL	TRTSDTM	N	Datetime of First Exposure to Treatment
ADaM	ADSL	TRT01A	C	Actual Treatment for Period 01
ADaM	ADSL	TRT01P	C	Planned Treatment for Period 01
ADaM	ADSL	USUBJID	C	Unique Subject Identifier

Please submit the requested information by ***October 5, 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

Required Variables for JMP Clinical

ADaM	ADSL	TRT01A	C	Actual Treatment for Period 01	Only one of ARM, TRT01A, or TRT01P is required
ADaM	ADSL	TRT01P	C	Planned Treatment for Period 01	Only one of ARM, TRT01A, or TRT01P is required
ADaM	ADSL	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	AE	AEBODSYS	C	Body System or Organ Class	
SDTM	AE	AEDECOD	C	Dictionary-Derived Term	
SDTM	AE	AEENDY	N	Study Day of End of Adverse Event	
SDTM	AE	AEREL	C	Causality	
SDTM	AE	AESEV	C	Severity/Intensity	Either AESEV or AETOXGR is required; values must be Mild, Moderate, Severe, Life Threatening, or Death
SDTM	AE	AESTDY	N	Study Day of Start of Adverse Event	
SDTM	AE	AETOXGR	C	Toxicological Grade	Either AESEV or AETOXGR is required; values must be Mild, Moderate, Severe, Life Threatening, or Death
SDTM	AE	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	AE	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	CM	CMDECOD	C	Standardized Medication Name	
SDTM	CM	CMENDY	C	Study Day of End of Medication	
SDTM	CM	CMSTDY	C	Study Day of Start of Medication	
SDTM	CM	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	CM	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	DM	AGE	N	Age	
SDTM	DM	ARM	C	Description of Planned Arm	
SDTM	DM	RACE	C	Race	
SDTM	DM	RFENDTC	C	Subject Reference End Date/Time	
SDTM	DM	RFSTDTC	C	Subject Reference Start Date/Time	
SDTM	DM	SEX	C	Sex	
SDTM	DM	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	DM	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	DS	DSCAT	C	Category for Disposition Event	
SDTM	DS	DSDECOD	C	Standardized Disposition Term	
SDTM	DS	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	DS	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets

SDTM	LB	LBDY	N	Study Day of Specimen Collection	
SDTM	LB	LBSTNRHI	N	Reference Range Upper Limit-Std Units	
SDTM	LB	LBSTNRLO	N	Reference Range Lower Limit-Std Units	
SDTM	LB	LBSTRESN	N	Numeric Result/Finding in Standard Units	
SDTM	LB	LBTEST	C	Lab Test or Examination Name	
SDTM	LB	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	LB	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	MH	MHBODSYS	C	Body System or Organ Class	
SDTM	MH	MHDECOD	C	Dictionary-Derived Term	
SDTM	MH	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	MH	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	VS	STUDYID	C	Study Identifier	Must be coded consistently across data sets
SDTM	VS	USUBJID	C	Unique Subject Identifier	Must be coded consistently across data sets
SDTM	VS	VSDY	N	Study Day of Vital Signs	
SDTM	VS	VSSTRESN	N	Numeric Result/Finding in Standard Units	
SDTM	VS	VSTEST	C	Vital Signs Test Name	

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/s/

Robert G Kosko
09/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Cardio-Renal Products
Attention: Devi Kozeli

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Robert G. Kosko, Jr., Pharm.D., M.P.H.
OND/OAP/DAVP 301-796-3979

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/28/10	N/A	202022	Original NDA	7/23/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TMC278	Standard	7030202	2/23/11

NAME OF FIRM: Tibotec, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: See Attached (location of material to be reviewed is located in appendix 1).
The network location is : \\CDSESUB1\EVSPROD\NDA202022\202022.ENX

SIGNATURE OF REQUESTOR
Robert G. Kosko, Jr.

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Renal Consult

The Division of Antiviral products is requesting a consult from the Division of Cardiovascular and Renal Drug Products to review renal-related safety data from NDA 202022 (rilpivirine, TMC278).

Background

Rilpivirine, an NME, is an anti-retroviral drug developed for the treatment of HIV-1 infection in combination with other antiretroviral drugs. Based on the mechanism of action on the life cycle of the human immunodeficiency virus, HIV drugs are classified into 6 classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Rilpivirine belongs to the NNRTI class.

Rilpivirine is primarily metabolized and excreted hepatically. About 6% of the administered dose was excreted in urine (less than 1% as unchanged rilpivirine). As such, no formal study in renally impaired patients has been conducted.

Adverse events from NNRTIs include neuropsychiatric events, liver toxicity, and rash. NNRTIs are also substrates of CYP3A4 enzymes and these agents can interact with commonly prescribed drugs. Renal toxicity has not been previously described for the NNRTI class.

However, tenofovir, among the NRTI used as part of the combination HAART regimen during the Phase 2 and 3 TMC278 trials, is known to have renal toxicity. Tenofovir is principally eliminated by the kidney. 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. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment

During TMC278 pre-clinical studies, kidneys were not identified as a site of major toxicity. In 4-week and 13-week studies in mice there was minimal to moderate nephropathy primarily in high dose females. Kidney toxicity was not seen in rats and dogs (longer term studies were completed in those species). During Phase 1 and Phase 2 studies, renal toxicity was not identified as an apparent adverse event of special interest.

Two registrational Phase III trials, with a Week 48 cut-off date for analyses have been submitted in support of full marketing authorization. The two clinical trials, TMC278-C209 and TMC278-C215 are identical except for the type of background regimen used to construct the full HAART regimen. In C209, subjects received a fixed background regimen consisting of Truvada (tenofovir/emtricitabine (TDF/FTC)). In C215, the background regimen contained 2 investigator-selected N(t)RTIs: either Epizicom (abacavir/lamivudine (ABC/3TC)), Combivir (zidovudine/lamivudine (AZT/3TC)), or TDF/FTC.

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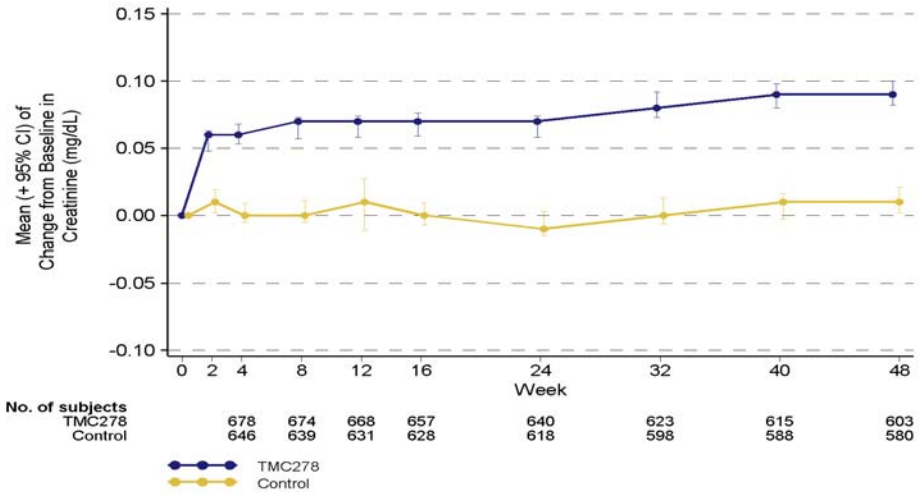
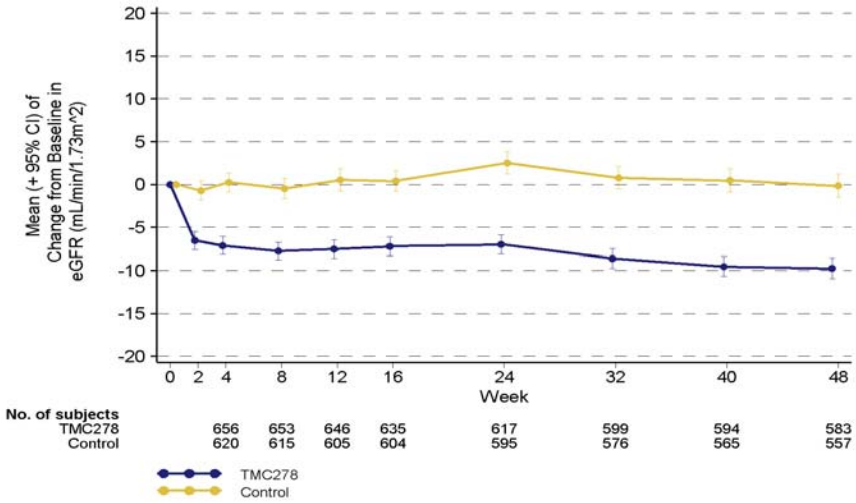
The review of the Phase 3 topline safety summary suggested there appears to be a drug related increase in serum creatinine (compared to baseline) as well as a decrease in creatinine clearance, CrCl (compared to baseline). Although the events were not graded (i.e. not >Grade 1), there appears to be a clear difference between TMC278 and the control arm (see graph below).



Mean Change (±95% CI) from Baseline in Creatinine Over Time (Phase III Week 48 Pooled Analysis of C209 and C215



Mean Change (±95% CI) from Baseline in eGFRcreat Over Time (Phase III Week 48 Pooled Analysis of C209 and C215); calculated based on serum creatinine using MDRA formula

Cystatin C study was conducted to evaluate whether the effect of TMC278 on serum creatinine reflected a true change in GFR or could have an alternative explanation (e.g interaction with the tubular secretion of creatinine). The Cystatin C study was a sub-study of C215. Based on the study result, the Sponsor has concluded that TMC278 does not have effect on glomerular filtration (see table below).

Table 2: TMC278-C215: Actual Value and Change from Baseline in $eGFR_{cyst}$

Visit	Parameter	TMC278 N = 340 n	TMC278 N = 340 Mean (95% CI)	Control N = 338 n	Control N = 338 Mean (95% CI)
Baseline	Actual Value	330	98.4 (95.76; 101.00)	329	99.3 (96.97; 101.56)
Week 2	Actual Value	325	101.1 (98.43; 103.76)	312	105.0 (102.47; 107.57)
	Change from Baseline	321	+2.6 (1.15; 3.98)	308	+5.3 (3.75; 6.80)
Week 24	Actual Value	312	120.2 (116.82; 123.58)	297	130.6 (126.37; 134.77)
	Change from Baseline	304	+21.6 (18.95; 24.23)	288	+31.3 (27.88; 34.81)

N = number of subjects per treatment group; n = number of observations
Source: Data on file

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Consult Question

The Division of Antivirals would like to ask for your independent evaluation of the safety of TMC278 results as it relates to renal adverse events, laboratory toxicities, and the cystatin C study results.

Specifically,

1. Please comment on the totality of the renal-related safety data
2. Do you concur 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?

NDA 202022 is submitted electronically (Global Submit). Please refer to Appendix 1 for locating the study reports and datasets.

The review time clock is 10 months, with a PDUFA goal date of May 23, 2010. We greatly appreciate your response by February 23, 2010.

Appendix 1

Launch GSReview for viewing eCTD documents.

0000 Original Application

- 2.7 Clinical Summary

- 5. Clinical Study Reports
  - 5.3.5 Reports of Efficacy and Safety Studies
    - -5.3.5.1 Study Reports of Controlled Clinical Studies
      - -5.3.5.1 tmc278-tidp6-c215- A Phase III, randomized,…
        - -5.3.5.1.3 Study Report Body
          - TMC278-C215 Clinical Report Addendum (Cystatin study)
        - -5.3.5.1.25. Individual Subject Data Listing (datasets)
    - -5.3.5.3 Reports of analysis of Data from More than One Study
      - - 5.3.5.3 tmc278-c904- Pooling TMC278 Phase III Trials
        - -5.3.5.3.25 Individual Subject Data Listing

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/s/

Robert G Kosko
09/28/2010

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 16, 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
Yodit Belew, M.D., Clinical Reviewer

Subject: Comments Regarding July 23, 2010 Submission

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

Please provide narratives for the following subjects with skin events ("exfoliation"). The narrative should include description of the skin events, duration, time/date of event and any other adverse events or laboratory toxicities that occurred during the time of the skin events. All concomitant medications should also be included in the narratives.

Subject ID
209-0386
209-0394
209-0505
209-0808
209-0835
209-0914
215-0801

Please submit the requested information by September 27, 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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/s/

Robert G Kosko
09/16/2010

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: August 23, 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
Yodit Belew, M.D., Clinical Reviewer
Karen Winestock, Chief, Project Management Staff

Subject: Comments Regarding July 23, 2010 Submission

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

1. Please resubmit the laboratory datasets subcategorized based on the type of lab (e.g. LB1 would contain all liver related laboratory analytes- ALT, AST, Alk phos, bilirubin; LB2 would include hematology related laboratory analytes; LB3 would include chemistry related analytes etc…). The currently submitted datasets are subcategorized based on subject's ID (e.g. LB1 includes subjects ID from 0001 to 0127; LB2 includes subjects ID128-252; LB3 includes subjects ID 253-389, etc.) making laboratory data analysis extremely cumbersome.

2. Please submit a pediatric waiver and/or deferral to your NDA. Please refer to the Guidance for Industry document entitled, "How to Comply with the Pediatric Research Equity Act" for detailed instructions.

Please submit the requested information by September 27, 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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/s/

Robert G Kosko
08/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202022

NDA ACKNOWLEDGMENT

Tibotec, Inc.
Attention: Debora Monshizadegan
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Ms. Monshizadegan:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TMC278

Date of Application: July 23, 2010

Date of Receipt: July 23, 2010

Our Reference Number: NDA 202022

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 21, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call me at (301) 796-3979 or the Division's main number (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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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/s/

Robert G Kosko
07/29/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 67,699

MEETING MINUTES

Tibotec, Inc.
Attention: Debora Monshizadegan
Manager, Global Regulatory Affairs
1125 Trenton-Harbourton Rd
Titusville, NJ 08560

Dear Ms. Monshizadegan:

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

We also refer to the meeting between representatives of your firm and the FDA on June 3, 2010. The purpose of the meeting was to discuss the content and format of your NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Robert G. Kosko, Jr., Pharm.D., M.P.H. at (301) 796-3979 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA Meeting
Meeting Date and Time:	June 3, 2010 1:00 PM – 3:00 PM
Meeting Location:	Building 22, Room 1311
Application Number:	IND 67,699/IND 106,252
Product Name:	TMC278 (rilpivirine, RPV)/ Emtricitabine, Rilpivirine Hydrochloride, Tenofovir Disoproxil Fumarate Tablet
Proposed Indications:	Treatment of HIV-1 infection
Sponsor/Applicant Name:	Tibotec, Inc./Gilead Sciences, Inc.
Meeting Recorder:	Robert G. Kosko, Jr., Pharm.D., M.P.H. Linda C. Onaga, M.P.H.

FDA ATTENDEES

1. Dave Roeder, Associate Director for Regulatory Affairs, OAP
2. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
3. Jeffrey Murray, M.D., M.P.H, Deputy Director, DAVP
4. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
5. Yodit Belew, M.D., Clinical Reviewer, DAVP
6. Julian O'Rear, Ph.D., Virology Team Leader, DAVP
7. Lisa Naeger, Ph.D., Virology Reviewer, DAVP
8. Damon Deming, Ph.D., Virology Reviewer, DAVP
9. Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader, OTS/OCP/DCP4
10. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, OTS/OCP/DCP4
11. L. Peyton Myers, Ph.D., Acting Pharmacology and Toxicology Team Leader, DAVP
12. Mark Seaton, Ph.D., Pharmacology and Toxicology Reviewer, DAVP
13. Greg Soon, Ph.D., Biometrics Team Lead, Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IV (OTS/OB/DBIV)
14. Tom Hammerstrom, Ph.D., Biometrics Reviewer, OTS/OB/DBIV
15. Dorota Matecka, Ph.D., Acting CMC Lead, OPS/ONDQA/DNDQA II)
16. Yong Wang, Ph.D., CMC Reviewer, OPS/ONDQA/DNDQA II
17. Karen Winestock, Chief, Project Management Staff, DAVP
18. Robert Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager, DAVP
19. Linda Onaga, M.P.H., Regulatory DAVP
20. Twanda Scales, Safety Regulatory Project Manager, OSE
21. Antoine El Hage, Ph.D., Division of Scientific Investigations
22. Justin Koteff, Pharm.D., OTS/OCP/DCP4 Fellow

SPONSOR ATTENDEES

Tibotec, Inc. Representatives:

1. Katia Boven, M.D., Senior Director Global Clinical Development, Tibotec, Inc.
2. Herta Crauwels, Ph.D., Senior Manger, Clinical Pharmacology, Tibotec, Inc.
3. Robin Keen, Vice President, Global Regulatory Affairs, Tibotec, Inc.
4. Debbie Lettani, M.Sc., Associate Director, Global CMC Regulatory Affairs, Tibotec, Inc.
5. Gaston Picchio, Ph.D., Senior Director, Clinical Virology, Tibotec, Inc.
6. Laurence Rimsky, Ph.D., Director, Global Regulatory Affairs, Tibotec, Inc.
7. Kati Vandermeulen, M.Sc., Director, Global Regulatory Affairs, Tibotec, Inc.
8. Tony Vangeneugden, Ph.D., Senior Director, Biostatistician, Tibotec, Inc.
9. Simon Vanveggel, M.Sc., Senior Manager, Biostatistician, Tibotec, Inc.
10. Frans Van Velsen, Ph.D., Senior Director, Pre-Clinical Development & Toxicology, Tibotec, Inc.
11. Peter Williams, Ph.D., Senior Director, Compound Development Team Leader, Tibotec, Inc.
12. Brian Woodfall, Ph.D., Vice President, Global Clinical Development, Tibotec, Inc.

Gilead Sciences, Inc. Representatives:

1. Steven Chuck, M.D. Vice President, HIV Therapeutics
2. Pamela Danagher, M.Sc., Senior Director, Regulatory Affairs
3. Shalini Gidwani, M.Sc., Senior Manager, Regulatory Affairs

1. BACKGROUND

Tibotec, Inc. (Tibotec) is developing a non-nucleoside reverse transcriptase inhibitor (NNRTI), TMC278 (rilpivirine, RPV), for the treatment of HIV-1 infection in treatment naïve patients. On March 24, 2010, Tibotec requested a meeting to obtain feedback and agreement from the Division related to the New Drug Application (NDA) filing of TMC278. This request was granted on March 31, 2010 as a Type B pre-NDA meeting. The background document was submitted to the Division on May 3, 2010.

The objective provided by Tibotec for the June 3, 2010 meeting was to engage the Division in a discussion regarding the suitability of the content and format of the upcoming NDA for TMC278.

Gilead Sciences, Inc. (Gilead) is developing emtricitabine (FTC), rilpivirine hydrochloride (RPV), tenofovir disoproxil fumarate (TDF) fixed-dose combination (FDC) tablets as a complete regimen for the treatment of patients with HIV-1 infection. Gilead entered into a licensing agreement with Tibotec, the Sponsor of IND 67,699 for RPV to develop and pursue registration of once daily, fixed-dose product combining Tibotec's RPV and Gilead's FTC and TDF. Gilead intends to submit their NDA after the NDA for the single agent RPV has been submitted by Tibotec.

On March 24, 2010, Gilead requested a meeting to obtain feedback and agreement from the Division related to the NDA filing strategy for the fixed dose combination product. This request was granted on March 31, 2010 as a Type B pre-NDA meeting. The background document was submitted to the Division on May 4, 2010.

The objectives provided by Gilead for the June 3, 2010 meeting were as follows:

Meeting Note: After granting separate meetings for Tibotec and Gilead, the sponsors informed the Division of Antiviral Products that they wanted to have a joint meeting. In addition, the Division was informed after the meeting that combined meeting minutes would be acceptable.

Before discussing the individual Sponsor questions, the FDA made a statement regarding the timeline for the review of TMC278:

- *Based on the information the Division has to date, the Division has concluded that TMC278 will be reviewed under a standard, 10 month review.*
- *The FDA paused to allow the Sponsors to respond. Gilead had comments but these were deferred until after Tibotec's questions were discussed.*

2. TIBOTEC PRELIMINARY QUESTIONS AND RESPONSE

The Sponsor's questions are depicted in bold type, followed by FDA response from the June 3, 2010 meeting in italics. Sponsor discussions are in regular font.

2.1. Does the Division agree that the 48-week data from two independent, adequate and well-controlled trials (C209 and C215) support the filing and review of the NDA for TMC278?

- *Yes.*

2.2. Does the Division agree that the proposed indication, as written in section 1.3 of this document, is supported by the data from C209 and C215?

- *Determination of the proposed indication is a review issue.*

2.3. Does the Division agree that the 48-week pooled safety analysis of C209 and C215 support the filing and review of the NDA?

- *Yes.*

2.4. Does the Division agree that the overall safety exposure of patients enrolled in TMC278 trials is adequate to support the filing and review of the NDA?

- *Yes.*

2.5a. Does the Division agree with the proposed presentation of data (b) (4) in the USPI?

- ***Content of the USPI toxicity display***
  The goal of the USPI is to present fair and adequate information about the drug profile. For example, depending on what a specific drug's profile had been, (b) (4) (b) (4) is a review issue.
- ***P values***
  (b) (4)
- ***Denominator***
  When calculating the events for laboratory toxicities, the total number of patients (i.e. ITT) should be used as the denominator, (b) (4)

2.5b. Does the Division agree a similar table presentation, (b) (4) , could also be proposed/or inclusion in the USPI?

- *Again, the goal of the USPI is to present fair and adequate information about the drug profile. Previous USPI toxicity displays have included reporting of* (b) (4) *is a review issue.*
- *The sponsor noted that significance testing was* (b) (4) *is not appropriate.*
- (b) (4) *is also a review issue.*

2.6. Does the Division agree with the proposed plan for presentation of drug-drug interaction data in the USPI?

- *The FDA will send additional responses to Tibotec regarding modifications to the drug-drug interaction tables (see section 5).*

- *The FDA recommended that Tibotec include the RPV dosage regimen in the drug-drug interaction tables for consistency with other NNRTI labels (with the exception of etravirine).*
- *The FDA recommended against the use of table footnotes to indicate the RPV dosage regimen in response to a question from Tibotec.*

2.7. Does the Division agree with the proposal for the 120 Day Safety Update Report including the proposed content, data cut-off and timeline for submitting the safety update report during the NDA review period?

- *The purpose of the 120 Day Safety Update Report is to provide safety data on any ongoing clinical trials and not to submit new non-safety related study results from ongoing trials. Therefore the information submitted as part of the 120 Day Safety Update Report should be limited to safety related reports. The report should include all deaths, all discontinuations due to SAEs and line listings of all SAEs along with the CRFs. In addition, case narratives may be requested for some SAEs and deaths. The proposed timeline for submission of the Safety Update Report is acceptable.*
- *The Division noted that in addition to the Phase 2b and 3 studies, listed are studies C154, HIV1001 and new sub-studies from C209 (vitamin D study) and C215 (cystatin C study). The Division requested additional details about HIV1001.*

  Tibotec clarified that HIV1001 is a drug-drug interaction study between EFV and TMC278.

2.8. Does the Division agree that the data of a Phase I drug-drug interaction trial looking at ways to combine TMC278 and proton pump inhibitors can be submitted for the Division's review in the 120 Day Safety Update Report during the NDA review period without affecting the review timelines?

- *Data and results from all trials Tibotec wants reviewed should be included in the NDA at the time of NDA submission, especially if the trial results provide information on the effective use of TMC278.*

  Tibotec replied that the NDA will have data from an already completed drug-drug interaction trial between PPIs and TMC278 that demonstrated decreased TMC278 exposure with PPI coadministration. C154 is an additional trial to investigate how to potentially compensate for the effect of PPIs on TMC278.

- *FDA stated that if the additional drug-drug interaction results are submitted as part of the 120 Day Safety Update, the information may not be* (b) (4) *' if RPV is approved for marketing.*

Tibotec asked if preliminary data from C154 could be submitted with the NDA and the final trial report and data be submitted as they become available.

- *The FDA recommended Tibotec submit as much data as possible as early as possible. Additionally, if preliminary data are submitted, it was recommended that Tibotec specify the differences between the preliminary and final data when the final trial report is submitted.*

2.9. Does the Division agree that the Vitamin D and cystatin C data from C209 and C215, respectively, can be submitted for the Division's review in the 120 Day Safety Update Report during the NDA review period, without affecting the review timelines?

- *Based on the topline renal safety report submitted in the briefing package, the Division considers the cystatin C data to be an important component of the Division's renal evaluation. The data and results for cystatin C need to be included with the submission of the NDA and not with the 120 day safety update. If not submitted at the time of the NDA submission, it will be considered a filing issue.*
- *With regards to the Vitamin D data, it is not clear to the FDA what Tibotec plans to do with the study results. It appears that the study may have been conducted based on the study results observed in the MONET (TMC114 and EFV) study. The Division asked for clarification on Tibotec's intents, including if they are planning to propose to inclusion of the results in the label.*

Tibotec replied that they are currently evaluating the study results and their intents will depend on the findings of the study results.

- *FDA in turn replied that if Tibotec would like us to review the data and results of the vitamin D study during the review cycle, the data should be submitted at the time of the NDA submission. The results should not be submitted as a 120 Day Safety Update Report.*

2.10. Does the Division agree with the proposal regarding submission of the SDTM datasets for the Week 96 analysis of trial C204, if needed, with the 120 Day Safety Update Report or upon request?

- *If the Week 192 SDTM datasets have the appropriate variables so the FDA can create and analyze the Week 96 data easily, the SDTM datasets for the Week 96 analysis are not needed with the safety update.*

2.11. Recognizing that the decision regarding a need for an FDA Advisory Committee Meeting prior to the approval of an NDA will be addressed during the review, does the Division anticipate that the TMC278 NDA will be the subject of an FDA Advisory Committee Meeting based on the available data presented in this package supporting the NDA?

- *The current FDA thinking is all new molecular entities will be presented before an Advisory Committee; therefore TMC278 NDA will likely have an Advisory Committee Meeting. A final decision will be made at the time of filing.*
- *The FDA recommended Tibotec include a justification in their NDA submission for why an Advisory Committee Meeting would not be necessary.*

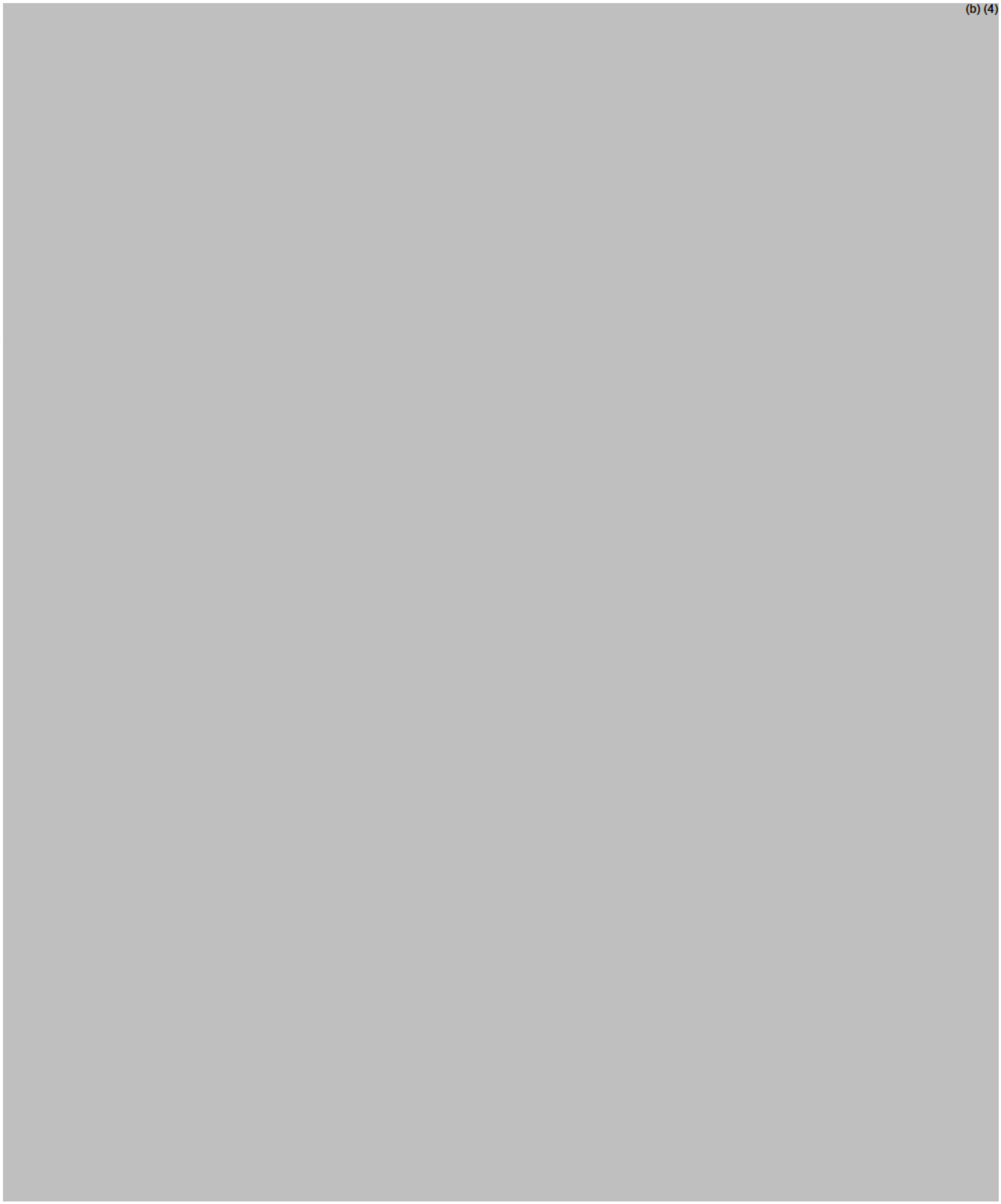
2.12. Does the Division agree with Tibotec's proposal regarding the provision of financial disclosure information?

- *Yes.*

3. GILEAD PRELIMINARY QUESTIONS AND RESPONSE

(b) (4)

(b) (4)



4.0 ADDITIONAL DISCUSSION

Tibotec, Inc.:

- The FDA advised the Sponsor to explore when the virologic failures occurred (i.e. within the first 24 weeks versus the second 24 weeks) and the timing of discontinuations.
- The FDA requested that in addition to cross-referencing the DMF, the Sponsor include the drug substance specification, information on any characteristics of the drug substance that are relevant to dosage form performance, and contact information and site responsibilities for all drug substance manufacturing, testing, packaging and labeling facilities.
- The FDA requested the Sponsor include long-term stability data at 30°C/75% RH (in addition to the 25°C/60% RH data) for the primary stability batches of the drug product.
- The FDA requested the Sponsor state their plans to include a non-US version of the drug product in the NDA submission.
- With respect to virology assays, the FDA confirmed with the Sponsor that the primary analysis would be done with Amplicor and the secondary analysis would be done with TaqMan.

Gilead Sciences, Inc.:

(b) (4)

5.0 ACTION ITEMS

Tibotec, Inc.:

- *The FDA will send additional responses to Tibotec for modifications to the drug interaction tables.*
- *Tibotec and Gilead will inform the FDA of a revised timeline for NDA submission.*

Gilead Sciences, Inc.:

(b) (4)

6.0 POST-MEETING COMMENTS

Tibotec, Inc.:

- In response to Question #6 presented in your May 3, 2010 background document, DAVP requests that "With or Without Co-administered Drug" be included in the heading. We also recommend the inclusion of the rilpivirine dosage regimen in the drug-drug interaction tables to be consistent with the presentation of the drug-drug interaction data in the labels for other antiretroviral medications and consider this essential information for interpreting the drug-drug interaction data. DAVP does not believe that the inclusion of this information will increase the risk of patients potentially overdosing on rilpivirine. A footnote may be added, where appropriate, to indicate a rilpivirine dosage regimen that is not approved. DAVP's revisions regarding the presentation of drug-drug interaction data in the rilpivirine label are displayed below.

DAVP revisions for the presentation of proposed rilpivirine drug-drug interaction data in the USPI

(b) (4)

Tibotec, Inc. and Gilead Sciences, Inc.:

- After the meeting, the Division of Scientific Investigations presented a request to each Sponsor concerning data collection forms for all clinical sites.

- The Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that the sponsor clearly identifies, in a single location (either in the NDA itself or prior to submission), all manufacturing facilities associated with this NDA, including the address, FEI, and specific manufacturing responsibilities for each site, and the type of testing performed (if applicable). Each facility must be ready for inspection upon application submission so that the inspection may be planned as soon as possible. Ease of accessibility to manufacture facility information can facilitate the NDA review process.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67699	GI-1	TIBOTEC INC	TMC278

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

/s/

DEBRA B BIRNKRANT
06/21/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,699

Tibotec, Inc.
Attention: Debora Monshizadegan
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Ms. Monshizadegan:

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

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2007. The purpose of the meeting was to discuss proposed Phase III trials.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Debbie Birnkrant, MD
Division Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 18, 2007
TIME:	10:00
LOCATION:	FDA, White Oak
APPLICATION:	IND 67.699
DRUG NAME:	TMC278
TYPE OF MEETING:	End of Phase II

FDA ATTENDEES: (Title and Office/Division)
Yodit Belew, MD- Medical Officer
Kendall Marcus, MD- Medical Officer Team Leader
Kimberly Struble, PharmD- Medical Officer Team Leader
George Lunn, PhD- Chemistry Reviewer
Tom Hammerstrom, PhD- Statistics Reviewer
Jenny Zheng, PhD- Clinical Pharmacology Reviewer, DCP4
Pravin Jadhav, PhD- Pharmacometrics Reviewer, OCP
Kellie Reynolds, PharmD- Deputy Director, DCP4
Kuei-Meng Wu, PhD- Pharmacology Reviewer
Corinne DuBourg, PharmD- Pharmacology Student Intern
Lisa Naeger, PhD- Microbiology Reviewer
Jules O'Rear, PhD- Microbiology Team Leader
Elizabeth Thompson, MS- Regulatory Project Manager
Tony DeCicco, RPh- Chief, Project Management Staff
Jeff Murray, MD, MPH- Deputy Division Director
Debra Birnkrant, MD- Division Director
Dave Roeder, MS- Associate Director, Regulatory Affairs
Ed Cox, MD, MPH- Office Director, OAP

EXTERNAL CONSTITUENT ATTENDEES:
Katia Boven, M.D., Director, Global Clinical Development
Marie-Pierre de Bethune, Ph.D., Vice President, Clinical Virology
Debbie Lettani, M.Sc., Assistant Director, CMC, Global Regulatory Affairs
Debbie Monshizadegan, Manager, Global Regulatory Affairs
Wim Parys, M.D., Vice President, Global Clinical Development
Monica Peeters, M.Sc., Director, Biostatistics
Laurence Rimsky, Ph.D., Director, Clinical Virology
Karin Van Baelen, Pharm.D., Vice President, Global Regulatory Affairs
Rolf Van Heeswijk, Ph.D., Associate Director, Clinical Pharmacology
Simon Vanveggel, M.Sc., Biostatistician
Frans Van Velsen, Ph.D., M.Sc. Pharmacy, Senior Director, Pre-Clinical Development & Toxicology
Peter Williams, Ph.D., Senior Director, Global Compound Development Team
Hua Zheng, M.D., Ph.D., Director, Global Regulatory Affairs
(b) (4)
Katrien Peeters, M.D., Director, Health Economics & Outcomes Research

BACKGROUND:
TMC 278 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. An End of Phase I meeting was conducted on January 12, 2005. With 48 week data for TMC278-C204 (Phase IIb study), it is Tibotec's intention to further pursue a Phase III program targeting the population of antiretroviral naïve patients in support of an initial regulatory approval. A briefing package was submitted June 15, 2007 (SN138). FDA sent responses to Tibotec's questions included in this package on July 16, 2007 via facsimile and email.

MEETING OBJECTIVES:
1. To obtain agreement from the Division on the overall adequacy for the proposed Phase III program in ARV-treatment naïve HIV-1 infected patients
2. To seek concurrence and input from the Division on our proposed safety management plan in Phase III trials
3. To seek agreement and input from the Division on the adequacy of the proposed Phase III program to support an NDA for traditional approval of TMC278 as a stand alone agent, and to support approval of subsequent sNDAs for TMC278 plus the designated background regimens as fixed dose combination (FDC) formulations, in ARV-treatment naïve HIV-1 infected patients
4. To seek advice from the Division on how to adequately demonstrate superior tolerability

DISCUSSION POINTS: Sponsor questions are in normal font and FDA responses are in bold font (provided via facsimile on July 16, 2007). Additional discussion that occurred during the face to face meeting is provided in italics.

Question 1: Does the Division agree that the available nonclinical package is supportive for clinical Phase III studies with TMC278 in HIV-1 infected subjects?

- **Yes**

Question 2: In view of the comprehensive nonclinical dataset for TMC278 and the long-term clinical safety data from the Phase IIb trial TMC278-C204, does the Division agree that the overall nonclinical dataset (completed studies plus the ongoing and planned studies including carcinogenicity studies) is sufficient to support submission of an NDA for TMC278 as single-agent tablets?

- **Yes**

Question 3: In view of the comprehensive nonclinical dataset for TMC278 and the long-term clinical safety data from the Phase IIb trial TMC278-C204, Tibotec concludes that no nonclinical combination studies are needed in support of an NDA for a Fixed Dose Combination (FDC) of TMC278 with either of the marketed NRTI backbone regimen (TDF/FTC or (b) (4) proposed for the Phase III studies. Does the Division agree with this position?

- **Yes**

Question 4: The investigation of the antiviral activity, mechanism of action, and the viral resistance are essential elements of the TMC278 development program. A list of the in vitro studies, and a summary of the planned resistance determinations is provided below. Does the

Division consider that these determinations are adequate to study the development of resistance and to support the submission of an NDA for TMC278?

- **Yes, however, TMC278 is similar in structure to TMC125 raising concerns about cross-resistance. Please determine the susceptibility to TMC278 of several TMC125 failure isolates representing the breadth of genotypic and phenotypic resistance.**

- **The K101P amino acid substitution results in large shifts in susceptibility to TMC278. Please identify all other subjects in the C202 study besides Patient #2020068 whose isolates had a baseline mutation at codon 101 and were one mutation away from K101P.**

- *The Division acknowledged agreement with Tibotec's overall plan for resistance determination. Tibotec indicated that the use of TMC278 upon failure on TMC125 (and vice-versa) is not considered a valid treatment option and therefore will not be studied clinically. The Division acknowledged that this is acceptable, but still requests that susceptibility of TMC125-resistant failure isolates be tested against TMC278.*

- *Tibotec agreed to identify patients in Study C202 who were one mutation away at baseline from a K101P substitution.*

Question 5a: Does the Division agree that the completed Phase I studies are adequate to support initiation of Phase III trials?

- **DAVP agrees that the completed Phase I studies are adequate to support initiation of Phase III trials. However, in the Phase III trials, the following should be considered:**
    1. **adjust TMC278 dose when it is taken with rifabutin, because rifabutin reduces the AUC of TMC278 by 46%**
    2. **disallow proton-pump inhibitors (e.g., omeprazole), because omeprazole reduces the AUC of TMC 278 by 40%, and TMC278 induces omeprazole metabolism**
    3. **evaluate the effect of the polymorphism of glutathione S-transferase (GST) mu on the pharmacokinetics of TMC278, because GST mu is involved in the metabolism of TMC278, and GST mu is subject to genetic polymorphism and is only expressed in 55-60% of individuals.**

Question 5b: Does the Division agree that the proposed Phase I program (including the completed, ongoing and planned studies) is adequate to support submission of an NDA for TMC278?

- **To support submission of an NDA of TMC278, drug-drug interaction studies with warfarin and paclitaxel are recommended, because TMC278 inhibits CYP 2C8/9/10 with I/Ki > 0.1. If you plan to use protease inhibitors other than darunavir, drug-drug interaction studies with those protease inhibitors may be needed.**

- **In the relative BA study (Study 117), 25 mg and 100 mg Phase III tablets were used. However, the planned Phase III studies will use 75 mg tablets. Do you plan to conduct a relative BA study with Phase II tablets and 75 mg Phase III tablets?**

- **Your previous GST induction study was inconclusive. Do you plan to restudy the GST induction?**

- *DAVP requested the data from the mass balance study for review on the effect of the polymorphism of GST mu on the pharmacokinetics of TMC278 (DAVP confirmed receipt of this submission after the meeting). Based on presentation by Tibotec (refer to SN150 for slide presentation), DAVP agreed that no additional clinical study is necessary to evaluate the role of GST mu polymorphism and that the GST induction study does not need to be repeated.*

- *DAVP suggested increasing the dose of TMC278 during combination with rifabutin. Tibotec indicated that patients who develop TB during the Phase III studies would be discontinued because a dose adjustment of rifabutin when combined with EFV is needed, and this cannot be accomplished in a double-blinded study. Therefore, rifabutin will not be used in the Phase III trials. DAVP agreed.*

- *DAVP expressed concerns about the potential for concomitant administration of proton pump inhibitors (PPIs) to reduce TMC278 exposure and alter efficacy, because of the drug-drug interaction result with omeprazole. Tibotec addressed concerns (see SN150 for slides). However, because of the potential of unmonitored use of PPIs as OTC medications, DAVP acknowledged that it is better to study the effect during Phase III to avoid uncertainties when the drug is marketed. DAVP stated they would reconsider whether PPIs should be allowed in Phase III, and suggested Tibotec identify a method to collect information regarding outcome of patients who use PPIs in the Phase III trials. Tibotec agreed.*

- *DAVP agreed that no additional bioavailability study is necessary with respect to the 75mg Phase III tablet.*

- *DAVP agreed Tibotec can provide additional in vitro drug information regarding potential interactions with CYP2C8 and CYP2C9 substrates. We will discuss the need for additional in vivo interaction studies following review of the in vitro results.*

Question 6: Considering the data showing a limited role of renal clearance in the elimination of TMC278, does the Division agree with Tibotec's proposal not to perform a trial in subjects with renal impairment?

- **No. The Division requests that a study in patients with renal impairment be conducted; however, subjects with creatinine clearance below 50 cc/min should not be enrolled due to concerns regarding renal toxicity associated with TMC278.**

- **Controversy exists regarding the impact of severe renal impairment on hepatic metabolism. Therefore, a renal impairment study is still considered desirable for a drug eliminated primarily via hepatic metabolism unless it also has a relatively wide therapeutic index. Even when renal impairment is likely to have little or no effect on a drug's PK, the impact of dialysis on the PK of a drug should be considered. Patients on dialysis may require higher doses of certain drugs than patients with**

normal renal function. Since TMC278 can reduce creatinine clearance, there is more concern regarding the safety in subjects with renal impairment.

- *Based on information presented (see SN150 for slides), DAVP agreed that Tibotec would not need to conduct a study of TMC278 pharmacokinetics in subjects with renal impairment at this time. However, the Division would like to review additional renal toxicity data (biomarker data obtained from definitive QTc study) before making a final decision on the requirement for a study of TMC278 PK in subjects with renal impairment.*

Question 7: After the review of the enclosed Dose Selection Rationale (see Attachment 5.6), does the Division agree that the oral dose regimen of 75 mg q.d. is appropriate for the proposed Phase III program (TMC278-TiDP6-C209 and TMC278-TiDP6-C215)?

- **Yes.**

Question 8: After review of the enclosed draft Phase III protocols, does the Division agree that the proposed trials, TMC278-TiDP6-C209 and TMC278-TiDP6-C215, in the ARV-treatment naïve HIV-1 infected population are appropriate and acceptable with regards to the following elements?

8a. Overall trial design

- **Yes. The choice of primary endpoint and method of handling missing data are acceptable. The randomization, blinding, and control arms are acceptable.**

- **The randomization is stratified on screening or baseline viral load so the primary analysis should also be stratified. The 95% confidence interval for the Cochran-Mantel-Haenszel stratified difference in proportions with HIV-1 RNA sustained at <50 copies/mL should be the primary basis for inference.**

- **The criteria for early switching are acceptable. However, in the interest of consistency across arms, any subject who meets any one of the three early switching criteria should be considered a viral failure at that time for the purpose of calculating viral endpoints.**

- **The proposed non-inferiority margin of 12% is acceptable.**

- **Finally, the final statistical analysis plan must be submitted for FDA review prior to enrolling the first patient, not much later at database lock. The statistical section of the current draft can be considered final with the single amendment mentioned above.**

8b. Stratification factor

- **Yes**

8c. Sample size calculation, choice of non-inferiority margin (12%)

- **Yes**

8d. Proposed backbone regimen

- **Yes**

8e. Active comparator

- **Yes. However, please be aware that the AE profile of ABC/3TC may overlap with TMC278 and assessment of causality of AE may be difficult. In addition, the Division recommends that subjects with Grade 3-4 laboratory results, including neutropenia and thrombocytopenia, be excluded from the trial.**

- *Following discussion regarding using the Cochran-Mantel-Haenszel as the primary basis for inference for the 95% confidence interval, DAVP accepted Tibotec's proposal to apply logistic regression as primary analysis method for the primary endpoint.*

- *DAVP recommended that Tibotec ensure that adequate numbers of subjects with high viral load are recruited into the Phase III studies in order to observe virologic resonse in this population of patients. DAVP also recommended that Tibotec reinforce the need for investigators to discontinue patients who meet any of the three criteria for virologic failure to avoid discontinuation bias between the two groups. Tibotec agreed.*

Question 9a:
Question 9b:

- **No. Please refer to comments regarding your** (b) (4) **We do not agree with your plan to conduct a study to** (b) (4)

- **If you choose to perform** (b) (4) **, please be advised that study results cannot be submitted for inclusion in the package insert and they cannot be used for marketing purposes.**

- *DAVP stated that* (b) (4) (b) (4)

- (b) (4) *, more severe AE and more frequent AE-*

related discontinuations were observed in the TMC278 groups. Less common but medically important AE Adverse events such as renal dysfunction, anemia, QTc prolongation, and decreased serum cortisol level were seen only in the TMC278 group. The consequences of these AE cannot be adequately presented in an HIV Treatment Tolerability Index.

- *Tibotec expressed concerns that the patient's perspective is not being captured. DAVP explained that patient's reported AEs are collected as part of the study (via spontaneous AE reporting) and all pertinent safety data will be reflected in the label. Safety profile from TMC278 can therefore be fairly compared against other NNRTI using information provided in labels. DAVP stated that* (b) (4)

Question 10: Does the Division agree with the safety management plan for the proposed Phase III program, specifically for the following four aspects?

10a. No monitoring of endocrine parameters

- **We wish to defer this question. At this point we are awaiting recommendations from our Endocrinology Division to assess if and what types of parameters are needed for screening and/or monitoring endocrine AE.**

10b. Proposal for the cardiovascular safety monitoring and management

- **We recommend that you add ECG monitoring at Week 2.**

10c. Screening for HLA-B*5701 in patients who participate in trial TMC278-TiDP6-C215 to minimize the chance of abacavir-related hypersensitivity reaction

- **Yes**

10d. Omission of the coagulation test based on the Phase IIb (TMC278-C204) and Phase I data

- **Yes**

- *DAVP agreed to the proposed safety monitoring plan for HLA-B*5701 screening, cardiovascular monitoring and omission of coagulation test. DAVP will provide recommendations on exclusion criteria for patients at risk of developing QTc prolongation for Tibotec to consider in finalizing the selection criteria in the Phase III protocols.*

Question 11:

- **The Division agrees with the overall development plan for Phase 3.**

- *DAVP agreed that the proposed Phase III program is adequate to support the TMC278 NDA based on 48 week data.*

Question 12:

- **Yes.**

- *DAVP agreed that the proposed Phase III program, with additional adequate pharmaceutical quality information and clinical demonstration of bioequivalence, is adequate to support NDAs for the proposed FDCs.*

Question 13:

- **The Division defers this question at this time.**

Question 14:

- **The Division defers this question at this time.**

Question 15:

- **The Division agrees with your initial plan to further study the effect of TMC278 on the endocrine system prior to initiating a pediatric study.**

ACTION ITEMS:

1. Tibotec will provide TMC278 susceptibility data to DAVP at time of filing for several TMC125 failure isolates representing the breadth of genotypic and phenotypic resistance.
2. Tibotec will provide data to DAVP (at time of filing) on patients in study TMC278-C202 whose isolates had a baseline substitution at codon 101 and were one mutation away from K101P.
3. Tibotec will provide a rationale for or against in vivo drug-drug interaction (DDI) studies with specific substrates for CYP2C8/9, on the basis of the in vitro DDI results with paclitaxel and warfarin.
4. Renal function estimates from cystatin C in the QTc study (TMC278-C131) will be provided to the Division in December.
5. Tibotec will provide the final statistical analysis plan for review by DAVP prior to the database lock for the Phase III trials.
6. DAVP recommended that enough subjects with baseline HIV-1 viral load >300,000 copies/ml be included in the trials. This request is due to the results from the phase 2 study where a trend of lower virologic response rate in subjects who start with high baseline viral load was noted.
7. DAVP requested safety management plans for hepatoxicity and renal toxicity.
8. Tibotec will provide narratives for patients who discontinued with hepatitis in the TMC278-C204 trial.
9. Division requested more prominent wording in Phase III protocols on management of clinically suspected hypersensitivity reactions, including recommendation to permanently stop abacavir and not rechallenge patients discontinued for suspected hypersensitivity reactions.

10. Tibotec will provide a copy of Advisory Board meeting minutes to DAVP regarding evaluation of endocrine parameters. DAVP will provide Tibotec with feedback regarding question 10a once the consult to Endocrinology Division has been received.
11. DAVP will provide recommendations for exclusion criteria for patients at risk of developing QTc prolongation.
12. Tibotec will provide literature references in regards to the effect of ARVs on QTc interval.
13. Tibotec will add ECG monitoring-= at Week 2 in both studies.
14. Tibotec will provide topline results and ECG datasets for the "thorough QT study" by December 2007.
15. DAVP agreed to review a draft protocol for proposed Phase IIIb development program for ARV-experienced patients; Tibotec to submit draft protocol within next three months.

ATTACHMENTS/HANDOUTS:

Please see SN 150 for slides that were presented at the meeting by Tibotec, Inc.

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

/s/

Debra Birnkrant
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