

5. Does the Division agree with the proposed method of calculating the overall p-value and the proposal for presentation of the primary efficacy parameter results from the DUET trials for the proposed USPI?

DAVP response:

- a. Efficacy evaluation will be based on each study separately as was pre-specified in the protocol.
- b. The calculation of p-values from pooled analyses will be a review issue. Be advised that the pooled analyses should control for study in addition to other factors mentioned in Section 5.2.1 of the background package.
- c. The Division favors use of a tabular format in reporting the primary efficacy results in the USPI. This format has been used previously by approved antiretroviral drugs.
- d. Please provide separate presentations of the pooled results from the DUET results based on de novo use of enfuvirtide.
- e. Your proposal for presentation of the pooled results from the DUET results will be a review issue.
- f. Please be aware that p-values are not included in the label.

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

DAVP response:

/ / / / / /

7. Does the Division agree with the proposed process and documentation for identifying adverse drug reactions (ADRs) from the TMC125 clinical database?

DAVP response: Yes.

8. Does the Division agree with the method for the identification and analysis of clinical endpoints? Given the results of the 24-week analysis of DUET-1 and DUET-2 for clinical endpoints, does the Division agree the data is adequate to support inclusion in the USPI?

DAVP response: The method for analysis of clinical endpoints lacks adjudication by an independent expert panel. We propose submission of all data related to AIDS defining illnesses for review of these events. Inclusion of these results will be taken into consideration. In the past, the results from analyses of clinical endpoints have not been consistently included in the USPI.

Meeting: Tibotec acknowledged the value of adjudication, indicated they were in process and inquired if they could submit the adjudicated analysis of clinical endpoints with the safety update in October 2007 or wait until traditional approval. The Division advised submission with the safety update and indicated they would consider adjudicated clinical endpoints.

9. **Does the Division agree with the proposal for the safety update including the proposed content, data-cutoff and timeline of submitting the safety update report during the accelerated approval NDA review period?**

DAVP response: In accordance with the requirements of 21CFR 314.50 (d)(5)(vi)(b), we recommend the safety update include the same information as required in the integrated safety summary and contain case report forms for all deaths and discontinuations due to adverse events. In addition, we request that the safety update be submitted no later than 3 months into the review clock.

Meeting: The Division requested updated discontinuations including at minimum reasons and narratives, with case report forms (CRFs) if possible. For the Early Access Program (EAP), include updated deaths. The Division reiterated their request that the safety update be submitted no later than 3 months after NDA submission or mid-October 2007. Tibotec agreed.

10. **Does the Division agree with the plan with regard to incorporating drug-drug interaction data with TMC125 generated by sponsors other than Tibotec in the file**

DAVP response: The Division agrees with the plan, if we have reviewed the study and the data are in another drug label.

11. **Does the Division agree with the pharmacology/toxicology information provided in response to the February 12, 2007 FDA communications provide adequate information in order to support the NDA?**

DAVP response: The pharmacology/toxicology information is adequate for the NDA submission.

12. **Does the Division agree that the inclusion of the preliminary PK results from clinical trial TMC125-C173 in the NDA is sufficient to allow inclusion of information for dispersion of tablets in water in the dosage and administration section of the USPI?**

DAVP response:

- a. The Division does not agree. We need to review the full report for study C173 (to be submitted in September 2007) to determine whether we will include dispersion dosing information in the USPI.

Meeting: Tibotec asked if submission of study C173 would cause a clock stop for the NDA. The Division replied that the study is small and therefore would not.

- b. From the CMC perspective, it will be important to have data from a one-time short term stability study of the dispersion in water to demonstrate that there are no safety concerns related to degradation over the use time.

13. Does the Division agree with the proposed Pediatric development program and deferral request for the accelerated approval NDA?

DAVP response: The Division agrees with the current proposal for the pediatric development program. We agree that a request for deferral is reasonable at this time. Please provide us with the current status of all pediatric studies.

14. Does the Division agree that the week 48 analyses of DUET-1 and DUET-2 and an updated Summary of Clinical Safety are adequate to support the traditional approval for TMC125?

DAVP response: The Division agrees that Week 48 analyses of DUET-1 and DUET-2 and an updated Summary of Clinical Safety are adequate to support submission for traditional approval.

Meeting: Tibotec inquired if an updated Summary of Clinical Pharmacology and Efficacy should be included in the submission for traditional approval. The Division replied that all summaries should be updated.

15. Does the Division agree that the reports of the carcinogenicity trials can be submitted when available and do not need to be part of the traditional approval filing?

DAVP response: Carcinogenicity reports should be submitted prior to, or be included in the traditional approval application.

Additional Comments from DAVP sent via telephone facsimile on May 18, 2007:

16. Please submit all data related to deaths and study discontinuations between screening and randomization.

Meeting: Tibotec described the information tabulated in reports and inquired if the Division wanted more data. The Division replied that the data in the database would be sufficient.

17. Please limit any presentations to 15 minutes. Presentations should include review of pertinent safety issues, including rash with and without constitutional symptoms, neuro-psychiatric events, amylase elevations, cardio-vascular events and any potentially complex issues.

18. Please conduct an analysis to assess the success of identifying TMC125 resistance-associated substitutions. Determine for the failure isolates the average number of amino acid changes in reverse transcriptase above background in the TMC125 recipients and the fraction of these accounted for by identified substitutions.

Meeting: Tibotec agreed. The Division indicated that the purpose is to capture low frequency mutations.

19. Please submit the resistance data in the HIV resistance template format (see FDA Guidance for Submitting HIV resistance Data). Please include the resistance data from TMC125-C227. We recommend you submit the resistance dataset as soon as it is available.

20. Please submit virology information in section 5.3.5.4 Other Study Reports and Related Information (see <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>).

Antiviral information:

- a. Biochemical, cell culture, etc. study reports including descriptions of methodology
- b. Biochemical, cell culture, etc. data
- c. Animal model(s) study reports including descriptions of methodology
- d. Animal model(s) data
- e. *In vivo* (clinical) study reports including descriptions of methodology
- f. *In vivo* (clinical) data:
 - i. Viral load, resistance, other (in FDA format: see "Antiviral Product Development-- Conducting and Submitting Virology Studies to the Agency" and associated guidance at <http://www.fda.gov/cder/guidance/index.htm>)
- g. *In vivo* (clinical) assays (methodologies and performance characteristics):
 - i. Viral load
 - ii. Genotype

21. Requests for special safety analyses to be included in the NDA submission will be provided in a separate communication.

Meeting: The Division will send a fax describing the requested special safety analysis to Tibotec in about a week.

Additional Comments from OSE sent via telephone facsimile on May 18, 2007:

22. If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.

23. For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

- a. Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fml.htm>
- b. Development and Use of Risk Minimization Action Plans: <http://www.fda.gov/cder/guidance/6358fml.htm>
- c. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: <http://www.fda.gov/cder/guidance/6359OCC.htm>

24. If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA application.

25. Please submit the proprietary name and all associated labels and labeling for review as soon as available.

Additional topics of discussion during the meeting:

The Division requested that Tibotec submit in the NDA an example of the HIV RNA and CD4 results that the central lab sends to the DUET sites.

The Division requested a specific data format for the patient population pharmacokinetic analysis and indicated that a template will be sent to Tibotec in a fax in about a week.

The Division requested a resistance dataset and indicated that a request will be sent by fax in about a week.

ACTION ITEMS:

The Division will send a fax describing requested special safety analysis, population analysis and resistance dataset to Tibotec in about a week.

POST MEETING UPDATE:

The Division action item was completed. A fax describing requested special safety and population analyses and a resistance dataset was sent to Tibotec on June 11, 2007.

**APPEARS THIS WAY
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Jeffrey Murray
10/17/2007 02:33:03 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Chemistry Request for Information (Request number 2) NDA 22-187	

Total no. of pages including cover:

Comments: see next page

Document to be mailed: NO

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 1, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

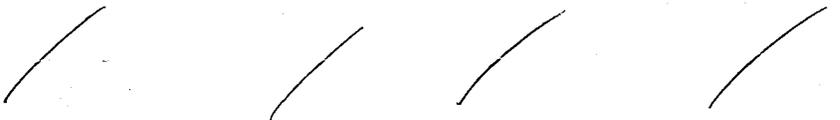
From: Anne Marie Russell, Ph.D., Regulatory Project Manager

Through: Sharmista Chatterjee, Ph.D., Chemistry Reviewer, Office of New Drug Quality Assessment/Division of Pre-Marketing Assessment II (ONDQA/DPAII)

Concur: Elaine Morefield, Ph.D, Director, Division II, Office of New Drug Quality Assessment

Subject: NDA 22-187 Chemistry Request for Information (Request number 2)

The following comments are being conveyed on behalf of Dr. Sharmista Chatterjee, chemistry reviewer and are directed toward your July 18, 2007 submission entitled "New Drug Application." Please provide a response by October 16, 2007.

1. Include an acceptance criterion for _____

2. Provide any available data that demonstrate in-process homogeneity during drug product manufacturing at various manufacturing scales. Provide details of the sampling method in terms of location and/or time of sample procurement. This data request includes:


3. We recommend inclusion of the following in-process controls in the section: 'Description of Manufacturing Process and Process Controls' (3.2.P.3.3):

/ / / / /

4. Include in the manufacturing flow chart for TMC125 100-mg tablets (Figure 1, section 3.2.P.3.3) the critical process parameters ranges for

5. Resolve the following discrepancies in the batch record (Batch PO62001532):

/ / / / /

6. Provide any available information that shows what happens if

/ / / / /

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

Anne Marie Russell
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CSO

fax sent 10/1/07

Elaine Morefield
10/2/2007 12:10:32 PM
CHEMIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-187

Tibotec, Inc.
Attention: Susan Fiordeliso
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 200
Yardley, PA. 19067

Dear Ms. Fiordeliso:

Please refer to your July 17, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC-125 (etravirine) 100 mg tablets.

We also refer to your submissions dated June 4, 2007 and July 6, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on September 18, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues or requests for information:

Statistics:

1. Please clarify if copies of the laboratory source documents of HIV RNA-Amplicor, HIV RNA-Ultrasensitive and CD4± cell counts for studies TMC125-C206 and TMC125-C216 are available at the sites. If such documents are not available please describe:
 - a. How this information was communicated to the investigators and the sponsor.
 - b. How and where these original source documents are maintained.
2. Please provide the address and phone number of the central laboratory used for studies TMC125-C206 and TMC125-C216.
3. If external vendors were used to generate or manage the treatment allocation codes for studies TMC125-C206 and TMC125-C216, please provide their addresses and telephone numbers. In addition, please disclose to FDA any financial or partnering agreements between Tibotec and the external vendors.

4. Please send the original source documents of the treatment randomization schedules generated for each patient in studies TMC125-C206 and TMC125-C216 to FDA directly. If external vendors were used to generate or manage the treatment allocation codes for studies TMC125-C206 and TMC125-C216, please have the external vendors submit the following information to the FDA
 - a. The treatment allocation codes and information on when the vendors received/generated the original codes.
 - b. Certification that the documents are the original source documents and that the treatment allocation codes were generated/received on the date mentioned in part a (above) prior to study initiation.
5. Please submit all other source documents of treatment allocation codes (e.g., from your Clinical Pharmaceutical Operations or drug packaging group).
6. Please provide your standard operating procedures for randomization treatment code generation, unblinding and release of randomization codes, along with corresponding flow charts.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Anne Marie Russell, Ph.D., Regulatory Project Manager, at (301) 796-2014.

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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Jeffrey Murray
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-187

NDA ACKNOWLEDGMENT

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

Dear Ms. Fiordeliso:

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

Name of Drug Product: TMC-125 (etravirine) 100 mg tablets

Review Priority Classification: Priority (P)

Date of Application: July 17, 2007

Date of Receipt: July 18, 2007

Our Reference Number: NDA 22-187

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 18, 2007 in accordance with 21 CFR 314.101(a).

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for

NDA 22-187

Page 2

a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above 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

If you have any questions, call Anne Marie Russell, Regulatory Project Manager, at (301) 796-2014.

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 Birnkrant
9/17/2007 03:25:33 PM
NDA 22-187



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 3, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Chemistry Facilities NDA 22-187	

Total no. of pages including cover:

Comments: see next page

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 3, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager

Through: Mark Seggel, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment/Division of Pre-Marketing Assessment II (ONDQA/DPAII)

Concur: Norman Schmuff, Ph.D., Branch Chief, ONDQA/DPAII

Subject: NDA 22-187 Chemistry facilities

The following comment is being conveyed on behalf of Dr. Mark Seggel, chemistry reviewer and is directed toward your June 4, 2007 submission (SN453) entitled "New Drug Application (Part 1 of 2)."

Please confirm in writing that the below list of facilities and their functions is complete and accurate, and that the facilities are ready for inspection.

Facility	Function
Janssen Pharmaceutica N.V. Janssen Pharmaceuticaaan 3 B-2440 Geel, Belgium Registration Number: 3002807337	Manufacturing, packaging, and release testing of TMC125 Spray Dried Powder
Janssen Pharmaceutica N.V. Lammerdries 55 B-2250 Olen, Belgium Registration Number: 3002807334	testing of TMC125 Spray Dried Powder
Janssen-Cilag S.P.A. Via C. Janssen Borgo S. Michele 04010 Latina, Italy Registration number: 3002807333	Manufacturing, packaging, release testing, and marketed product stability testing of TMC125 100-mg Tablets
Ortho-McNeil Pharmaceutical, Inc. Route 202 South Raritan, NJ 08869-0602 Registration Number: 2211100	Secondary packaging of TMC125 100-mg Tablets

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

Anne Marie Russell
7/3/2007 02:24:56 PM
CSO

fax was sent 7/3/07

Norman Schmuft
7/3/2007 05:55:12 PM
CHEMIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63, 646 (SN 450)

Tibotec, Inc.
Attention: Ms. Susan Fiordeliso,
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Ms. Fiordeliso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC125.

We refer to your November 21, 2006 submission (SN450) requesting a Type C meeting, including your meeting background information and questions. We also refer to your March 2, 2007 submission (SN 509) containing replies to our initial written responses.

We further refer to our correspondences provided via telephone facsimile on February 7, 2007 which contained our initial responses to the questions submitted in your meeting background package and on March 23, 2007 which contained our follow-up responses to your replies submitted in SN 509.

The purpose of this Type C Pre-NDA rollout planning meeting was to discuss the format and content of your planned New Drug Application (NDA). The date scheduled for this meeting was February 13, 2007. This meeting was rescheduled as an April 17, 2007 teleconference with our statistical team.

The official minutes of the meeting are enclosed, including pre-meeting communications and the April 17, 2007 teleconference minutes. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Anne Marie Russell, Ph.D., Regulatory Health Project Manager, at (301) 796-2014.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: April 17, 2007
TIME: 11:00 AM – 12 noon Eastern Daylight Savings Time
APPLICATION: 63,646
DRUG NAME: TMC125 (entravirine)
TYPE OF MEETING: Type C Meeting - teleconference

FDA ATTENDEES:

Division of Antiviral Products (DAVP):

Kendall Marcus, M.D.	Medical Team Leader
Fraser Smith, Ph.D.	Statistical Reviewer
Greg Soon, Ph.D.	Statistical Team Leader
Anne Marie Russell, Ph.D.	Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Monika Peeters, M.Sc.	Director, Biostatistics
Katrien Janssen, M.Sc.	Associate Biostatistician
Chris Corbett, M.Sc.	Biostatistics
Steven Nijs	Biostatistics
Brian Woodfall, M.D.	Senior Director, Medical
Susan Fiordeliso	Manager, Global Regulatory Affairs
Robin Keen	Senior Director, Global Regulatory Affairs

BACKGROUND:

Tibotec requested a Type C meeting in submission SN450, dated November 21, 2006, received November 22, 2006. The purpose of the meeting was to discuss the format and content of the planned New Drug Application (NDA). The background package contained twenty one questions as discussion points for the meeting. The meeting was scheduled for February 13, 2007.

On February 7, 2007, DAVP provided responses to all questions via telephone facsimile. On February 12, 2007 DAVP requested a postponement due to inclement weather. Tibotec replied to DAVP's responses in submission SN509, dated March 2, 2007, received March 5, 2007. On March 23, 2007, DAVP provided responses to SN509 via telephone facsimile. Tibotec requested a teleconference meeting to discuss the remaining statistical questions. The teleconference was held on April 17, 2007.

DISCUSSION POINTS:

Agreement was reached by means of pre-meeting communications for many questions, and the few outstanding issues were discussed during the teleconference.

Below the original questions in the background package are listed, followed by pre-meeting communications and teleconference minutes. For clarity, Tibotec pre-meeting communications are in **bold text** and DAVP pre-meeting communications are in normal text. Teleconference meeting minutes are in *italicized text*.

QUALITY

Question 1: Does the Division agree with the proposal of submitting the TMC125 drug substance data and information in a DMF and submitting the drug product data and information in the NDA?

On December 20, 2006, DAVP sent the following response via telephone facsimile:

This proposal is acceptable to the Division. We remind you that relevant information about DMFs can be found at <http://www.fda.gov/cder/dmf/index.htm> and about eCTDs can be found at <http://www.fda.gov/cder/regulatory/erst/ectd.htm>. To expedite the review process we request that you submit a desk copy of the DMF and any subsequent amendments to the DMF to the review chemist.

On February 7, 2007, DAVP sent the following response via telephone facsimile:

As we indicated in our earlier response to your question on December 20, 2006, your plans to include the drug substance (DS) information for TMC-125 in a DMF are acceptable to us. We would like to make you aware of an alternate approach which would also allow you to have one place to keep DS information current, and cross-reference this in future eCTD NDAs (if more than one dosage forms are eventually developed). Because you are planning to submit the first NDA for TMC-125 as an eCTD, you could include and maintain the DS information in this NDA, and simply cross-reference it in future eCTD applications. This approach would utilize one of the strengths of the eCTD system, and may offer some simplification of regulatory filing relative to the DMF alternative if confidentiality is not an issue.

NONCLINICAL

Question 2: Does the Division agree with the proposal to include data from all ongoing nonclinical studies or externally published studies with a January 2007 cut-off date in the Nonclinical Overview and Nonclinical Summary?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes. However, any remarkable toxicity findings, carcinogenicity in particular, should still be submitted to the IND.

Question 3: Does the Division agree with the proposal to provide study protocols for the nonclinical studies only upon request?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

Question 4: Does the Division agree with the proposal of providing the data line listings electronically as scanned files?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

Question 5: Does the Division agree with this proposal on the definition of element 'duration' in the SFF?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes, the category element 'duration' should be applied to only repeat-dose studies. Single dose studies should be under their own category. The defining duration terms for the repeat-dose studies are acceptable.

Question 6: Is the proposal for the submission of the literature references acceptable to the Division?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

CLINICAL

Question 7: Does the Division agree with the proposal to include the Virology Summary as a separate Module 2.7.2?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes, please send it in as Module 2.7.3.2

On March 2, 2007, Tibotec sent the following response in submission SN509:

**Tibotec will provide access to the Virology Summary from both locations:
Module 2.7.2 and Module 2.7.3.2**

Question 8: Is the proposed draft outline of the Summary of Clinical Efficacy (Module 2.7.3) and Summary of Clinical Safety (Module 2.7.4) acceptable to the Division?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

Question 9: Does the Division agree that the interaction data generated from TMC125-C106 is irrelevant to current clinical practice and that interaction data with boosted saquinavir from TMC125-C123 is clinically relevant?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

Question 10: Does the Division agree with the proposal to include interaction data using TMC125 administered as formulation TF002 from studies TMS125-C105 and TMC125-C109 as relevant to the F060 formulation?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes.

Question 11: Are the proposed statistical methods as described in the SAP and GAM complete and acceptable to the Division?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

1. The definition of the intent-to-treat population in Section 2.2 in the SAP is incorrect. By the intent-to-treat, it means that the subjects should be analyzed according to the treatment group they are randomized to rather than the treatment they actually receive.

On March 2, 2007, Tibotec sent the following response in submission SN509:

The ITT population will be further clarified in the SAP. The ITT population consists of all randomized subjects who took at least one dose of the trial medications. Subjects will be analyzed in the treatment group to which they were randomized.

2. The following comments are for the primary efficacy analysis in Section 3.1.3.1 in the SAP. Note, Comments a, b and c below were sent via telephone facsimile on December 5, 2006 as the feedback for the submission SN452.

- a. We prefer the test for the treatment by the use of ENF interaction to be performed based on the difference of the treatment effects estimated by CMH method between ENF stratum since the primary analysis is based on CMH test.

On March 2, 2007, Tibotec sent the following response in submission SN509:

This change is already made in the SAP following the Division's earlier comments.

- b. The testing statistics for the two subgroups are independent and therefore the Hochberg procedure which is slightly more powerful can be used instead of the Bonferroni-Holm procedure.

On March 2, 2007, Tibotec sent the following response in submission SN509:

This change is already made in the SAP following the Division's earlier comments.

- c. The primary efficacy analysis will be performed using the CMH test which is fairly robust with respect to small stratum; and therefore TMC114 stratification should still be maintained although the number of subjects who previously used TMC114 is very limited.

On March 2, 2007, Tibotec sent the following response in submission SN509:

This change is already made in the SAP following the Division's earlier comments.

- d. The imputed baseline plasma viral load (<30000 , ≥ 30000) is included as a covariate in the CMH tests. Please explain how to impute the baseline plasma viral load.

On March 2, 2007, Tibotec sent the following response in submission SN509:

If baseline viral load is missing, the screening viral load is used to impute the baseline value. Since the baseline viral load is a covariate in the statistical models, there needs to be a value for all patients in order to include all patients in the analysis.

- e. If the treatment by the use of ENF interaction is significant at the 0.2 significance level, then separate CMH test will be performed for i) the subjects using ENF 'de novo', or ii) the subjects either re-using or not using in the underlying ART. For Strata ii, the sponsor states that "the CMH test will be control for 'Use of ENF' (de novo, not using, re-using) and imputed baseline plasma viral load (<30000, >=30000)". We assume that the use of ENF in Strata ii is classified as "not using" versus "re-using" instead of "de novo", "not using" or "re-using".

On March 2, 2007, Tibotec provided the following response in SN509:
In the version of the SAP that was sent to the division for review in the pre-meeting background package (SN450), there was a mistake in the description of the CMH test that is going to be used when the interaction is significant at the 0.2 significance level. If the interaction term is significant, the ENF factor will not be used anymore in the CMH test in each of the 2 separate strata.

On March 23, 2007, DAVP sent the following response via telephone facsimile:

You state that you were not going to adjust for ENF use in the CMH analysis in the second group of subjects (1) not using or (2) re-using ENF. However, you should be able to adjust for ENF use since there are two categories of ENF. What was the rationale for changing the analysis plan so that there would be no adjustment for ENF use in the second group of subjects?

There is another potential problem that could come up: If the treatment by ENF use interaction term is significant because treatment effects in subjects 'Not using' ENF are different from treatment effects observed in subjects 'Re-using' ENF, it will be necessary to do 3 separate subgroup analyses for (1) de novo ENF subjects (2) Subjects not using ENF and (3) Subjects Re-using ENF.

In our April 17, 2007 teleconference:

Tibotec, said that the Week 24 analyses were done. There was a clear interaction with respect to the TMC125 treatment effect in subjects using ENF de novo (de novo subjects) and subjects not using ENF de novo (non-de novo subjects). The TMC125 treatment effect in de novo subjects was not statistically significant but was statistically significant in non-de novo subjects.

In addition, Tibotec performed additional analyses that DAVP requested and found that there was no interaction involving the TMC125 treatment effect in the two groups of non-de novo subjects (those not using ENF and those re-using ENF); i.e.; there was a treatment effect in subjects not using ENF and in those re-using ENF.

DAVP agreed that what they had done seemed to satisfy the request and requested these additional analyses along with

the pre-specified analyses be included with the NDA. Tibotec agreed to do so.

3. Several formal DSMB analyses for the primary efficacy endpoint are planned to be performed during the trial, and you estimate the overall significance level for the final primary efficacy analysis will be 0.04825 in order to control the overall type I error rate at 0.05. Please provide the details of which alpha spending function is used. Please also provide the SAP for the DSMB analysis.

On March 2, 2007, Tibotec provided the following response in SN509:

For TMC125-C206 and TMC125-C216, the SAPs for the DSMB analyses will be included in the NDA: separate SAPs were available for the open DSMB analyses and the pooled DSMB analyses. The alpha spending function that was used in the open DSMB analyses is described in the DSMB charter that was sent to the division on February 3, 2006 (SN288) and in the SAP for the open DSMB analyses. The group sequential approach using the Lan and Demets approximation to the O'Brien and Fleming stopping boundary was used in order to control the overall experiment wise error rate of 5% (including the primary analysis which is conducted after 24 weeks). This approach defines an alpha-spending function. The significance level that comes out of this function will be used to evaluate the difference between the 2 treatment groups in the formal DSMB analyses prior to the primary trial analysis, while maintaining the overall probability of Type I error. The specific alpha level for each formal DSMB analysis was based on the proportion of total information available at the time of the DSMB analysis. Using this method, the boundary values are very extreme early in the study, while the values become less extreme as the trial progresses. The formula for calculating the Lan-Demets alpha spending function is as follows:

$$\alpha(t) = 2 - 2 \times \Phi \left(\frac{Z_{1-\alpha/2}}{\sqrt{t}} \right)$$

where:

- *t* is the information fraction (i.e. the amount of information available at the time of interim analysis relative to the total information available at primary analysis)
- $\alpha(t)$ denotes the cumulative exit probability at information fraction *t*
- Φ is the cumulative standard normal distribution function

The information fraction and the critical p-values used on each of the analyses for C206 and C216 are presented in the table below, where Row 1 is for the 2nd open DSMB analysis, Row 2 for the 3rd open DSMB analysis and Row 3 is for the Primary analysis. (No subjects reached 24 weeks of treatment in the 1st open DSMB analysis). Note that the DSMB analyses for both DUET studies were performed at the same time but the amount of information varied, therefore, the table presents the final numbers based on the exact amount of information available at each analysis that was actually done.

TMC125-C206		TMC125-C216	
Information Fraction	p-value	Information Fraction	p-value
0.0670	0.00000	0.0878	0.00000
0.2337	0.00005	0.5076	0.00596
1	0.04998	1	0.04814

Question 12: Does the Division agree with the proposal regarding submission of datasets?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

CLINICAL

1. Please submit date variables in numeric format, not in character format.

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "Data are loaded into the JMP program, which recognizes two data formats: numeric and character. Study date data need to be read in as numeric format so that study date calculations are possible. We know from our experience with Prezista study date values that JMP read the following variable "AESDTC start date" with the value "2004-01-21" as character which made study date calculations laborious. An example of data read as numeric, are lab values. Note also our related comment #2 for Q12 which requests the derived variable that reports the date as the Study Day (i.e. Day 34)."

Tibotec appreciates the inconvenience for the Division to handle character dates in JMP. Tibotec will provide, for all tabulation (SDTM) datasets holding character date-time fields, in addition to each character date-time field, two numeric fields: one numeric date field (date9.format) and one numeric time field (time5.). The naming convention for the numeric date and time variables will be similar to the naming convention of the analysis (ADaM) datasets.

The character date-time fields will be retained in the tabulation (SDTM) datasets in order for the Division to have access to partial dates e.g. when month-year of a start date is known but day is unknown numeric date fields can not be derived from these partial date values.

Tibotec would appreciate for OIM to be informed about the additional numeric date and time fields in the tabulation (SDTM) datasets. Validation of the tabulation (SDTM) datasets in WebSDM will generate errors because the numeric date and time fields are not allowed per CDISC Implementation Guide (SDTM Implementation guide version 3.1.1).

On March 23, 2007, DAVP sent the following response via telephone facsimile:

After consultation with our Office of Business Process Support (OBPS), formerly known as Office of Information Management (OIM), regarding the errors generated, we request that date variables in numeric format be added to the analysis (ADaM) datasets.

2. In addition to the standard date variable, please include a data variable that reports the date as the Study Day (i.e., Day 34).

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "The Division agrees that it is a permissible but not a required variable. It is acceptable if they are available only in the ADaM datasets for Phase II and III and the pooled analysis for Phase I."

Tibotec will provide the Study Day information in the ADaM datasets for Phase II/III and the pooled analysis for Phase I trials.

CDISC Data Recommendations:

3. Variables that are common across both the tabulation (SDTM) datasets and analysis (ADaM) datasets should have identical sets of values. For example, the unique subject identifier (USUBJID) should be unique (identical) across both the tabulation and analysis data sets. In the prior submission, the value of USUBJID for a particular patient in the tabulation data did not match the value of USUBJID for the same patient in the analysis data.

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "The Division is referring to the file for Prezista when they discuss "prior submission" in the comment."

Tibotec agrees with this recommendation. The variables common across tabulation (SDTM) datasets and analysis (ADaM) datasets will have identical sets of values for the Duet trials (TMC125-C206, TMC126-C216), TM125-C211 and TMC125-C229.

4. If a lab test is reported in more than one unit then the variables that represent the lab test name (LBTEST and LBTESTCD) should identify both the lab test and the unit. For example, in the laboratory datasets of the prior NDA, CD4 counts when measured as absolute counts and CD4 counts when measured as a percent were both given values of LBTEST="CD4 (% and Dir. Abs.)" and LBTESTCD="CD4 +". We would prefer to have, for example, LBTEST="CD4 (%)" and LBTESTCD="CD4PCNT" when the unit of measure is a percent and LBTEST="CD4 (Dir. Abs.)" and LBTESTCD="CD4ABS" when the unit of measure is an absolute count.

On March 2, 2007, Tibotec provided the following response in SN509:

Tibotec agrees with this recommendation. If a lab test is reported in more than one unit Tibotec will provide in the [LB] domain for the LBTEST and LBTESTCD variables lab test values which identify both the lab test and unit.

5. The following is taken from the notes for the variable LBTESTCD in the SDTM 3.1.1 Implementation Guide:

Short name of the measurement, test, or examination described in LBTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in LBTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g., '1TEST'). LBTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: ALT, LDH.

Values such as "CD4+" are therefore not recommended because of the use of the "+" symbol.

On March 2, 2007, Tibotec provided the following response in SN509:

Tibotec agrees with this recommendation and will provide the Division with a [LB] domain where the LBTEST and LBTESTCD variable values are in compliance with SDTM Implementation Guide (3.1.1) specifications.

6. Reference start and stop dates (RFSTDTC and RFENDTC) should be non-missing for all subjects who take any study drug (both the control and test drug). Values were missing for control subjects. If a start or stop date is not known, then a set method should be used for imputing a date.

On March 2, 2007, Tibotec provided the following response in SN509:

Tibotec agrees with this recommendation. The reference start and stop dates (RFSTDTC and RFENDTC) of the [RF] will be non-missing for all subjects who take any study drug (both the control and test drug).

7. The following structural errors were identified by WebSDM:
 - a. The variables VISIT and VISITNUM were included in the following datasets, but are not in the SDTM standard: AE, CM, EX, and SC. Because the data in these datasets are not visit-related, there is no need to include VISIT and VISITNUM in the datasets.

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "It is OK to include the variables in the datasets."

Tibotec will retain the permissible variables VISIT and VISITNUM in the [AE], [CM], [EX] and [SC] domains (SDTM Implementation guide version 3.1.1).

The VISIT and VISITNUM variables have values indicating the data are event based (VISIT value 'NON-VISIT RELATED', VISITNUM value '-1').

The values for VISIT and VISITNUM in the [AE] domain are 'NON-VISIT RELATED' and '-1' respectively for all AEs except if the AE is a cutaneous event. In this case Tibotec defined values are used where the annotated CRF provides a detailed description of the VISIT and VISITNUM values for the cutaneous events. VISIT and VISITNUM for cutaneous events in the [AE] domain have a linking role to the Tibotec defined domain [LS] where detailed data are provided with regard to the cutaneous events.

- b. The variable LBSTDTC appears in the LB datasets, but is not an SDTM standard variable. If deemed necessary, this variable can be added to SUPQUAL.

On March 2, 2007, Tibotec provided the following response in SN509:

The LBSTDTC variable in the [LB] domain holds the date-time data of lab test analysis. The LBSTDTC variable, in case of retest analysis results, serves as a key variable to uniquely identify a lab measurement record. Per SDTM version 1.1 timing variables (--STDTC) are permissible variables. Tibotec proposes to retain the LBSTDTC variable in the [LB] domain.

- c. No data definition file (metadata) was found for the TS domain.

On March 2, 2007, Tibotec provided the following response in SN509:

Tibotec will ensure all of the submitted tabulation datasets (including TS domain) are defined in the data definition file.

STATISTICAL

8. Please submit the raw datasets and the corresponding annotated case report forms in addition to the final analysis datasets for the individual studies. Please also submit the SAS programs used to derive the analysis datasets from the raw datasets; and those used to generate the tables and graphics for the primary efficacy endpoint and the key secondary efficacy endpoints.

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "The Division is referring to the DUET trials for the SAS programs. It's acceptable that the raw datasets for early trials are not available in CDISC format; however, the review team needs the raw datasets in SAS transport files."

All raw datasets will be provided as SAS transport files in CDISC format.

SAS transport programs which will be included are:

- **To derive the viral load ADaM dataset from SDS**
 - **To analyze the virologic response parameters: CMH test and logistic regression analysis.**
 - **To analyze the change in log₁₀ viral load from baseline: ANCOVA model**
- However, no SAS programs will be submitted to generate graphical presentation of the results.**

On March 23, 2007, DAVP sent the following response via telephone facsimile:

If other raw datasets that were not in CDISC format were used in your SAS analysis programs or SAS programs used to create ADaM datasets, these will also need to be provided as part of the NDA submission.

In our April 17, 2007 teleconference:

Tibotec agreed to submit date variables in numeric format in the analysis (ADaM) datasets.

CLINICAL PHARMACOLOGY

9. Clinical pharmacology agrees with having all pharmacokinetic data from the individual trials submitted in the Submission Data Standards (SDS) but also ask you to submit the pooled PK dataset for TMC125-C203 and TMC125-C223 (TF035 formulation) and TMC125-C206 and TMC125-C216 (F060 formulation) in the SDS. Also if possible, please submit all or at least a portion of the Clinical Pharmacology/Biopharmaceutics summary based on Question Based Review (QBR) template (Sections 2, 3, and 4 as highlighted). See attached QBR template in Appendix. Some sections of the template are not relevant to this NDA. Your assistance will allow us to complete the review and provide feedback in a more timely manner. Finally as a reminder, we would like you to address the potential utility of 'dose-individualization' with TMC125 in the Clinical Pharmacology/Biopharmaceutics summary.

On March 2, 2007, Tibotec provided the following response in SN509:

The pooled PK dataset for formulation TF035 from trials TMC125-C203 and TMC125-C223 and for formulation F060 from trials TMC125-C206 and TMC125-C216 will be provided in the Submission Data Standards. The Summary of Clinical Pharmacology and Biopharmaceutics will conform to the Question Based Review template as requested. The potential utility of 'dose individualization' with TMC125 will be addressed in the summary of Clinical Pharmacology Module 2.7.2.

VIROLOGY

10. Please include the therapeutic drug monitoring data (Cmin and IQ data) in the virology datasets.

On March 2, 2007, Tibotec provided the following response in SN509:

The Cmin and IQ data will be included in the virology datasets of TMC125-C206 and TMC125-C216.

Question 13: Does the Division agree with the proposal regarding submission of the CRFs in the NDA?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes, however, the Division also requests that CRFs be submitted from all subjects who prematurely discontinued study, regardless of the reason for discontinuation. In addition, please submit a random sampling of CRF from subjects who have responded to therapy with TMC125.

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "The Division is referring to the DUET trials only and defines random as 5% of subjects who respond to the treatment. Please submit a proposal for selection and presentation of the CRFs and the Division will comment."

As requested by the FDA, we will also submit CRFs for the DUET trials (TMC125-C206, TMC125-C216) for all subjects who prematurely discontinued study, regardless of the reason for discontinuation, as well as a 5% random sampling of CRF from subjects who have responded to therapy with TMC125.

A dataset containing all subjects that respond to treatment i.e. undetectable viral load (< 50 copies/mL) at week 24, will be sorted by

USUBJID (subject identifier) and a random number using the ranuni function in SAS with a fixed seed of 8 will be assigned to each of these subjects. The data set will be sorted again by this random number and the first 5% of subjects will be selected.

The additional CRFs will be grouped – together with the CRFs for deaths, other serious adverse events (AEs), AEs leading to discontinuation and AEs of special interest – by the study site property element in the Study Tagging File. Because there will be no hyperlinks from the Clinical Study Report to these additional CRFs, we will add an extension to the document name of these additional CRFs to differentiate between responders (Subject Id-Resp) and subjects who prematurely discontinued the study for reasons other than (serious) adverse events (Subject Id-DO-Other).

Question 14: Does the Division agree with the proposal regarding submission of CRFs during review?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

Question 15: Does the Division agree with the proposal for submitting DSMB meeting minutes?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

Question 16: Does the Division agree with the proposal regarding submission of ECG data?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

Question 17: Does the Division agree with the proposed level of reporting for ongoing trials?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

Question 18: Is the proposal for the submission of literature references acceptable to the Division?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

Question 19: Is the proposal for the submission of data from non-Tibotec sponsored trials acceptable to the Division?

On February 7, 2007, DAVP sent the following response via telephone facsimile:
Yes.

REGULATORY

Question 20: Is the plan for rolling submission of the TMC125 accelerated approval NDA acceptable to the Division?

On December 20, 2006, DAVP sent the following response via telephone facsimile from the chemistry reviewer:

We note that the initial submission will be in May 2007, CMC data will be submitted in June 2007, and the remaining clinical data will be supplied in July 2007. From a CMC perspective, if the manufacturing sites are ready for inspection in May 2007 inclusion of this information in the May 2007 submission would expedite the review process. Other disciplines may also wish to respond to this question at a later date.

**On March 2, 2007, Tibotec provided the following response in SN509:
Tibotec agrees to provide the CMC data in the May 2007 submission and the manufacturing sites will be ready at that time for inspection.**

On February 7, 2007, DAVP sent the following response via telephone facsimile:

From a regulatory standpoint, the plan is acceptable in general, with the following comments:

1. The eCTD module heading text should follow the cited guidance verbatim. For example, your proposed Module 5.3.1 Reports of Biopharmaceutical Studies should be Reports of Bioavailability Studies.

**On March 2, 2007, Tibotec provided the following response in SN509:
The Division offered the following clarification via telephone and email:
"This comment was made in error".**

Tibotec appreciates the reminder and will follow the cited guidance, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications April 2006, and the associated Comprehensive Table of Contents and Hierarchy for all module heading text.

2. Locate Virology Summary in Module 2.7.3.2

**On March 2, 2007, Tibotec provided the following response in SN509:
Tibotec will make the Virology Summary available in Module 2.7.3.2 via link.**

Question 21: Does the Division agree with the proposal of providing the draft labeling in SPL and Word format?

On February 7, 2007, DAVP sent the following response via telephone facsimile:

Yes. Please confirm that you will comply with the implementation of the Physician's Labeling Rule (PLR) [21 CFR 201.56, 201.57].

**On March 2, 2007, Tibotec provided the following response in SN509:
Tibotec confirms that we will comply with the Physician's Labeling Rule.**

Additional comments from DAVP:

1. Please include the available information on the genotoxicity potential of process impurities and TMC-125 degradants in the March Pre-NDA background package. Please include synthetic intermediates and related substances, as well as by-products derived from solvents and reagents. You need not include information which you already submitted in SN-460 on
— and —

On March 2, 2007, Tibotec provided the following response in SN509:

The Division offered the following clarification via telephone and email: "The Division agrees that it is acceptable if the information is submitted in the first part of the rolling submission and not the pre-NDA package."

Tibotec appreciates this clarification since there is only about 1 month between submission of the pre-NDA background package in April and the submission of the first part of NDA in May. We will submit any available information in the NDA.

2. Please determine the average number of amino acid changes occurring in the TMC125 failure isolates compared to placebo failure isolates and the fraction of these not accounted for by identified resistance-associated substitutions.

**On March 2, 2007, Tibotec provided the following response in SN509:
Tibotec response:**

A) We will determine the average number of all amino acid changes in reverse transcriptase and protease in (1) TMC125 failure isolates and (2) placebo failure isolates (both including rebounders and non-responders).

B) We will determine the fraction of NRTI resistance associated mutations (IAS-USA defined list), NNRTI resistance associated mutations (Tibotec defined list) and PI resistance associated mutations (IAS-USA defined list). These lists have been included and agreed upon by the Division (see Question 12 on the template for dataset submission).

C) We will also determine the fraction of amino acid changes in reverse transcriptase or protease that is not included in the mutations described in B.

ACTION ITEMS from April 17, 2007 teleconference:

1. Tibotec will submit other raw datasets that are not in CDISC format if they were used in their SAS analysis programs or SAS programs used to create ADaM datasets, as part of the NDA submission.
2. Tibotec will submit the additional analyses along with the pre-specified analyses with the NDA.
3. Tibotec will submit date variables in numeric format in the analysis (ADaM) datasets.

Question-Based Review (QBR)

The QBR focuses on key questions pertinent to the review, and integrates information across studies. The examples below are some typical questions posed during the review of NDAs and sNDAs. These examples are not intended to be either inclusive of all, or exclusive of any, questions that specific reviews address. The specific questions for a given review depend on the characteristics of the drug, drug product, patient population, and indication. Reviewers should answer the questions using a deductive approach (i.e., starting with the conclusion and following with supportive details).

2. General clinical pharmacology

This section provides information pertinent to the PK and PD properties of the drug substance and drug product and their relationship to dose and each other.

- 2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
- 2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?
- 2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (*If yes, refer to 6, Analytical Section; if no, describe the reasons.*)
- 2.4 Exposure-response (refer to the following guidance for industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, <http://www.fda.gov/cder/guidance/5341fnl.pdf>)
 - 2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.
(*If necessary, indicate in your answer the degree of linearity or nonlinearity in the dose-concentration relationship and how PK parameters change with time on chronic dosing, however, do not provide data or details for those topics. Those topics are addressed in question 2.5.*)
 - 2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.
(*If necessary, indicate in your answer the degree of linearity or nonlinearity in the dose-concentration relationship and how PK parameters change with time on chronic dosing. However, do not provide data or details for those topics. Those topics are addressed in question 2.5.*)
 - 2.4.3 Does this drug prolong the QT or QTc interval? (*You must answer this question, unless this is addressed in the question above.*)
 - 2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (*In some cases, it may be possible to combine this with 2.4.2 and 2.4.3.*)
- 2.5 What are the PK characteristics of the drug and its major metabolite?
 - 2.5.1 What are the single dose and multiple dose PK parameters? (*Provide tables to refer to in subsequent questions in this section.*)
 - 2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
 - 2.5.3 What are the characteristics of drug absorption? (*This may include discussion of transporter or pH effect.*)
 - 2.5.4 What are the characteristics of drug distribution? (*Include protein binding.*)

- 2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? *(This may include table with results of mass balance study.)*
- 2.5.6 What are the characteristics of drug metabolism? *(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)*
- 2.5.7 What are the characteristics of drug excretion?
- 2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
- 2.5.9 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*
- 2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Intrinsic Factors

- 3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
- 3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.
- 3.2.1 Elderly (see Study of Drugs Likely to be used in the Elderly, <http://www.fda.gov/cder/guidance/old040fn.pdf>)
- 3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study? (Refer to International Conference on Harmonization; E11: Clinical Investigation of Medicinal Products in the Pediatric Population; <http://www.fda.gov/cder/guidance/4099FNL.PDF> and General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products; <http://www.fda.gov/cder/guidance/1970dft.pdf> and Appendix B in "Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications" <http://www.fda.gov/cder/guidance/5341fnl.pdf>)
- 3.2.3 Gender (see Study and Evaluation of Gender Differences in the
- 3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians (see 21 CFR 314; Final Rule on Investigational New Drug Applications and New Drug Applications (63 FR 6854, February 11, 1998); <http://www.fda.gov/oashi/patrep/demo.html> and Collection of Race and Ethnicity Data in Clinical Trials, <http://www.fda.gov/cder/guidance/5054dft.pdf>) is an important co-variate and should be discussed
- 3.2.5 Renal impairment (Refer to Appendix 3 — Figure 2, Renal Study Decision Tree, and Pharmacokinetics in Patients with Impaired Renal Function, <http://www.fda.gov/cder/guidance/1449fnl.pdf>)
- 3.2.6 Hepatic impairment (Refer to Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, <http://www.fda.gov/cder/guidance/3625fnl.pdf>.)
- What pharmacogenetics information is there in the application and is it important or not (Refer to Pharmacogenomic Data Submissions, <http://www.fda.gov/cder/guidance/5900dft.pdf>)
- 3.2.7 What pregnancy and lactation use information is there in the application?
- Other human factors that are important to understanding the drug's efficacy and safety

4. Extrinsic Factors

4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response? Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

4.2 Drug-drug interactions (Refer to Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In vitro, <http://www.fda.gov/cder/guidance/clin3.pdf>, and In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling, <http://www.fda.gov/cder/guidance/2635fnl.pdf>, and Appendix 3 — Figure 3, Drug-Drug Interaction Studies — Decision Tree). Some typical questions include:

4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

4.2.5 Are there other metabolic/transporter pathways that may be important?

4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

4.2.7 What other co-medications are likely to be administered to the target patient population?

4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions

**APPEARS THIS WAY
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**

/s/

Debra Birnkrant
5/14/2007 12:10:34 PM
IND 63,646

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>TIBOTEC INC Susan Fiordeliso 1020 STONY HILL ROAD SUITE 300 Yardley PA 19067 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>NDA022187</p>
<p>2. TELEPHONE NUMBER</p> <p>609-7307546</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>Etravirine</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3007329</p>
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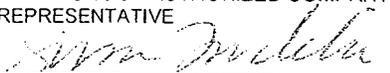
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE</p> <p>Manager Clinical Regulatory Affairs</p>	<p>DATE</p> <p>5 May 2007</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$896,200.00

Form FDA 3397 (03/07)

Close Print Cover sheet



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 63, 646

Tibotec, Inc.
Attn: Lamine Messaoudi, D.V.M.
Associate Director, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardly, PA 19067

Dear Dr. Messaoudi,

Please refer to the meeting between representatives of Tibotec Inc. and the FDA on June 17, 2005. The purpose of the meeting was to discuss specific Chemistry, Manufacturing and Control (CMC) aspects of the pharmaceutical development of TMC125.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2376.

Sincerely,

Stephen Miller, Ph.D.
Chemistry Team Leader
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF DAVDP/INDUSTRY MEETING

Date of Meeting: June 17, 2005
Meeting Type: End of Phase Two (CMC- Type B)
IND 63,646
Drug: TMC 125
Sponsor: Tibotec, Inc.

DAVDP Participants:

Stephen Miller, Ph.D., Chemistry Team Leader
George Lunn, Ph.D., Chemistry Reviewer
Andreas Pikis, M.D., Medical Officer
Kuei-Meng Wu, Ph.D, Pharmacology/Toxicology Reviewer
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer
Destry Sullivan, M.S., Regulatory Project Manager

External Participants, Tibotec, Inc:

Lars Bastiannse, VP, Compound Development Leader
Marie-Pierre de Bethune, VP, Clinical Virology
Richard Hoetelmans, Director, Clinical Pharmacology
Luc Janssens, Director, Chemistry Regulatory Affairs
Robin Keen, Sr. Director, Regulatory Affairs
Lamine Messaoudi, Assistant Director, Regulatory Affairs

Subject:

The purpose of the meeting was to discuss to discuss specific Chemistry, Manufacturing and Control (CMC) aspects of the pharmaceutical development of TMC125.

Discussion:

(Tibotec's questions and discussion are represented in **bold** font, and FDA's questions and discussion are represented in italicized font.)

6 Page(s) Withheld

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Deliberative Process

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/s/

Stephen Paul Miller
7/22/05 11:25:43 AM



IND 63, 646

Tibotec, Inc.
Attn: Lamine Messaoudi, D.V.M.
Associate Director, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardly, PA 19067

Dear Dr. Messaoudi,

Please refer to the meeting between representatives of Tibotec Inc. and the FDA on May 11, 2005. The purpose of the meeting was to discuss the results of the 12-week analysis of study TMC125-C223 and the 24-week analysis of study TMC125-C203, dose selection for the planned phase 3 studies, and the designs of the phase 3 protocols for treatment-experienced patients.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2376.

Sincerely,

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF DAVDP/INDUSTRY MEETING

Date of Meeting: May 11, 2005

IND 63,646

Drug: TMC 125

Sponsor: Tibotec, Inc.

DAVDP Participants:

Edward Cox, M.D., Deputy Director

David Roeder, ADRA, ODE IV

Debra Birnkrant, M.D., Division Director

Jeffrey Murray, M.D., Deputy Division Director

Kendall Marcus, M.D., Medical Team Leader

Andreas Pikis, M.D., Medical Officer

Jules O'Rear, Ph.D, Microbiology Team Leader

Kuei-Meng Wu, Ph.D, Pharmacology/Toxicology Reviewer

Stephen Miller, Ph.D., Chemistry Team Leader

Susan Zhou, Ph.D., Statistical Reviewer

Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader

Derek Zhang, Ph.D., Clinical Pharmacology Reviewer

He Sun, Clinical Pharmacology Reviewer

Guoxing Soon, Ph.D., Statistical Team Leader

George Lunn, Ph.D., Chemistry Reviewer

Destry Sullivan, M.S., Regulatory Project Manager

External Participants, Tibotec, Inc:

Lars Bastiannse, VP, Coumpound Development Leader

Marie-Pierre de Bethune, VP, Clinical Virology

Richard Hoetelmans, Director, Clinical Pharmacology

Luc Janssens, Director, Chemistry Regulatory Affairs

Robin Keen, Sr. Director, Regulatory Affairs

Lamine Messaoudi, Assistant Director, Regulatory Affairs

Wim Parys, VP, Clinical Research and Development

Monika Peters, Director, Biostatistics

Araz Raoof, Director, Preclinical Development

Monica Scholler, Associate Director, Clinical Pharmacology

Karin Van Baelen, VP, Regulatory Affairs

Brian Woodfall, Director, Clinical Development

We agree to continue cardiac monitoring during the phase 3 studies until we perform a definitive QT prolongation study.

Question 3: The investigation of viral resistance is an essential element of the TMC125 development program. A summary of the planned resistance determinations is provided below. Does the DAVDP consider the planned resistance determinations to study development of resistance adequate?

Overall, the plan is satisfactory. In a population experienced with drugs with the same molecular target, the primary interest is in the baseline genotype/phenotype and cross-resistance as defined clinically. Mutations developing during the course of therapy may be useful in understanding the development of resistance to the candidate, or, may be particular to the baseline mutations and not of general utility.

Question 4. After review of the enclosed Dose selection rationale document, does the DAVDP agree with the proposed dose of TMC125 100 mg b.i.d. (Formulation F060) as the recommended dose for use in the proposed Phase 3 trials based on the 800 mg b.i.d. (Formulation TF035) data from TMC125-C223 and TMC125-C203?

No, we do not agree with the proposed dose for phase 3 studies based on the 800 mg b.i.d. data from TMC125-C223 and TMC125-C203. In study TMC125-C203 no difference was observed in the first phase of the study between the placebo, 400 mg and 800 mg treatment groups, and in the second phase of the study, no treatment difference was observed between the 800 mg and 1200 mg treatment groups. In study TMC125-C223 no difference was observed between the 400 mg and 800 mg treatment groups. Because no consistent dose response relationship was observed across these studies, we would like to evaluate exposure response relationships.

To determine whether the proposed dose is acceptable, Dr. He Sun will evaluate the exposure-response information from the 2b studies (C203, C223). Based on his review, we hope to determine the range of acceptable exposure.

In follow-up to the exposure-response datasets you sent for studies 203 and 223, we will send queries as soon as possible after this meeting. Responses are needed prior to our completion of the exposure-response evaluation.

We request that you also provide 24-week data for study 223, when they are available.

Once the range of acceptable exposure is determined, we need to determine what dose can provide that exposure- (Formulation 035, to relate to Phase 2b doses; and Formulation 060, for evaluation in Phase 3). You are evaluating the 200 mg bid dose of formulation 060 and will have top line results in the second or third week of July. We need that information in order to provide dosing advice.

We also need to determine whether there are adequate safety data to proceed into phase 3 at the selected dose. If the exposure-response evaluation indicates that exposure at the

high end of exposure in Phase 2b is best (1200 mg bid formulation 035), there may not be enough safety data for Phase 3 to begin.

Do you have an explanation for the unexpectedly low concentrations observed following administration of 100 mg bid of formulation 060 in study C228? Also, do you know if TMC125 auto-induces its metabolism.

We do not have an explanation for the unexpectedly low concentrations observed following administration of 100 mg bid of formulation 060 in study C228. We do not believe that TMC125 auto-induces its metabolism, but we do not have definitive proof that it does not.

Question 5: After review of the enclosed Protocol Summary, does the DAVDP consider TMC125-C206 (treatment-experienced subjects), to be an appropriate and acceptable trial design with regard to the following elements: a) overall trial design, b) concept of dose adjustment in view of the interaction with TMC114, c) selected patient population, d) primary endpoint and stratification factors, e) sample size, f) definition of virologic failure, and g) safety monitoring?

a) Overall trial design

Overall, the study design is acceptable. However, many issues need to be addressed during the course of development but prior to initiation of phase 3 studies; for example, selecting a dose for the phase 3 studies, performing an interaction study between the new TMC125 formulation and TMC114, etc. In addition, we would like to emphasize that there is a potential risk of masking the efficacy of TMC125. In study TMC125-206, both treatment arms use the new TMC114/RTV as the only protease inhibitor. Therefore, if the efficacy of TMC114 meets your expectations, it might mask the efficacy of TMC125. To diminish this potential risk, please ensure that you enroll "deep salvage" patients.

b) Concept of a TMC125 dose adjustment in study C206, due to the interaction with TMC114?

You have proposed a dose adjustment of TMC125 when used with TMC114/r in study C206 because an interaction study with formulation 035 and TMC114/r resulted in a 35% decrease in TMC125 exposure. You plan to evaluate the interaction with formulation 060 and the proposed dose adjustment. Originally, you planned to adjust from the selected dose of 100 mg bid (without TMC114/r) to 200 mg bid (with TMC114/r).

DAVDP agrees with the concept of a TMC125 dose adjustment due to TMC 114/r interaction. We need to see results of the interaction study in the context of the selected dose of TMC125 (060) for phase 3.

You also indicated that a dose adjustment may not be needed because you will likely select a dose of 200 mg bid formulation 060, rather than 100 mg bid.

We cannot comment on a specific dose adjustment until further data are reviewed (dose selection, formulation comparison, and TMC114/r interaction).

There is a large interaction with tipranavir, so, therefore, we will not be able to use tipranavir with TMC 125. Dose adjustment will be based on the results of the drug interaction studies.

c) Selected patient population

With respect to the use of documented evidence of NNRTI resistance, your proposal is acceptable, provided that the vast majority of subjects have baseline genotypic evidence of resistance. With respect to the number of PI mutations at baseline, we have not reviewed sufficient resistance data for TMC114 to reach a conclusion. You should have a target C_{min} of 0.5 μM (~250 ng/mL); 77% of clinical isolates have an IC_{50} value <10nM, isolates with multiple NNRTI resistance mutations have a shift in susceptibility of <10 fold, and TMC125 is sequestered 2-3 fold in 50% human serum.

d) Primary endpoint and stratification factors

We prefer a dichotomous primary efficacy endpoint such as percentage of subjects with viral load < 400 copies/mL, < 50 copies/mL, at least 1 log₁₀ drop from baseline, or at least 0.5 log₁₀ drop from baseline. The rules for selecting one of these endpoints will be sent to you.

The number of baseline PI mutations may be associated with virologic response and should also be considered as a stratification factor in randomization, in addition to the T-20 use and level of plasma viral load at screening.

e) Sample size

The sample size of 300 per arm appears to be acceptable if the assumptions in the sample size calculation are reasonable. Please provide your rationale for these assumptions.

f) Definition of virologic failure

The proposed definition of virologic failure is acceptable.

g) Safety monitoring

The safety monitoring as proposed is acceptable. Please continue to monitor PT and PTT as we previously agreed.

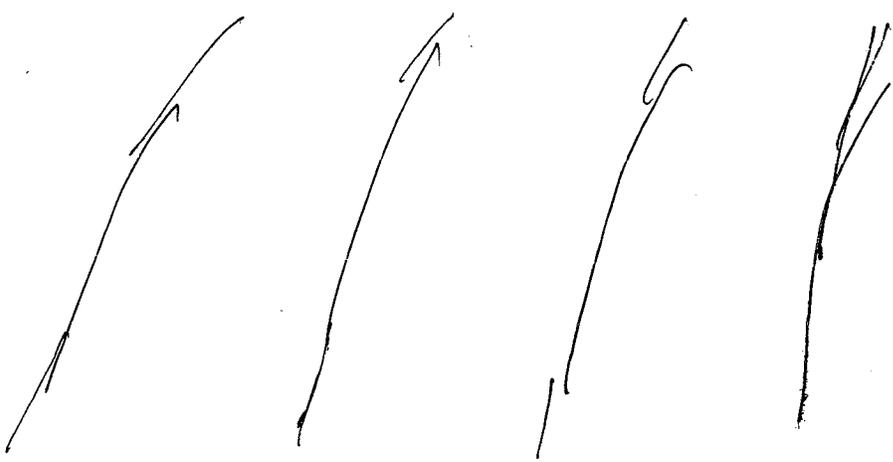
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 Deliberative Process



Question 9: Does the DAVDP agree with Tibotec's recommendation not to perform a trial in subjects with impaired renal function?

We need to see the results of the mass balance study before providing a final decision.

Discussion:

The mass balance study is complete and analysis is ongoing.

*Based on the statement that up to an AUC of 2000 ng*hr/mL there is no measurable parent drug in urine, we will likely agree with your position.*

Question 10: Are drug interaction results adequate to support use of other drugs with formulation 060?

You have conducted a large number of drug interaction studies- most with formulation 035. You plan to repeat the TMC114/r interaction study and the tenofovir interaction study with the new formulation (060). With formulation 035, both of those drugs caused a ~30-35% decrease in TMC125 concentrations. If the results are similar with the new formulation, the results of other previous interaction studies should apply to the new formulation. We will need further discussions if there is a large difference in the results between formulations.

We are concerned about possible differences in interactions due to the results of the steady-state formulation BA study. Single dose data indicated that 100 mg TMC125 (060) provided similar exposure as 800 mg of formulation 035. However, at steady state 100 mg bid of 060 provided approx 50% exposure relative to 800 mg bid 035.

You also need to indicate how you will determine the appropriate dose of TMC125 when administered with PIs other than TMC114/r. You should provide this information after the exposure-response analysis is complete and the 200 mg information is available for formulation 060.

Question 11: Tibotec plans to submit an NDA for TMC125 (including data in heavily experienced subjects from trials TMC125-C206 and TMC125-C223, data in less treatment experienced patients from trial TMC125-C227,

**_____ , for the treatment of HIV-1 infected adults.
The recommended dosing will be _____ b.i.d. _____**

a) Does the DAVDP concur that this NDA will be an adequate submission for accelerated approval in antiretroviral experienced patients?

It is premature to answer this question. Study TMC125-C223 is not a double-blind study and is not considered the best example for a supportive study. Two 'TMC125-C206' studies would be acceptable for accelerated approval.

How many patients, with respect to drug exposure, do you consider an adequate number for accelerated approval? What about doing a single phase 3 study (TMC125-C206) with a larger number of patients.

Usually, we ask for 400 to 600 patients. Please keep in mind that for a single trial the p value should be much lower compared to p values from two studies. The option of conducting one large TMC125-C206 type study could be explored, but two studies are the standard. If you consider a single trial as an option, please see the ICH guidelines.

b) Does the DAVDP consider the TMC125 development program eligible for a fast track designation?

Yes, we consider the TMC125 development program eligible for a fast track designation.

c) Does the DAVDP agree that 48 week data from trials TMC125-206 and _____ will be sufficient to support the traditional approval of TMC125?

It is premature to discuss this question.

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this page is the manifestation of the electronic signature.**

/s/

Debra Birnkrant
6/10/05 05:28:37 PM
IND 63,646



IND 63,646

Tibotec, Inc.
Attn: Lamine Messaoudi, D.V.M.
Associate Director, U.S. Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardly, PA 19067

Dear Dr. Messaoudi,

Please refer to the teleconference between representatives of Tibotec, Inc. and the FDA on January 11, 2005. The purpose of the teleconference was to discuss adverse events observed in the mouse 3-month repeated dose oral toxicity study the 3-month rat study.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF DAVDP/INDUSTRY TELECONFERENCE

Date of Teleconference: January 11, 2005

IND 63,646

Drug: TMC125

Sponsor: Tibotec, Inc.

DAVDP Participants:

Kendall Marcus, M.D., Medical Team Leader
Andreas Pikis, M.D., Medical Officer
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
K.M. Wu, Ph.D., Pharmacology/Toxicology Reviewer
Destry Sullivan, Regulatory Project Manager

External Participants, Tibotec, Inc.:

**Herman VanCauteren, Vice President, (V.P.), Drug Evaluation and
Preclinical Development**
Araz Raof, Director, Preclinical Leader
Johan Verbeeck, Lead Scientist
Wim Parys, V.P., Clinical Development
Brian Woodfall, Clinical Leader
Karin Van Baelen, V.P., Regulatory Affairs
Robin Keen, Director, Regulatory Affairs Leader
Lamine Messaoudi-Ass Dir. Regulatory Affairs

Subject:

The purpose of this teleconference was to discuss the adverse events observed in the mouse 3-month repeated dose oral toxicity study and the 3-month rat study.

Discussion:

(Tibotec's questions and discussion are represented in normal font, and FDA's questions and discussion are represented in **bold font**.)

The increased mortality caused by hemorrhagic cardiomyopathy and hemothorax observed in male mice in the mouse 3-month repeated dose oral toxicity study is concerning. Further, there is also concern about the PT and APTT prolongation observed in male rats in a 3-month rat study in which spray dried TMC125 was

administered via the diet. There has been speculation that the hemorrhagic cardiomyopathy observed in male mice may be due to vitamin K deficiency.

We ask that you provide evidence that the observed cardiomyopathy is due to hemorrhage and is not the result of a direct toxic effect of TMC125. Please also inform us if you plan to perform additional studies to prove that your hypothesis of vitamin K deficiency is correct.

Please refer to the publication by Allen et al [Toxicol Pathol 1991;19(4 Pt 2):589-596], which consolidates our theories related to hemorrhagic cardiomyopathy. Our hypothesis is reinforced by the prolonged PT and APTT observed in male rats in a 3-month rat study in which spray dried TMC125 was administered via the diet. We plan to investigate this in the future.

Do you plan to carry out any studies to clarify the observed findings (for example, a dietary compensation study with vitamin K supplementation)? Additionally, please describe the frequency of the liver function tests conducted in your clinical studies.

We have been consulting with experts in the field and will try to design the most appropriate study. We are particularly interested in investigating liver biomarkers such as transaminases, and may explore a dietary compensation study with vitamin K supplementation.

Liver function tests are conducted at Week 1, 4, and then every 4 weeks to Week 24 and then every 8 weeks to Week 48.

We note that the frequency of coagulation assessment is different between the European (TMC125-C203) and the U. S. (TMC125-C223) phase II studies. Please consider that coagulation assessment must be the same between the two studies and should be performed every 4 weeks. In addition, DAVDP recommends that troponins be added to the list and be checked at each scheduled visit. A draft guidance for troponin measurement is available on the CDER website, should you wish to explore this issue.

In addition, could you please provide clarification for the following clinical data:

Phase I studies

In multiple doses in healthy subjects you stated that there was only one episode of Grade 3 PTT prolongation and 2 episodes of Grade 2. All other elevations were Grade 1 in severity. Please clarify how many subjects had Grade 1 elevation of PT or PTT. Please also clarify what happened with repeat coagulation tests in these subjects.

Phase II studies

1. Study TMC125-C203

Prolonged PT:

Four patients developed Grade 3 abnormal PT. Three of these values returned to normal at the subsequent testing. For the fourth patient, the Grade 3 was the last time-point when information was available. Please provide follow up on this patient.

All other PT abnormalities were Grade 1 or 2 in severity. Please clarify how many patients had Grade 1 and how many Grade 2. Please also provide follow-up on these patients.

Prolonged PTT

Grade 4. Two patients recorded a Grade 4 elevation of PTT. For one patient the PTT returned to normal at the next time-point. For the other patient, the elevated value was the last time-point available. Please provide follow-up on this patient.

Grade 3. Please provide follow-up on patient with Grade 3 PTT.

All other PTT abnormalities were Grade 1 or 2 in severity. Please clarify how many patients had Grade 1 and how many Grade 2. Please also provide follow-up on these patients.

2. Study TMC125-C223

Prolonged PT

There were one Grade 1 and one Grade 2 elevations of PT. Please provide follow-up on these patients.

Prolonged PTT

Please provide follow-up information on the patient with Grade 2 elevation of PTT.

Your plans for new preclinical studies should be submitted as soon as possible, as this information will be necessary to evaluate the continuation of your clinical studies. Please also submit the final report(s) for the animal studies as soon as possible.

You should aggressively monitor patients in the clinic for the markers indicative of these AEs. Any observed AEs should be explained in more detail.

We agree to your request for submission of study proposals and the monitoring plan.

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ON ORIGINAL

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

/s/

Debra Birnkrant
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IND 63,646