DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 67,699

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

Dear Ms. Monshizadegan:

Reference is made to your Proposed Pediatric Studies Request submitted on March 27, 2008, for TMC278 to IND 67,699 for treatment of HIV-1 infection.

To obtain needed pediatric information on TMC278, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

Type of studies:
Multiple-dose pharmacokinetic, safety and activity study(ies) of TMC278, in combination with other antiretroviral agents, in HIV-1-infected, treatment-naive pediatric patients.

The objective of this study(ies) will be to determine the pharmacokinetic and safety profile of TMC278 across the age range studied, identify an appropriate dose (or doses) for use in HIV-1-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment. Efficacy will be extrapolated from adequate and well controlled studies in adults, and these pediatric studies are intended to provide additional information needed to support labeling this product for use in the pediatric population.

This study(ies) must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication to be studied:
Treatment of HIV-1 infection in treatment-naive pediatric patients from birth to 18 years of age.

Age group in which studies will be performed:
HIV-1-infected, treatment-naive pediatric patients from birth to 18 years of age.

Drug Information

Dosage form: Age-appropriate formulation
Route of administration: Oral
Regimen: To be determined by development program

The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric study(ies).

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice to indicate that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:
Based on available toxicity information about your product, provide specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection must include, but not be limited to:

- QTc prolongation and related cardiac adverse events
- Rash, including Stevens-Johnson syndrome
- Hepatotoxicity
- Endocrine adverse events

Safety of TMC278 must be studied in an adequate number of pediatric subjects to characterize adverse events across the age range. A minimum of 100 subjects with at least 24-week safety data at the recommended dose or higher is required.

Statistical information, including power of study and statistical assessments:
Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. A minimum number of pediatric subjects (as stated below in Table 1) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for

dose selection. Final selection of sample size for each age group must take into account all potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range. For each age group, the mean apparent systemic clearance and apparent volume of distribution must be estimated within a standard error of 20% or less.

Table 1

Age Range	**Minimum number of pediatric subjects**
Birth to < 6 weeks	8
6 weeks to < 6 months	6
6 months to < 2 years	6
2 years to < 6 years	12
6 years to < 12 years	8
12 years to 18 years	6

The number of subjects should be approximately evenly distributed across the age range studied.

Study Endpoints:
Pharmacokinetics: Parameters such as C_{max}, C_{min}, $T_{max,}$ $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution.

Safety and tolerability: HIV-1-infected pediatric subjects must be followed for safety for a minimum of 24 weeks at the recommended dose or higher. In addition, submit long-term safety data for HIV-1-infected pediatric subjects who have received TMC278.

Activity: Assessment of changes in plasma HIV RNA levels and in CD4 cell counts at a minimum of 24 weeks treatment.

Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving TMC278, particularly from those who experience loss of virologic response.

Labeling that may result from the studies:
Draft labeling must be submitted with appropriate sections of the label (i.e., information regarding dosing, safety, and activity in HIV-1-infected pediatric subjects) changed to incorporate the findings of the study(ies). You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that TMC278 is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers information regarding such labeling changes that are approved as a result of the study(ies) at least annually (or more frequently if FDA determines that it would be beneficial to the public health).

Format and types of reports to be submitted:
You must submit full or interim study reports containing at least 24-week data (which have not been previously submitted to the Agency) that address the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric subjects of ethnic and racial minorities. All pediatric subjects enrolled in the study(ies)

should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narratives and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at: http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/7087rev.htm.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before January 31, 2014. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed. Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9310.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm .

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Kanika Vij, Pharm. D., Regulatory Project Manager at (301) 796-9883.

Sincerely yours,
{See appended electronic signature page}

Ed Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 67699	TIBOTEC INC	TMC278

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/s/

EDWARD M COX
07/03/2008