Medical Officer Review
Amendment to Review of NDA 202-895

Date	November 20, 2011
From	Regina Alivisatos, M.D.
Subject	Medical Officer Review Amendment
NDA # and Supplement #	NDA 202895/000 and SNDA 21976/S-20
Applicant	Tibotec Inc.
Date of Original Submission	March 29, 2011
Original PDUFA Goal Date	September 30, 2011
Date of Major Amendment	September 28, 2011
Revised PDUFA Date	December 30, 2011
Proprietary Name / Established (USAN) names	Prezista (darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 300 mg tablets, 150 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

This is the second amendment to the NDA package. The first, authored by the Cross Discipline Team Leader, Dr. Yodit Belew, dated September 26, 2011, had as its subject the revised dosing recommendation made by the Division for subjects weighing 10 to less than 15 kg. This recommendation was subsequently accepted by the Applicant. Specifically, the Division recommended that for subjects 3 years of age and older and weighing 10 to less than 15 kg, the dose should be calculated based on darunavir 20 mg/kg co-administered with ritonavir 3mg/kg.

Several reasons led to this change in dosing recommendation to 20/3 mg/kg instead of the Applicant's proposed (b) (4) in subjects weighing 10- <15 kg. The primary reason was the Division's assessment of a revision to the population PK analysis submitted by the Applicant to correct for an error, primarily in subjects weighing 10 - <15 kg. In this revised analysis, these subjects would have mean AUC exposure that is 53% higher that the targeted mean adults exposure value. As the lower dose did not present similar pharmacokinetic concerns and had similar efficacy and safety it was determined that this dose was the appropriate one to be included in labeling.

In addition because of concerns that the initial dosing device supplied by the Applicant could lead to dosing errors, the device was changed to an (b) (4) syringe device. Details of this device were provided in the major amendment under review including instructions for use. Both the device and the instructions are acceptable to the Division as well as to DRISK and DMEPA.

The current amendment to the MOR has been included because of the, unsolicited by the Division, submission on September 27, 2011 (SNDA 202-895/SN 41) by the Applicant of clinical sites inspection reports from the EMA for the ARIEL study (TMC114-C228). The ARIEL study was the primary pharmacokinetic and clinical study submitted in both

the US and Europe in support of dosing recommendations for subjects weighing between 10 and 20 kg. The site reports generated concerns regarding the quality of the data submitted in support of the NDA submission from 3 of the sites including the Kenya site (N = 6), and two South African sites (Drs. Violari and Moultrie (N = 9). As the PDUFA due date of September 30, 2011 did not allow adequate time for review of the data as well as for the submission of additional explanatory data from the Applicant, the site inspection submission was deemed a major amendment and the review time was extended (FAX communication to Tibotec 9/29/11). In a FAX dated October 6, 2011 the Agency requested that the Applicant supply the following:

- Provide a copy of your assessment to the inspection reports issued by the EMA (CHMP). In addition, submit your rationale for using/accepting the data from the three sites inspected in support of pediatric labeling for children 3 to <6 years of age.

- Please clarify whether any (b) (4) darunavir and ritonavir long term stability data has been generated (b) (4) .

- In regards to darunavir/ritonavir samples from the TMC114-C228 trial that were stored at (b) (4), please provide information on the following: a) the number of trial sites and the number of subjects at each site that had darunavir/ritonavir samples stored at (b) (4), b) the total number of darunavir/ritonavir samples at each trial site that had samples stored at (b) (4), and c) the maximum length of time

The Applicant's response to the Division's RFI for the first question is the subject of this amendment. The Chemistry Reviewer, Dr. M Paciga, will provide an in depth review of stability and temperature issues, however his assessment indicated that based on stability data and reported temperature deviations significant changes in product quality or performance are not expected.

Review of Response to RFI Question 1:

A single study TMC114-C228 was submitted in support of use of darunavir in the pediatric population ages 3 - < 6 years (NDA 202-895). Study TMC114-C228 is the only study conducted in this age group and the patients were treated with a new oral solution formulation.

Study TMC114-C228 is an ongoing, open-label, Phase 2 trial to evaluate the pharmacokinetics, safety, and antiviral activity to support dose recommendations by body weight of darunavir in combination with low-dose ritonavir (DRV/r) and other antiretroviral (ARV) agents, in treatment-experienced HIV-1 infected children ages from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/r are being evaluated in combination with other ARVs over a 48-week treatment period. The study was conducted in two parts. The first two weeks of the

TMC114-C228 trial were designed to support dose recommendations of DRV/r in the studied population. The pharmacokinetic profile of DRV/r dosed twice daily at the initially selected dose at steady-state in the studied population was evaluated at Week 2. Safety, tolerability and antiviral activity were also assessed at the Week 2 timepoint. Based on the PK analyses and simulations, dosing was adjusted primarily at or around week 12 of treatment. It should be noted that although these adjustments were made, they were made based on inaccurate information due to the omission of certain data. Follow-up analyses revealed that these adjustments ultimately led to unacceptably high Cmax and AUC in the lower weight band but were acceptable in the upper band. Two weeks after the dose adjustment, an additional pharmacokinetic assessment was performed, followed by another planned pharmacokinetic assessment at Week 24. Safety and tolerability, as well as antiviral activity, were also evaluated at these time points. The mean duration of DRV/r treatment from trial start up to the cut-off date of the Week-24 analysis was 30.5 weeks.

Subjects received DRV/r according to their body weight. The initial dose of DRV was 20 mg/kg in combination with ritonavir 3 mg/kg. According to their body weight, subjects received a DRV dose between 200 and 380 mg twice daily and a ritonavir dose between 32 and 48 mg twice daily. DRV/r was taken together with an optimized background regimen (OBR).

Twenty-seven treatment-experienced subjects (15 male and 12 female) were enrolled in the study and were stratified by weight and received DRV/r according to their respective weight band- 14 subjects (51.9%) in the 10 to < 15 kg weight group, and 13 subjects (48.1%) in the 15 to < 20 kg weight group. At the time of the Week-24 analysis, 1 subject had prematurely discontinued (due to an AE [vomiting], grade 2, not related to DRV).

The primary efficacy endpoint in this trial was plasma viral load < 50 copies/mL at Week 24. In the initial analysis, the virologic response defined as the percentage of subjects with a confirmed virologic response (plasma viral load < 50 copies/mL) was 59% (16/27) based on the FDA snapshot analysis. Nine subjects were classified as virologic failures and there was one each with missing data and no data because of early discontinuation.

In Table 1 below is the distribution of patients by country. As noted above concerns regarding the integrity of the submitted data were raised by the EMA inspectors for the Kenyan and the South African sites. In dispute are 16 patients, 6 from Kenya and 10 from S Africa. An initial review of the inspection reports raised serious concerns about the Kenyan site whereas there were fewer issues noted from the S African sites.

Subjects enrolled in Trial 228

Country	Number of Sites Enrolling	Number of Subjects Enrolled	Number Prematurely Discontinued
Argentina	3	4	0
Brazil	3 (2 enrolled)	6	1
Kenya	2	6	0
South Africa	3	10	0
India	1	1	0

The Applicant also submitted a Marketing Authorization Application (MAA) to EMA on May 4, 2011. The application consisted of trial TMC114-C228 which was also submitted to the US FDA. As a part of the MAA review process, between August 24 and September 2, 2011, the EMA Inspectorate conducted clinical site inspections at three sites in Kenya and S. Africa (Dr. Kimutai, Dr. Moultrie, and Dr. Violari) that were part of the TMC114-C228 study. The inspection reports were provided to the Applicant on Sept 26, 2011 and subsequently provided to NDA 202-895 (sequence 0041) on Sept 29, 2011. The initial inspection reports consisted of multiple minor and few major and critical issues as defined by the EMA for each site. A finding that was common to each of the three inspection reports, involved inconsistencies in data in the Week 24 dataset when compared to the Week 48 dataset. Other issues included:

- Lack of calibration of storage area thermometers *(minor)*
- Storage temperature went below the recommendations of the sponsor (minor).
- Lack of documentation of lower temperatures in the monitoring reports
- No timely notification of temperature excursion(major)
- No timely evaluation of the usage of IMP was performed by investigator site and sponsor (major).

A number of issues were specific to the Kenya site and included:

- No PPB approval for the conduct of the trial from 1st September 2010 to 24th November 2010 due to delay in renewal (major)
- Investigator TMF was not adequately maintained
- Monitoring not adequate
- The site was closed on the 21st June 2011, despite the fact that all necessary documents were not in the appropriate files
- Ethics correspondence, including letters from the ERC (dated 24th August 2011 and June 24th 2011) and a notification to the ERC regarding trial closure (dated 21st June 2011) were misfiled in the Temperature and Humidity Log Section.
- Correspondence was not filed in chronological order.
- Correspondence was filed in duplicate within the same section of the file, for example, letters to the ERC dated 28th September 2009, regarding submission of KEMRI protocol Version 2.0, and, dated 29th September, regarding clarification of approved protocols and PILs.

- Correspondence was filed in duplicate across different sections for no logical reason. For example the Continuing Review Reports were filed in the section entitled "interim, annual and final reports" and section entitled "cover letter, application forms section".
- Letters were on file in duplicate, but with different handwritten dates on the letters. For example the letter to the PPB regarding resubmission of IB, Safety Updates and Insurance for the trial.
- A document entitled "KEMRI SSC Protocol \ 1570 Reviewer comments (Site responses embedded in bold), signed and dated by Kimutai 11th March 2009, was on file with the PPB correspondence.
- Issues with consent form review committee make-up as well as with the consent form itself and the procedures followed in obtaining informed consent. Issues included translation, omission of dosing instructions, the performance of genetic testing etc. (Critical)
- Inaccurate documentation in the eCRF of the physical exam findings at screening, at baseline, similar issues for previous treatments and medical history,

The inspection reports were reviewed by the Applicant and responses were provided to the EMA on Oct 31, 2011 and to the Division on November 9. 2011.

For the Kenya site, a review of the Applicant's responses revealed that most of the issues were acknowledged as indicative of "sloppy work". Corrective actions taken for future projects included a commitment by the Applicant to ensure adequate training of all personnel involved in a trial as well as the hiring of a specific onsite clinical monitor who will ensure timely and adequate documentation of all parts of the trial. Issues such as inadequate representation of pediatricians of the informed consent committee were also acknowledged and will be avoided in future trials.

Comment: The Division acknowledged that the Applicant will in the future correct the issues that were found by the EMA inspectors however the informed consent issues are deemed too significant to allow for the inclusion of the data from the Kenya site into the data used to make a final decision regarding the approvability of the application.

With regards to the inconsistencies found between the 24 and 48 week datasets across the sites, Tibotec performed a detailed assessment of both datasets. Overall, there were 228 inconsistencies in the Week-24 dataset for the entire trial that were already corrected prior to inspection, by the time of the Week-48 analysis. When excluding the inconsistencies for laboratory data (a local laboratory was used for the site of Dr. Kimutai in Kenya, and the (b) (4) laboratory for the other sites), 130 corrected inconsistencies were shown to be related to the inspected sites (3 sites, 15 subjects) and 47 corrected inconsistencies were related to the non-inspected sites (8 sites, 12 subjects). The inconsistencies identified are either additions or corrections of the Week-24 dataset, generally pertaining to screening and baseline data.

There were no consequences of the inspection findings on the handling on the safety of the subjects in the trial (the trial subjects were monitored according to local medical standards). There were no negative consequences for the pharmacokinetic/efficacy/safety conclusions of the primary Week-24 and Week-48 analyses and the local Kenyan lab results did not affect the main objective of the trial.

Comment: From a clinical standpoint the inclusion of all patients who received any dose of study drug in the safety analysis is standard procedure and the exclusion of any of the 27 treated subjects would be unreasonable. From an efficacy standpoint however, the Kenya site patients were excluded for the reasons stated above. It should also be noted however that as per the Clinical Pharmacology Reviewer, Dr. Stanley Au, all Kenyan patients' data was previously excluded from the PK analyses and therefore no changes in the PK conclusions were expected.

The revised efficacy analysis excluding the three Kenyan patients originally included in the analysis (one virologic failure and two successes) is as follows:

Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL (FDA snapshot analysis/Original Dataset)
Week 24

n (%)	**DRV/r N = 27**
Virologic Success	16 (59.3)
Virologic Failure	9 (33.3)
No virologic data week 24-discontinued due to AE/death	1 (3.7)
Missing data week 24	1 (3.7)

N = # of responders, n = # of patients

Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL (FDA snapshot analysis/Revised Dataset)
Week 24

n (%)	**DRV/r N = 24**
Virologic Success	14 (58.3)
Virologic Failure	8 (33.3)
No virologic data week 24-discontinued due to AE/death	1 (3.7)
Missing data week 24	1 (3.7)

N = # of responders, n = # of patients

Therefore the exclusion of the Kenya patients did not substantively alter the efficacy analysis.

Conclusion and Recommendations: The Applicant submitted a response to the EMA inspection reports and deficiencies found at three of the sites where trial TMC114-C228 took place. The inspection reports and the response constituted a major amendment to the

NDA package. After review of both the inspection reports and the responses the Reviewer concluded that the Applicant performed inadequate monitoring at the respective sites, however generally the deficiencies did not affect the PK, efficacy and safety conclusions drawn from trial 228 regarding dosing in pediatric patients ages 3 – 6 and weighing between 10 and < 20 kgs. It was necessary to exclude the patients from the Kenya site because of significant deficiencies in the informed consent process. The exclusion of these patients did not affect the efficacy, safety or pharmacokinetic conclusions of trial TMC114-C228.

The Reviewer recommends an approval of NDA 202-895 with labeling as agreed upon including dosing for patients weighing between 10 - < 15 kg at the 20/3 mg/kg dose level and the exclusion of the Kenya patienys' data from the efficacy analyses presented in labeling.

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/s/

M R ALIVISATOS
12/13/2011