

## Cross-Discipline Team Leader Review- Amendment

<b>Date</b>	December 8, 2011
<b>From</b>	Yodit Belew, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review Amendment
<b>NDA/NDA #</b>	202895/21976
<b>Supplement #</b>	S-20 (to NDA 21976)
<b>Applicant</b>	Tibotec, Inc.
<b>Date of Submission</b>	March 29, 2011
<b>PDUFA Goal Date</b>	September 30, 2011
<b>Proprietary Name / Established (USAN) names</b>	Prezista(darunavir)
<b>Dosage forms / Strength</b>	New proposed dosage form: Oral Suspension Approved dosage forms: 600, 400, 150, 75 mg tablets
<b>Proposed Indication(s)</b>	Treatment of HIV infection
<b>Recommended:</b>	Approval

This amendment summarizes two important events that occurred after review of the pediatric data to NDAs 202895 and 21976 were completed. The first section of this amendment addresses the revised dosing recommendations that have been made for children 3 years of age and older and weighing 10 to less than 15 kg. The second section addresses why an action was not taken on the PDUFA goal date, September 30, 2011. Specifically, it discusses the information submitted by the Applicant which was considered a major amendment, what conclusions the review team reached after review of the information, and what the final recommendation is for the application.

### Section 1

A revision to the dosing recommendation has been made by the Division and 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 the recommendation that the 20/3 mg/kg (b) (4) be approved for dosing in children 10- <15kg:

- The Applicant submitted a revision to the population PK analysis to correct for an error, primarily in subjects weighing 10 - <15 kg.

Table 1 Comparative result of the mean AUC in the initial and adjusted dosage regimens to the mean target adult exposure of 62.3 mcg/mL\*hr

	Before Dose Adjustment			After Dose Adjustment		
	Overall	10 to <15 kg	15 to <20 kg	Overall	10 to <15 kg	15 to <20 kg
Original Analysis	107%	111%	104%	128%	140%	122%
Revised analysis	107%	110%	104%	129%	<b>153%</b>	113%

Source: Applicant's revised submission

Based on this revised analysis, subjects weighing 10 to <15 kg have mean AUC exposure that is 53% higher than the targeted mean adult exposure value.

- Changes in the dosing device

As discussed in the CDTL memo, DMEPA had recommended that the originally proposed (b) (4) be replaced by a syringe that is similar to what is currently available in the U.S. market. The Applicant submitted an alternative device (syringe) for marketing and has been accepted and recommended for approval by DMEPA. Although this syringe is similar to what is available in U.S. pharmacies, the dosing increments are much closer compared to the originally proposed (b) (4). Therefore, less precision could be expected when drawing the medication. Although this decrease in precision is likely to be by small amounts, it can potentially add to the overall increased dose of darunavir (b) (4), in particular for those weighing 10 to <15 kg.

In addition to the already higher exposure expected with the (b) (4) dosing, one could consider adding yet another level of complexity: a drug-drug-interaction scenario where the exposure could be further pushed to significantly higher exposure where no supportive safety data is available from the adult or pediatric trials.

We therefore reevaluated the PK/PD, antiviral activity and safety data for the two doses as well as the adult trials C202 and C213.

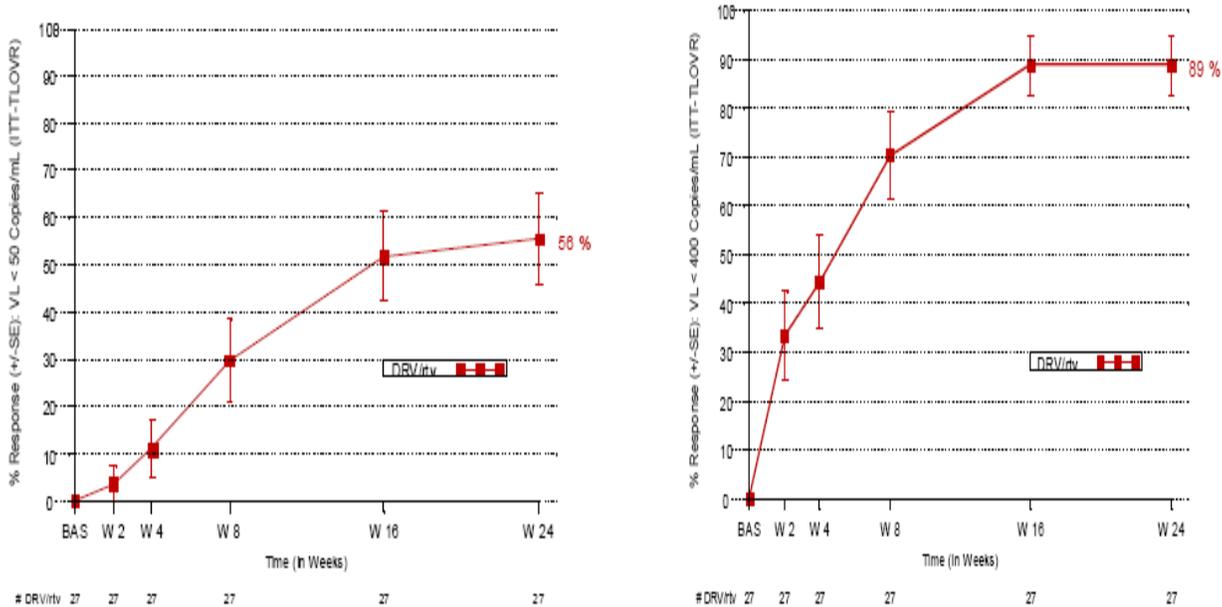
Pharmacokinetics The pre-defined targeted exposure was to be within 80%-130% of the mean adult AUC value (62.3) at the 600/100 mg dose. The mean AUC value at the 20/3 mg/kg dose falls within this range. On the other hand, the mean AUC value at the (b) (4) falls outside the range of the target- i.e. 53% higher than adult mean AUC. As previously discussed and demonstrated, the data analysis exposure-response/efficacy in the treatment experienced adults did not demonstrate a relationship for the two variables even when considering doses as low as 400 mg QD. Therefore the exposure-response information does not support the need for a higher darunavir dose. Had the 20/3 mg/kg yielded exposures below the targeted adult mean value, it would be reasonable to consider and accept the (b) (4) in order to avoid under dosing in children. But such is not the case.

The standard for pediatric HIV drugs approval within the Agency is primarily based on PK data- matching the pre-specified adult parameters. Efficacy (or antiviral activity) and safety data collected during the trials are used as supportive evidence. This is due to the nature of HIV pediatric trials- single arm, open label and not powered for true efficacy demonstration. In the case of C218, the primary endpoint- the pre-specified pharmacokinetic parameter was met with the 20/3 mg/kg dose.

One of the concerns about selecting the 20/3 mg/kg dose is the lack of long term antiviral activity/efficacy data. In order to address this issue, we looked at the mean exposure period for the 20/3 dose and also considered the patient population – what the average age is at the 10-<15 kg weight band and compared it to the treatment experienced adult population from studies C202 and C213.

Duration of exposure Although the 20/3 mg/kg dose is referred to as the initial dose (Week 2), the mean exposure time (weeks) for this dose is 12.9 weeks. Therefore there

is antiviral activity data for the 20/3 mg/kg dosing beyond a 2-week period. As summarized in the figure below, response rate was upward and positive during the first ~16 weeks.



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Figure 1A and B: Virologic Response Defined as the Percentage of Subjects with Viral Load <50 copies/mL (A) and <400 copies/mL (B) [ITT- TLOVR) Over Time

Patient population: The subjects enrolled in the adult clinical trials C202 and C213 were heavily treatment experienced. The mean time since first ART initiation (months) was 114 for C202 and 112 for C213. In addition, based on baseline phenotypic data, overall, 71% of the subjects in C202 and 63% of subjects in C213 were infected with virus resistant to all available PIs. Despite the significant amount of resistant viruses, 56-69% and 36-57% of the subjects had HIV-RNA <400 copies/mL and <50 copies/mL, respectively at the 600/100 mg dose. Similarly 52-68% and 37-54% of the subjects had HIV-RNA <400 copies/mL and <50 copies/mL, respectively, at the 400/100 mg dose (Table 2).

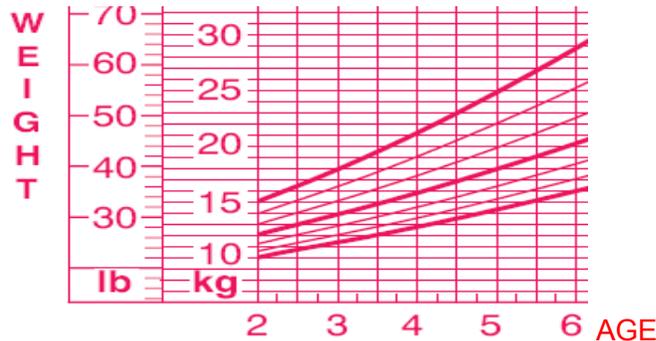
Table 2 Virologic outcome at Week 24

	<1 log drop in HIV RNA	VL<400 copies/mL	VL<50 copies/mL
<b>Trial TMC114-C202</b>			
400/100 qd	31/65=48%	25/65=38%	16/65=25%
800/100 qd	33/64=52%	26/64=41%	16/64=25%
400/100 bid	38/63=60%	33/63=52%	23/63=37%
600/100 bid	42/66=64%	37/66=56%	24/66=36% *
<b>Trial TMC114-C213</b>			
400/100 qd	45/64=70%	40/64=63%	27/64=42%
800/100 qd	45/63=71%	39/63=62% *	31/63=49%
400/100 bid	45/63=71%	43/63=68%	34/63=54%
600/100 bid	49/65=75%	45/65=69%	37/65=57%

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

\* = to be marketed dose

The pediatric subjects in the 10 - <15 kg weight band are not expected to have comparative levels of baseline resistance as they are considerably younger. The CDC growth chart (below) can be utilized to estimate the age range for this weight band. Based on the CDC growth chart, approximately 50% of children weigh 15 kg by age 3.5 years and less than 3 percentile weigh 15 kg by age 5.5 years.



Therefore, many if not most children weighing 10- <15 kg should not be older than 4.5 years of age. It is extremely unlikely that pediatric patients at such age will harbor resistant viruses to the same extent as the adult patients did. As evident by the baseline disease characteristics information obtained from trial C228, there is less resistance in this overall 3 to <6 years-old subject population compared to adults.

According to the Applicant, the median number of ARVs previously used in the pediatric subjects enrolled in C228 was 4; the median number of PIs, NRTIs, and NNRTIs previously used was 1, 2, and 1, respectively. Eleven subjects (40%) had used no PI; twelve subjects (44%) had used 1 PI, and 4 subjects (15%) had used  $\geq 2$  PIs. The previous PI most frequently used was lopinavir; the previous NNRTI most frequently used was nevirapine.

Protease mutations, primary PI mutations, PI RAMs, and DRV RAMs at baseline were collected. The majority of subjects had no primary PI mutations (23 subjects, 85.2%) and no DRV RAMs (25 subjects, 92.6%) at baseline; 21 subjects (77.8%) had  $\geq 3$  PI RAMs. The median number of primary PI mutations was 0 (range: 0 - 3), the median number of DRV RAMs was 0 (range: 0 - 2), and the median number of PI RAMs was 4 (range: 1 - 13). DRV RAMs L76V and L33F were observed in 1 subject and L76V was observed in 1 other subject (CRF ID 228-0015).

Finally, the number of susceptible drugs per class at baseline was also provided. At baseline, all subjects enrolled in the trial were infected with virus susceptible to  $\geq 5$  ARVs (including PIs, NRTIs, NNRTIs, fusion inhibitor, integrase inhibitor). All subjects were infected with virus susceptible to DRV and most subjects had also virus susceptible to the other commercially available PIs (ranging between 85.7% and 95.2% for the different PIs).

In summary, based on the baseline genotypic and phenotypic resistance profile, the baseline  $IC_{50}$  is not expected to be higher than what was observed in trials C202 and C213. This is an important factor as response to treatment is related to inhibitory quotient (IQ)- the ratio between steady state trough concentration and baseline  $IC_{50}$  (see below).

Pharmacometrics: Based on the adult data (C202 and C213), virologic response is related to the subject's darunavir IQ- the higher the IQ, the more likely that a subject will respond. The IQ appears to be primarily influenced by baseline  $IC_{50}$ . The 600/100 mg BID dose in adults correlated with an IQ sufficient enough to have an acceptable virologic success rate. Because the 20/3 mg/kg dose leads to exposures that are within 80 to 130% range of the adult exposure (from the 600/100 mg BID dose), and because the  $IC_{50}$  is not expected to be higher in this age group, the long term efficacy or durability of the 20/3 mg/kg can be expected to be similar to what was observed in treatment experienced adults.

Safety The overall mean duration of treatment from trial start up to the cut-off date of the analysis was 30.5 weeks. The mean duration of treatment after dose adjustment was 18.4 weeks. Although the (b) (4) dose appears to be generally safe and well tolerated for the 18.4 weeks it was administered, sparse data is available for subjects weighing 10 to <15 kg and with exposure >130%. Post dose adjustment, 6 subjects out of a total of 9 in the 10 to < 15 kg group had exposures above 130% of the target range for adults. Although no significant adverse events were reported, the lack of sufficient number of subjects in that weight band supporting higher exposure is concerning.

In conclusion, I recommend the approval of this pediatric NDA (202895) with the following dosing recommendations:

- 10 kg to < 15 kg: darunavir 20 mg/kg with ritonavir 3 mg/kg twice daily
- 15 kg to < 20 kg: darunavir 375 mg with 50 mg of ritonavir twice daily

The Applicant agrees with the dosing recommendations. Labeling revisions to the dosing section of the USPI are currently underway.

## Section 2

- Background

Trial TMC114-C228 is an international trial evaluating the pharmacokinetic, antiviral activity and safety of darunavir in children 3 to less than 6 years of age. The study report was submitted to both the US and European regulatory agencies in support of dosing recommendations for subjects 3 to less than 6 years of age and weighing between 10 and 20 kg.

Twenty-seven subjects were enrolled and stratified by weight band- 14 subjects (52%) in the 10 to < 15 kg weight group, and 13 subjects (48%) in the 15 to < 20 kg weight group. Table 3 summarizes the distribution of subjects by country.

**Table 3 Subjects enrolled in Trial 228**

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

As a part of the review process for marketing authorization, the EMA Inspectorate conducted clinical site inspections at 3 locations. On September 27, 2011, unsolicited new information [submission number (SN) 41] was submitted by the Applicant to NDA 202-895. The submission contained interim clinical sites inspection reports issued by the EMA for trial TMC114-C228.

DAVP has not routinely requested clinical site inspections for pediatric trials of antiretroviral drugs unless there was a specific concern identified. It should also be noted that the FDA does not rely on inspections conducted by other regulatory agencies to make regulatory decisions. As such, although the inspection reports were taken into consideration and reviewed, the final regulatory decision by the FDA is independent of other agencies.

The inspection reports generated concerns about the quality of the data from the 3 sites inspected by EMA: a Kenyan site, which enrolled six subjects, and two South African sites, which together enrolled nine subjects. Because the information was submitted 3 days before the PDUFA goal date, there was insufficient time for review of the data. Therefore, the information submitted was deemed a major amendment and the review time was extended to December 30, 2011. Furthermore, the review team needed additional information from the Applicant in order to conduct an adequate review. After the Applicant submitted the additional information requested, a full review of the information was conducted by the review team, in consultation with the Office of Scientific Inspection (OSI).

- Deficiencies identified by the report

The inspection reports identified several issues, ranging from 'minor' to 'critical', although most were considered 'minor' by the inspectorate.

In addition, there were 2 stability/storage temperature issues identified during inspections: 1) storage and stability of drug product (darunavir oral suspension, and possibly ritonavir) at temperatures in the range of 10-30° C and 2) storage of blood/plasma PK samples at (b) (4) rather than -20° C.

Please refer to the amendments by the chemistry reviewer and the clinical pharmacology reviewer for further detail on the issues related to plasma sample storage and drug product stability. In summary, it is unlikely that, storage of the drug product over the range of temperatures noted, before administration to patients would adversely affect product quality or performance. Further, storage of plasma at (b) (4) would not likely adversely impact chemical stability of the analytes (darunavir, metabolites).

The following are among the clinical violations noted from the South African sites:

- Inconsistencies in data in the Week 24 dataset when compared to the source document and when compared to the subset data included in the Week 48 data
- Procedure for identifying and classifying protocol deviations were insufficient

However, in addition to the data inconsistencies between source documents and datasets, the violations from the Kenyan sites appear to be more serious, and also include ethical violations:

- Issues with the Informed Consent Form (ICF) which arose during language translation:
  - The quality of translation was not adequately assessed.
  - The ICF lacked dosing and storing instructions that were included in the master version.
  - Risks associated with darunavir that were included in the master version were omitted.
  - Risks associated with ritonavir that were included in the master version were omitted.
  - Questionable if the signatures of the parents for some subjects were personally dated by the parents or the staff.
  - Unclear if counselors who administered the ICF had medical background and/or if they received training for ICF administration
- Subject identifiers on source documentation were not adequate.
- The clinical site, in general lacked experience and there were insufficient monitoring visits from the clinical research organization (CRO)
- Handling and processing of biological samples was not adequate. Issues with the local laboratory (which was used for diagnostics) included: lack of daily QC checks of analytical methods; failing to establish its own reference range but instead used outside laboratory reference ranges; incorrect patient identifiers were used on laboratory reports. Of note, per trial design, all laboratory testing were to be performed by a central laboratory (b) (4).

- Applicant's response to the inspection reports

The Applicant acknowledged the issues identified by the reports and believes it to be an indicative of "sloppy work" and plans to implement corrective actions for future projects.

With regards to the inconsistencies found between the 24 and 48 week datasets across the sites, the Applicant performed a detailed assessment of the datasets. Per Applicant, 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, safety and efficacy conclusions of the primary Week-24 and Week-48 analyses.

- DAVP's review of the inspection report and Applicant's response

After reviewing the inspection reports and the Applicant's response to the reports, the assessment made by the review team is that none of the issues identified in the two South African sites were considered significant enough to recommend exclusion of the data from these sites. The sites generally followed GCP and the data were not fraudulent or fabricated. In addition, there were no ethical violations related to the Informed Consent Form (ICF).

In addition to the major laboratory and clinical site concerns, of paramount concerns of the Kenyan site are the violations relating to the ICF. Based on review of the report, the events appear to be due to 'sloppy work' but the investigator had good intent. Nonetheless, these violations can be considered as ethical violations. Although the violations did not necessarily lead to unsound clinical data, it is questionable if the data was ethically obtained and thus questions the usability of the data to support the application.

Darunavir is an antiretroviral drug considered essential for this pediatric age group as it adds meaningful therapeutic benefit for treatment of HIV infection. Therefore, it is not without serious deliberation that the review team concluded the data from the Kenya site should be excluded. When considering the necessity of the data from this site, it is arguable that there is no critical need of the Kenyan data to justify its inclusion because adequate pharmacokinetic, safety and efficacy data exists from the other clinical sites. Therefore, the data from the Kenyan site should be excluded from analyses used to support dosing recommendation in this pediatric age group. The revised efficacy analysis after excluding the Kenyan data is comparable to the original result: 59% (original dataset) vs. 58% (revised dataset).

- Conclusions and recommendation

In addition to the types of clinical trial violations, one has to consider the type of disease, the patient population for which the study was conducted and the unmet medical need that exists for the patient population. Consider the following: HIV infection is a life-threatening disease, if untreated; the pediatric patient population is in need of additional antiretroviral drugs; and darunavir has been shown to be safe and effective for treatment

of HIV infection in patients 6 years of age and older. Therefore, the data from this trial should be considered crucial. Unless there is ethical misconduct or fraudulent data, every effort should be made to utilize the data. In addition, data collected from pediatric research subjects (i.e. children 3 to 6 years of age) who participated with full consent should not be easily discarded.

As stated previously, the Kenya site violations are serious and question the ethics in which the trial was conducted. Therefore, the data from this site should be excluded. However, the violations from the South African sites do not lead to conclusions that question the integrity of the data. In lieu of the fact that the data remains uncompromised, there are no scientific or ethical bases to exclude the South African data from analyses.

In summary, the trial results were re-analyzed excluding subjects from the Kenyan site. The final pharmacokinetic, safety and efficacy conclusions generally remained unchanged.

The overall recommendation for this NDA application is approval. The Applicant has agreed with the recommendations made by the Division (i.e. exclusion of the Kenyan data). Labeling changes to reflect the revised number of subjects who contributed to the analyses have been made by the Applicant and are acceptable.

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YODIT BELEW  
12/14/2011