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APPLICATION NUMBER:

202895Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review- Amendment

Date	December 8, 2011
From	Yodit Belew, M.D.
Subject	Cross-Discipline Team Leader Review Amendment
NDA/NDA # **Supplement #**	202895/21976 S-20 (to NDA 21976)
Applicant	Tibotec, Inc.
Date of Submission	March 29, 2011
PDUFA Goal Date	September 30, 2011
Proprietary Name / Established (USAN) names	Prezista(darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 600, 400, 150, 75 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	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 instead of (b) (4) mg/kg 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%	**153%**	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 that the targeted mean adults 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 25/3 mg/kg, in particular for those weighing 10 to <15 kg.

In addition to the already higher exposure expected with the 25/3 mg/kg 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 25/3 mg/kg 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) mg/kg 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.

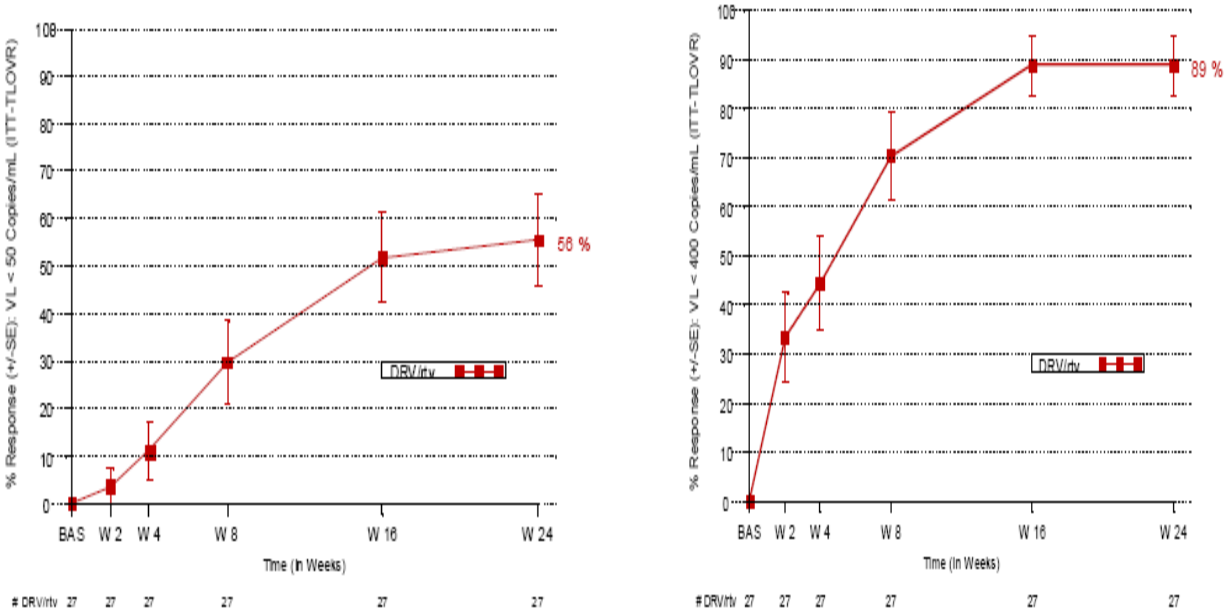


Figure 1A and B: Virologic Response Defined as the Percentage of Subjects with Viral Load <50 copies/mL (A) and <400 copies/mL (B) [ITT- TLOVR) Over Time

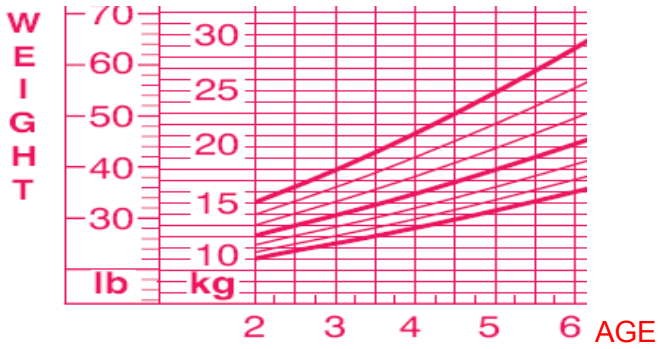
Patient population: The subjects enrolled in the adult clinical trials C202 and C213 were heavily treatment experienced. The mean time since first ART initiation (months) was 114 for C202 and 112 for C213. In addition, based on baseline phenotypic data, overall, 71% of the subjects in C202 and 63% of 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
Trial TMC114-C202			
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% *
Trial TMC114-C213			
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 extend 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 ≥ 2 PIs. The previous PI most frequently used was lopinavir; the previous NNRTI most frequently used was nevirapine.

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