OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 21976/S-27 (SDN 704) & NDA 202895/S-4 (SDN 63)
Submission Number (Date)	2 July 2012
Drug Name	Darunavir
Proposed Indication	Treatment of HIV-1 infection in pediatric subjects 3 to 6 years old (twice daily dosing)
Clinical Division	DAVP
Primary CP Reviewer	Stanley Au, Pharm.D., BCPS
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Shirley Seo, Ph.D.
Secondary PM Reviewer	Kevin Krudys, Ph.D.
Applicant	Janssen

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The main purpose of this review is to assess the labeling changes regarding the population pharmacokinetic estimates of darunavir exposure with twice daily dosing in pediatric subjects weighing 10 to < 20 kg based on Week 48 analysis of data from the TMC114-C228 trial (Table 1).

Table 1: Proposed Labeling Changes of Population Pharmacokinetic Estimates of Darunavir Exposure in Pediatric Subjects Based on Week 48 Analysis of Data from Study TMC114-C288

Table 2: Population Pharmacokinetic Estimates of Darunavir Exposure (Study TMC114-C230, Study TMC114-C212 and Study TMC114-C228) Following Administration of Doses in Tables 2 and 3

			Study TMC114-C228 PREZISTA/ ritonavir twice daily*	
Parameter	Study TMC114-C230 PREZISTA/ ritonavir once daily[β] N = 12	Study TMC114-C212 PREZISTA/ ritonavir twice daily N = 74	10 to less than 15 kg[‡] N = 10	15 to less than 20 kg[§] N = 13

AUC_{24h} (ng·h/mL) †				
Mean ± Standard Deviation	84390 ± 23587	126377 ± 34356	137896 ± 51420	157760 ± 54080
Median (Range)	86741 (35527-123325)	127340 (67054-230720)	124044 (89688-261090)	132698 (112310 – 294840)
C_{0h} (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ± 1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542-3776)	3888 (1836-7821)	4126 (2456-9361)	3927 (3046 – 10292)

N = number of subjects with data.

* Subjects may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group.

† AUC_{24h} is calculated as AUC_{12h}*2

‡ Calculated from individual pharmacokinetic parameters estimated for Week 2 and Week 4, based on the Week 48 analysis that evaluated a darunavir dose of 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily.

§ The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) PREZISTA oral suspension twice daily with 48 mg (0.6 mL) ritonavir oral solution twice daily in TMC114-C228. Calculated from individual pharmacokinetic parameters estimated for Week 2 post-dose adjustment visit; Week 24 and Week 48 based on the Week 48 analysis that evaluated a darunavir dose of 380 mg twice daily. ᵝ Summary statistics for population pharmacokinetic parameter estimates for DRV after administration of DRV/rtv at 800/100 mg q.d. in treatment-naïve HIV-1 infected subjects from 12 to < 18 years of age – Week-48 Analyses

Source: Sponsor's prezista-uspi-annotated, Table 13

Reviewer's comments:

The sponsor applied a previously developed model to the newly available data from the TMC114-C228 trial up to 48 weeks treatment. For details and reviews of previous model development in adults and children, please refer to the pharmacometric review of NDA 21-976 by Christine Garnett, NDA 21-976 S-09 by Kevin Krudys and NDA 21-976 S-20 (TMC114-C228 trial up to 24 weeks treatment) by Jiang Liu. The updated dataset included 235 observations from 20 children aged 3 to 6 years old. The model was adequate for individual exposure estimation based on the general model assessment (e.g., assessment of goodness-of-fit plots and shrinkage on CL).

Compared to the data from TMC114-C228 trial up to 24 weeks treatment, there were two additional subjects (Subjects 009 and 017) who were categorized in the 15 to <20 kg weight group in the Week 48 analysis because their body weight had increased after the

Week 24 analysis. However, during our review we noticed that Subject 017 was still receiving DRV 360 mg twice daily as in the 10 to <15 kg group in the population dataset, instead of DRV 380 mg twice daily in the 15 to <20 kg group. In response to a comment sent to the applicant, the summary statistics of the population PK exposure estimates for the 15 to <20 kg group was further revised to exclude subject 17 and only the pharmacokinetic data associated with 380 mg twice daily dosing of darunavir for subject 9 was included.

1.2 Recommendations

The proposed labeling changes of population PK estimates of darunavir exposure are acceptable.

2 PERTINENT REGULATORY BACKGROUND

Darunavir (DRV), a HIV protease inhibitor (PI), in combination with low-dose ritonavir (RTV) is currently approved for the use in treatment-experienced adults and pediatric subjects aged 3 to < 18 years old as a twice-daily regimen. The approval of DRV in pediatric subjects aged 3 to 6 years old was issued in 2011 based on Week 24 analysis of data from the Phase II trial TMC114-C228. The current supplement proposes to update labeling in pediatric subjects aged 3 to 6 years old based on the Week 48 analysis of data from the Phase II trial TMC114-C228.

Appendix 1-Review of darunavir and ritonavir bioanalytical information relevant to the TMC114-TiDP29-C228 trial

Primary Clinical Pharmacology Reviewer: Stanley Au, Pharm.D., BCPS

Secondary Clinical Pharmacology Reviewer: Shirley Seo, Ph.D.

The additional bioanalytical information for darunavir and ritonavir that was submitted with the week 48 supplement for the TMC114-TiDP29-C228 trial was reviewed. There were no issues identified that would be anticipated to result in major differences in the reported plasma concentration data for the TMC114-TiDP29-C228 trial. Table 2 below summarizes selected darunavir and ritonavir method validation and bioanalysis information for the TMC114-TiDP29-C228 trial.

Table 2- Relevant method validation and bioanalysis items for the TMC114-TiDP29-C228 trial

Analyte	Darunavir (TMC114, (b) (4)), ritonavir (b) (4)) First analyzed sample drawn: November 10, 2009 Last sample analysis: April 1, 2011
Anticoagulant used for: Method validation Collecting blood samples in the trial	Heparin Heparin
Temperature subject samples were stored at trial site	-20˚C at some sites (for a maximum of 20 days for primary samples included in the trial), and at -70˚C at other sites (for a maximum of 7 days for primary samples included in the trial).
Temperature subject samples were stored at satellite site	- 20°C (at central laboratory for a maximum of 221 days).
Temperature subject samples were stored at the bioanalytical laboratory	- 20°C (prior to analysis, samples were stored for a maximum of 71 days).
Temperature(s) long term stability experiments were conducted	- 20°C and -70˚C (at (b) (4)) and -20˚C at Janssen's bioanalytical laboratory.
Duration of validated long term stability for the analyte	At (b) (4), -20°C and -70°C long term stability was evaluated after 163 days for darunavir and ritonavir. At Janssen's bioanalytical laboratory, long-term stability was evaluated after 1597 days at -20°C for darunavir and ritonavir.
Total number of analytical runs	14 for darunavir, 13 for ritonavir
Number of analytical runs that passed	11 for darunavir, 11 for ritonavir

Number of analytical runs that failed (include reasons for failure and corrective action taken, if any)	3 for darunavir, 2 for ritonavir Failed run AN-10-6 for both compounds: too many quality control samples outside the criteria. Failed run AN-11-7 for both compounds: unacceptable contamination in one run. Failed run AN-11-13 for darunavir: too many quality control samples outside the criteria. Corrective actions: -Too many quality control samples outside the criteria: Since the same set of QCs was successfully used in previous runs, it was anticipated that the failure of this run was not caused by the QCs, but by a processing error in this run, and therefore no corrective action was taken. -Unacceptable carry-over: Solved in a next analytical run; no corrective action was taken.
ISR	Not performed

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/s/

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