OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202895 (SDN 66 and 67) NDA: 21976 (SDN 721 and 722)	Submission Date: August 3, 2012
Brand Name	Prezista®
Generic Name	Darunavir
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Secondary Reviewer	Kevin Krudys, Ph.D.
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OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Janssen Research and Development
Currently marketed formulations	Darunavir tablets; 75 mg, 150 mg, 400 mg, 600 mg, 800 mg Darunavir oral suspension (100 mg/mL)
Proposed darunavir dosage regimens (tablets or oral suspension) coadministered with ritonavir (tablets/capsules or oral solution)	Once daily dosing with food: 10 kg to less than 15 kg: Darunavir 35 mg/kg coadministered with ritonavir 7 mg/kg 15 kg to less than 30 kg: 600 mg of darunavir coadministered with 100 mg of ritonavir 30 kg to less than 40 kg: 675 mg of darunavir coadministered with 100 mg of ritonavir 40 kg and greater: 800 mg of darunavir coadministered with 100 mg of ritonavir
Proposed Indication for the Application	Treatment of HIV-1 infection in treatment naïve pediatric patients or treatment-experienced pediatric patients with no darunavir resistance associated substitutions 3 to less than 18 years old
Review Type(s)	Supplemental New Drug Application, priority review (pediatric supplements): 21976 SDN 721, 202895 SDN 66 (supplement for once daily darunavir/ritonavir dosing in HIV-1 infected pediatric patients 12 to < 18 years old) 21976 SDN 722, 202895 SDN 67 (supplement for once daily darunavir/ritonavir dosing in HIV-1 infected pediatric patients 3 to < 12 years old)

Table of Contents

1 Executive Summary

This review summarizes the clinical pharmacology results for a trial (TMC114-C230) evaluating once daily dosing in treatment naïve adolescents 12 to 18 years old weighing at least 40 kg and a subtrial evaluating once daily dosing in treatment experienced pediatric subjects 3 to < 6 years old. Additionally, population pharmacokinetic modeling and simulation was utilized to derive once daily pediatric dosing recommendations for pediatric subjects 3 to less than 12 years old weighing 10 kg to less than 40 kg.

Darunavir, co-administered with ritonavir (both medications are HIV-1 protease inhibitors), is indicated for use in the treatment of HIV-1 infection in combination with other antiretroviral medications. In treatment naive and treatment experienced adult patients with no darunavir resistance associated substitutions, the recommended dosage regimen is 800 mg of darunavir coadministered with 100 mg of ritonavir once daily with food. In treatment experienced adult patients with one or more darunavir resistance associated substitutions, the recommended dosage regimen is 600 mg of darunavir coadministered with 100 mg of ritonavir twice daily with food. The recommendations for darunavir twice daily dosing for HIV-1 infected children 3 to less than 18 years old that weigh at least 10 kg using darunavir tablets or oral suspension concurrently with ritonavir tablets/capsules or oral solution is displayed in Table 1 and Table 2 below. Using the same darunavir and ritonavir formulations, for the current submission that expands darunavir/ritonavir pediatric dosing to include once daily dosing in pediatric patients weighing at least 10 kg, the applicant's original proposed dosage regimens are listed in Table 3 and Table 4.

Table 1-Current darunavir/ritonavir twice daily dosing recommendations for HIV-1 infected children weighing 10 kg to less than 15 kg (administered with food) using darunavir oral suspension and ritonavir oral solution

Body weight (kg)	**Dose (Darunavir 20 mg/kg with ritonavir 3 mg/kg twice daily with food)**
Greater than or equal to 10 kg to less than 11 kg	Darunavir 200 mg (2 mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 11 kg to less than 12 kg	Darunavir 220 mg (2.2 mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 12 kg to less than 13 kg	Darunavir 240 mg (2.4 mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to 13 kg to less than 14 kg	Darunavir 260 mg (2.6 mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to 14 kg to less than 15 kg	Darunavir 280 mg (2.8 mL) with ritonavir 48 mg (0.6 mL)
ritonavir oral solution: 80 mg/mL	

Table 2-Current darunavir/ritonavir twice daily dosing recommendations for HIV-1 infected children weighing at least 15 kg (administered with food) using darunavir oral suspension or tablets and ritonavir oral solution or tablets/capsules

Body Weight (kg)	Dose (twice daily with food)
Greater than or equal to 15 kg to less than 30 kg	Darunavir 375 mg† (3.8 mL) with ritonavir 50 mg (0.6 mL)
Greater than or equal to 30 kg to less than 40 kg	Darunavir 450 mg# (4.6 mL) with ritonavir 60 mg (0.75 mL)
Greater than or equal to 40 kg	Darunavir 600 mg (6 mL) with ritonavir 100 mg (1.25 mL)
ritonavir oral solution: 80 mg/mL, ritonavir capsules or tablets: 100 mg † The 375 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 3.8 mL for suspension dosing. # The 450 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 4.6 mL for suspension dosing.	

Table 3-Applicant's original proposed darunavir/ritonavir once daily dosing recommendations for HIV-1 infected children weighing 10 kg to less than 15 kg (administered with food) using darunavir oral suspension and ritonavir oral solution

Body weight (kg)	Dosage regimen (Darunavir 40 mg/kg with ritonavir 7 mg/kg once daily with food)
Greater than or equal to 10 kg to less than 11 kg	(b) (4)
Greater than or equal to 11 kg to less than 12 kg	
Greater than or equal to 12 kg to less than 13 kg	
Greater than or equal to 13 kg to less than 14 kg	
Greater than or equal to 14 kg to less than 15 kg	
ritonavir oral solution: 80 mg/mL	

Table 4-Applicant's original proposed darunavir/ritonavir once daily dosing recommendations for HIV-1 infected children weighing at least 15 kg (administered with food) using darunavir oral suspension or tablets and ritonavir oral solution or tablets/capsules

Body Weight (kg)	Dose (once daily with food)
Greater than or equal to 15 kg to less than 30 kg	Darunavir 600 mg (6 mL) with ritonavir 100 mg (1.25 mL) once daily
Greater than or equal to 30 kg to less than 40 kg	(b) (4)
Greater than or equal to 40 kg	Darunavir 800 mg (8 mL)with ritonavir 100 mg (1.25 mL) once daily
ritonavir oral solution: 80 mg/mL, ritonavir capsules or tablets: 100 mg	

Supplements to the darunavir New Drug Application was submitted by the applicant to complete the fulfillment of postmarketing requirements for deferred pediatric trials as required by the Pediatric Research Equity Act (PREA). The postmarketing requirements specify that pediatric trials should be conducted in treatment naïve subjects 3 to less than 12 years old and 12 to less than 18 years old.

The trial results and conclusions for the TMC114-C230 trial, the TMC114-C228 subtrial, and the population pharmacokinetic modeling and simulation are discussed in the Summary of Important Clinical Pharmacology and Biopharmaceutics Findings (section 1.3).

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application. However, based on the analyses that were conducted for the review and discussions with the applicant, the proposed darunavir/ritonavir once daily dosing recommendations for pediatric patients were revised. The revised once daily dosing recommendations for pediatric patients are listed in Table 5 and Table 6.

Table 5-Revised darunavir/ritonavir once daily dosing recommendations for HIV-1 infected children weighing 10 kg to less than 15 kg (administered with food) using darunavir oral suspension and ritonavir oral solution

Body weight (kg)	Dosage regimen (Darunavir 35 mg/kg with ritonavir 7 mg/kg once daily with food)
Greater than or equal to 10 kg to less than 11 kg	Darunavir 350 mg (3.6 mL) with ritonavir 64 mg (0.8 mL) once daily
Greater than or equal to 11 kg to less than 12 kg	Darunavir 385 mg (4 mL) with ritonavir 64 mg (0.8 mL) once daily
Greater than or equal to 12 kg to less than 13 kg	Darunavir 420 mg (4.2 mL) with ritonavir 80 mg (1 mL) once daily
Greater than or equal to 13 kg to less than 14 kg	Darunavir 455 mg (4.6 mL) with ritonavir 80 mg (1 mL) once daily
Greater than or equal to 14 kg to less than 15 kg	Darunavir 490 mg (5 mL) with ritonavir 96 mg (1.2 mL) once daily
ritonavir oral solution: 80 mg/mL The 350 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 3.6 mL for suspension dosing. The 385 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 4 mL for suspension dosing. The 455 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 4.6 mL for suspension dosing. The 490 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 5 mL for suspension dosing.	

Table 6-Revised darunavir/ritonavir once daily dosing recommendations for HIV-1 infected children weighing at least 15 kg (administered with food) using darunavir oral suspension or tablets and ritonavir oral solution or tablets/capsules

Body Weight (kg)	Dose (once daily with food)
Greater than or equal to 15 kg to less than 30 kg	Darunavir 600 mg (6 mL) with ritonavir 100 mg (1.25 mL) once daily
Greater than or equal to 30 kg to less than 40 kg	Darunavir 675 mg (6.8 mL) with ritonavir 100 mg (1.25 mL) once daily
Greater than or equal to 40 kg	Darunavir 800 mg (8 mL) with ritonavir 100 mg (1.25 mL) once daily
ritonavir oral solution: 80 mg/mL, ritonavir capsules or tablets: 100 mg The 675 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 6.8 mL for suspension dosing	

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this supplement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The TMC114-C230 trial enrolled HIV-1 infected pediatric subjects 12 to less than 18 years old weighing at least 40 kg at screening. The pediatric subjects that were enrolled were naïve to HIV-1 antiretroviral treatment with a baseline HIV-1 viral load of 1000 copies/mL or greater.

At week 24 and week 48, the pharmacokinetics of darunavir was evaluated. Noncompartmental analysis was conducted using the Week 2 darunavir pharmacokinetic data. The results are displayed in Table 7.

Table 7-Darunavir pharmacokinetic parameters derived using noncompartmental analysis at week 2 with darunavir 800 mg combined with ritonavir 100 mg once daily

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**800/100 mg DRV/rtv q.d. + Background Regimen**		
n		10[a]	
Week 2			
C_{0h}, ng/mL	2172	±	1096
C_{min}, ng/mL	1589	±	768.2
C_{max}, ng/mL	6721	±	1700
t_{max}, h		3.00 (1.00-6.00)	
AUC_{24h}, ng.h/mL	81880	±	26300
FI, %	158.1	±	46.86
CL/F, L/h	11.28	±	5.776

[a] n = 12 for C_{0h}, C_{max} and t_{max}

Additionally, the darunavir pharmacokinetic data up to week 48 was analyzed using population pharmacokinetic analysis. The results are displayed in Table 8.

Table 8-Median darunavir pharmacokinetic parameters derived using population pharmacokinetic analysis up to week 48 with darunavir 800 mg combined with ritonavir 100 mg once daily

Parameter	AUC_{24h} (µg.h/mL)	C_{0h} (ng/mL)	CL/F (L/h)	$C_{ss, ave}$ (ng/mL)
N	12	12	12	12
Mean	84.4	2141	10.5	3516
SD	23.6	865	4.29	983
Geometric mean	80.7	1930	9.92	3364
CV (%)	28	40	41	28
Median	86.7	2234	9.23	3614
Min	35.5	542	6.49	1480
Max	123	3776	22.5	5139

Minimal differences in the C_{max}, $AUC_{(0-24h)}$, and C_{0h} at week 2 and for $AUC_{(0-24h)}$, and C_{0h} up to week 48 were observed for once daily dosing in HIV-1 infected, treatment naive adolescents compared to treatment naïve adults. For comparative purposes, the available darunavir pharmacokinetic parameters that were derived using noncompartmental analysis and population PK analysis with darunavir 800 mg combined with ritonavir 100 mg once daily in HIV-1 infected treatment naïve adults from the TMC114-C211 trial are displayed in Table 9 and Table 10.

Table 9-Darunavir pharmacokinetic parameters derived using noncompartmental analysis from the TMC114-C211 trial with darunavir 800 mg combined with ritonavir 100 mg once daily

Pharmacokinetic Parameter	DRV/rtv 800/100 mg q.d.		
mean ± SD, t_{max}: median (range)	Week 4 N = 9	Week 24 N = 13	Week 48 N = 10
C_{0h}, ng/mL	1826 ± 1003	1786 ± 838.0	2133 ± 1220
C_{24h}, ng/mL	1440 ± 513.9	1644 ± 726.9	1447 ± 705.7
C_{min}, ng/mL	1189 ± 409.6	1419 ± 671.0	1352 ± 687.8
C_{max}, ng/mL	5471 ± 1320	5804 ± 1558	6756 ± 1683
t_{max}, h	3.0 (1.0 – 4.1)	3.0 (0.9 – 4.0)	3.5 (0.8 – 6.0)
AUC_{24h}, ng.h/mL	64230 ± 18210	66950 ± 18610	75620 ± 26440
λ_z, 1/h*	0.0458 ± 0.0133	0.0438 ± 0.0184	0.0530 ± 0.0197
$t_{1/2\alpha}$, h*	16.8 ± 7.3	19.25 ± 9.59	15.03 ± 6.36
$C_{ss,av}$, ng/mL	2675 ± 757.5	2808 ± 766.9	3156 ± 1100
FI, %	166.6 ± 48.7	160.9 ± 39.4	185.3 ± 60.8

Table 10-Darunavir pharmacokinetic parameters derived using population pharmacokinetic analysis from the TMC114-C211 trial (week 48 report) with darunavir 800 mg combined with ritonavir 100 mg once daily

Parameter	Median (Range)
N	335
AUC_{24h}, ng.h/mL	87854 (45000; 219240)
C_{0h}, ng/mL	2041.2 (368.1; 7241.6)

N = number of subjects.

Population pharmacokinetic modeling and simulation was utilized to derive once daily darunavir/ritonavir dosing recommendations for HIV-1 infected subjects 3 to less than 12 years old. Please see the Pharmacometrics review in section 4 for details regarding the

population pharmacokinetic modeling and simulation. A dedicated pediatric trial evaluating once daily darunavir/ritonavir dosing in HIV-1 infected subjects 6 to less than 12 year olds was not conducted. However, as part of the TMC114-C228 trial that evaluated twice daily dosing in treatment experienced 3 to less than 12 year olds, a two week once daily subtrial was conducted. The pharmacokinetic data from this trial was included as part of the population pharmacokinetic modeling and simulation. The darunavir/ritonavir dosage regimen that was evaluated was 40 mg/kg of darunavir coadministered with approximately 7 mg/kg of ritonavir once daily for children weighing less than 15 kg, and darunavir/ritonavir 600 mg/100 mg once daily for children weighing 15 kg or greater. Detailed information about the subtrial is included in section 3 of this review.

Table 11 provides a summary of the predicted darunavir pharmacokinetic parameters that were derived using population pharmacokinetic analysis for various darunavir/ritonavir once daily dosage regimens for pediatric subjects in three different weight groups: 10 kg to less than 15 kg, 15 kg to less than 30 kg and 30 kg to less than 40 kg. The applicant provided predicted darunavir exposures for the approved darunavir/ritonavir twice daily dosage regimens and their proposed darunavir/ritonavir once daily dosage regimens (see Table 1 to Table 4) and the predicted darunavir exposures for alternative once daily dosage regimens were derived by the Pharmacometrics reviewer.

Additionally, Table 11 provides a comparison of the percentage differences for various pediatric darunavir/ritonavir once daily dosage regimens for the following:

A) Darunavir plasma exposures in treatment-naïve pediatric subjects in three different weight groups: 10 kg to less than 15 kg, 15 kg to less than 30 kg and 30 kg to less than 40 kg compared to darunavir/ritonavir 800 mg/100 mg once daily dosing in treatment-naive adults. The differences in darunavir exposures were evaluated to determine whether potential efficacy issues are anticipated for the various once daily pediatric dosage regimens.

B) Darunavir plasma exposures in treatment-naïve pediatric subjects in three different weight groups: 10 kg to less than 15 kg, 15 kg to less than 30 kg and 30 kg to less than 40 kg compared to the twice daily dosing recommendations in the darunavir U.S. prescribing information for the same weight group. The differences in darunavir exposures were evalauted to determine whether potential safety issues are anticipated for the various once daily pediatric dosage regimens.

For the revised darunavir/ritonavir once daily dosing recommendations that are outlined in Table 5 and Table 6, minimal differences in darunavir exposures are anticipated for the median C_{0h} and $AUC_{[0\text{-}24h]}$ when comparing the percentage differences to adults and the median $AUC_{[0\text{-}24h]}$ and C_{max} when comparing the percentage differences to twice daily dosing in the same weight group, in evaluating whether potential efficacy or safety issues are anticipated, respectively. Additonally, based on the available exposure-safety information for darunavir, no clinically significant safety issues are anticipated for the revised darunavir/ritonavir once daily dosing recommendations.

Table 11-Comparison of predicted darunavir exposures with once daily dosing in pediatric subjects weighing 10 to <40 kg compared to once daily dosing in treatment naïve adults (C_{0h} and $AUC_{[0-24h]}$) or with twice daily dosing in the same pediatric weight group ($AUC_{[0-24h]}$ and C_{max})

		Median C_{0h} (ng/mL)	% difference from adults	**Median $AUC_{(0-24h)}$ [mcg*hr/mL]**	% difference from adults	**Median $AUC_{(0-24h)}$ [mcg*hr/mL]**	% difference from BID exposure (same weight group)	**Median C_{max} (ng/mL)**	% difference from BID exposure (same weight group)
10 to less than 15 kg	30 mg/kg	2202	108	77.2	88	77.2	75	5692	102
	35 mg/kg	***2570***	***126***	***90***	***102***	***90***	***87***	***6641***	***120***
	40 mg/kg	2937	144	103	117	103	100	7590	137
15 to less than 30 kg	475 mg	1947	95	73.9	84	73.9	63	5545	89
	550 mg	2255	110	85.5	97	85.5	73	6420	103
	600 mg	***2460***	***121***	***93.3***	***106***	***93.3***	***80***	***7004***	***113***
30 to less than 40 kg	600 mg	1826	89	74.5	85	74.5	67	5642	95
	675 mg	***2084***	***102***	***83.8***	***95***	***83.8***	***75***	***6347***	***106***
	750 mg	2316	113	93.1	106	93.1	83	7052	118
	800 mg	2470	121	99.3	113	99.3	89	7522	126

Table 12-Predicted darunavir exposures in treatment naïve adults (TMC114-C211 trial) and in pediatric subjects with twice daily dosing (TMC114-C228 trial) based on the recommended dosage regimens in the darunavir U.S. prescribing information that were used as reference values for Table 11

	Median C_{0h} (ng/mL)	**Median $AUC_{(0-24h)}$ [mcg*hr/mL]**	**Median C_{max} (ng/mL)**
Adults	2041	87.9	6790*
10 to 15 kg	3270	103	5557
15 to < 30 kg	3547	117	6222
30 to < 40 kg	3329	112	5963

*derived using noncompartmental analysis (week 48 data)

The Office of Scientific Investigations was requested to conduct an inspection of (b) (4) the bioanalytical laboratory that analyzed the darunavir and ritonavir plasma samples for the TMC114-C228 once daily dosing subtrial and the TMC114-230 trials. Only the TMC114-230 trial was inspected. The request to inspect the TMC114-C228 once daily dosing subtrial was declined by the Office of Scientific Investigations. No 483 observations were issued for (b) (4). An inspection report was not available at the time the Clinical Pharmacology review was finalized.

The following results from the TMC114-C230 trial, the TMC114-C228 subtrial, and the population pharmacokinetic modeling and simulation support the proposed once daily darunavir/ritonavir dosage regimens in Table 5 and Table 6:

- In treatment naïve adolescents receiving darunavir/ritonavir 800 mg/100 mg once daily, based on a comparison of the population pharmacokinetic parameters, when compared to treatment naïve adults, the median $AUC_{(0\text{-}24h)}$ and C_{0h} was lower by 1% and higher by 9%, respectively. Based on a comparison of the noncompartmental pharmacokinetic parameters, the mean week 2 C_{max} in treatment naïve adolescents was lower by less than 1% versus the week 48 mean C_{max} in treatment naïve adults.

- In evaluating potential differences in efficacy, for the three weight bands (10 kg to less than 15 kg, 15 kg to less than 30 kg and 30 kg to less than 40 kg), when comparing the percentage differences to adults, the C_{0h} is anticipated to be higher by up to 26%. For the 10 kg to less than 15 kg and the 15 kg to less than 30 kg weight bands, the $AUC_{[0\text{-}24h]}$ is anticipated to be higher by up to 6% and lower by 5% in the 30 to less than 40 kg weight band.

- In evaluating potential differences in safety, for the three weight bands (10 kg to less than 15 kg, 15 kg to less than 30 kg and 30 kg to less than 40 kg), when comparing the percentage differences to the same weight group, the $AUC_{[0\text{-}24h]}$ is anticipated to be lower by up to 25% and the C_{max} is anticipated to be higher by up to 20%.

Based on the minimal differences in darunavir exposures that were either observed or predicted, the results support the conclusion that no clinically significant efficacy or safety issues related to darunavir exposures are anticipated for the revised darunavir/ritonavir once daily dosing recommendations for pediatric patients weighing 10 kg to less than 40 kg and for darunavir/ritonavir 800 mg/100 mg in adolescents for treatment naïve patients or patients with no darunavir resistance associated substitutions.

2 Labeling Recommendations

(b) (4)

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3 Appendices

3.1 Individual Trial Reviews

3.1.1 TMC114-C230 trial

1. Title

A Phase II, open-label trial, to evaluate pharmacokinetics, safety, tolerability and antiviral activity of darunavir/ritonavir once daily in treatment-naïve HIV-1 infected adolescents aged between 12 and < 18 years. Week-48 final analysis.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple clinical trial sites in France, Spain, Italy, the United Kingdom, the United States, and Ukraine from August 21, 2009 to March 31, 2011.

3. Objectives

The primary objective of the trial was to evaluate the pharmacokinetics and antiviral activity of darunavir when combined with ritonavir in HIV-1 infected pediatric subjects 12 to less than 18 years old.

4. Trial Design

TMC114-C230 was an open label clinical trial that enrolled HIV-1 infected pediatric subjects 12 to less than 18 years old weighing a minimum of 40 kg at screening. The trial design included enrolling male and female HIV-1 infected pediatric subjects that were naïve to antiretroviral treatment for HIV-1 infection with a HIV-1 viral load of 1000 copies/mL or higher. For the background regimen, either zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC), as fixed dose combination formulations or as individual formulations, was used.

5. Excluded Medications, Restrictions or Exceptions

Use of CYP 3A inducers was not permitted from 14 days from baseline until the end of the treatment period and CYP 3A substrates with a narrow therapeutic index were not permitted from baseline until the end of the treatment period.

6. Dosage and Administration

Subjects received 800 mg of darunavir with 100 mg of ritonavir once daily within 30 minutes after finishing a meal. There were no restrictions on the type of meal that could be administered.

7. Rationale for Doses Used in the Trial

The dosage regimen that was administered, darunavir/ritonavir 800 mg/100 mg once daily, is consistent with the recommended darunavir/ritonavir dosage regimen for treatment naïve adults or treatment experienced adults with no darunavir resistance associated substitutions.

8. Drugs Used in the Trial

Information regarding the darunvair formulation that was administered in the trial is displayed in Table 1. The darunavir 400 mg tablet formulation that was administered in the trial (F030) is the formulation that is marketed in the United States. The ritonavir capsules that were administered in the trial appear to be marketed in the European Union. However, based on information that was provided during the NDA review for the darunavir oral suspension (NDA 202895), there are no differences in either the composition or bioavailability of the U.S. and European marketed ritonavir capsules, tablets, and oral solution.

Table 1-Information on the darunavir formulation administered in the TMC114-C230 trial

Investigational Product	Batch Number
DRV 400 mg tablet (F030)	9AG8407 9EZ0100

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Darunavir and ritonavir blood samples were obtained at week 2 at predose and up to 24 hours postdose. At weeks 4, 24, and 48, two darunavir and ritonavir blood samples were obtained. When doses were administered in the morning, the first sample was collected prior to dose administration and the second sample was collected a minimum of one hour or later after the first blood sample. When doses were administered in the evening, the samples were collected a minimum of one hour apart.

Bioanalysis

The method and bioanalysis of darunavir and ritonavir are acceptable. Darunavir and ritonavir plasma samples were analyzed using a validated LC/MS/MS method in lithium heparin anticoagulated plasma by (b) (4) (a partial validation was later conducted and the calibration curve range for both darunavir and ritonavir was modified to include a lower limit of quantification of 5 ng/mL and the upper limit of quantification of 10000 ng/mL). The blood samples for analysis of darunavir and ritonavir were collected in tubes containing heparin as an anticoagulant but it appears that the

anticoagulant that was used was sodium heparin. However, an experiment that was conducted to determine whether there are any accuracy or precision issues with using different anticoagulants was conducted and no issues were identified.

For the TMC 114-C230 plasma samples that were analyzed for darunavir, the lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report, except for the low QC. For the TMC114-C230 trial, precision and accuracy were evaluated using plasma darunavir QC samples at three concentration levels: 15 ng/mL, 500 ng/mL, and 8000 ng/mL. The corresponding darunavir inter-run accuracy values were 0.7% for 15 ng/mL, -0.4% for 500 ng/mL, and -0.8% for 8000 ng/mL. The darunavir inter-run precision values were 4.6% for 15 ng/mL, 1.8% for 500 ng/mL, and 2.3% for 8000 ng/mL. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC114-C230 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at 15 ng/mL, 500 ng/mL, and 8000 ng/mL. The corresponding ritonavir inter-run accuracy values were -2% for 15 ng/mL, 0.4% for 500 ng/mL, and -1% for 8000 ng/mL. The ritonavir inter-run precision values were 2.2% for 15 ng/mL, 3.5% for 500 ng/mL, and 3.3% for 8000 ng/mL.

For the TMC114-C230 trial, the darunavir and ritonavir plasma samples were stored at the trial sites, (b) (4) and the bioanalytical laboratory (b) (4). At the clinical trial sites, samples were stored either at -20°C for a maximum of 12 days for the primary samples or at -80°C for a maximum of 2 days for the primary samples. At (b) (4), samples were stored at -20°C for a maximum of 366 days. At the bioanalytical laboratory, samples were stored at -20°C for a maximum of 33 days prior to analysis. The long term stability darunavir and ritonavir data of 1597 days at-20°C generated by (b) (4) and 163 days at both -20°C and -70°C generated by (b) (4) covers the duration of long term stability data necessary for the TMC114-C230 trial.

The FDA Office of Scientific Investigations (OSI) was requested to conduct an inspection of the bioanalytical laboratory that analyzed darunavir and ritonavir plasma samples for the TMC114-C230 trial. No 483 observations were issued for (b) (4). An inspection report was not available at the time the Clinical Pharmacology review was finalized.

Pharmacokinetic Assessments

At week 2, noncompartmental analysis was performed. For the noncompartmental analysis, darunavir and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, C_{0h}, C_{min}, and $AUC_{(0-24h)}$. For the population PK analysis, darunavir $AUC_{(0-24h)}$ and C_{0h} were derived. The population PK analysis was conducted using data up to week 24 and also up to week 48.

Statistical Analysis

For the noncompartmental analysis, descriptive statistics were calculated for darunavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values.

10. Results

10.1 Subject Demographics and Disposition

Table 2-TMC114-C230 subject demographics

Demographic Parameter	DRV/rtv 800/100 mg q.d.
Sex, n (%), N	**12**
Female	8 (66.7)
Male	4 (33.3)
Age (years) at Screening, N	**12**
Mean (SE)	14.6 (0.49)
Median (Range)	14.4 (13; 17)
Height, cm, N	**12**
Mean (SE)	158.4 (2.30)
Median (Range)	158.8 (144; 172)
Body Weight, kg, N	**12**
Mean (SE)	50.5 (2.12)
Median (Range)	50.5 (40; 62)
Body Mass Index, kg/m^2, N	**12**
Mean (SE)	20.1 (0.67)
Median (Range)	20.3 (16; 23)
Z-score for Height, N	**12**
Mean (SE)	-0.4 (0.33)
Median (Range)	-0.6 (-3; 2)
Z-score for Weight, N	**12**
Mean (SE)	-0.1 (0.19)
Median (Range)	0.0 (-1; 1)
Z-score for BMI, N	**12**
Mean (SE)	0.1 (0.20)
Median (Range)	-0.1 (-1; 1)
Race, n (%), N	**12**
Black or African American	5 (41.7)
White	7 (58.3)
Ethnicity, n (%), N	**12**
Hispanic or Latino	1 (8.3)
Not Hispanic nor Latino	11 (91.7)

N = number of subjects; n = number of observations

Table 3-Baseline HIV-1 infection information

Baseline Characteristic	DRV/rtv 800/100 mg q.d.
Log_{10} Viral Load (copies/mL), N	**12**
Mean (SE)	4.72 (0.172)
Median (Range)	4.92 (3.6; 5.5)
CD4+ Cell Count (x 10^6/L), N	**12**
Mean (SE)	316.9 (29.3)
Median (Range)	282.0 (204; 515)
Percentage CD4+, N	**12**
Mean (SE)	20.6 (2.53)
Median (Range)	18.30 (12.1; 40.8)
Baseline Viral Load, n (%), N	**12**
< 20 000 copies/mL	2 (16.7)
20 000 - < 100 000 copies/mL	5 (41.7)
≥ 100 000 copies/mL	5 (41.7)
Duration of HIV Infection (years), N	**12**
Mean (SE)	3.8 (1.35)
Median (Range)	1.7 (0; 13)
DRV FC, N	**12**
Mean	0.60
Median (Range)	0.60 (0.3; 1.2)
Clinical Stage of HIV Infection[31], n (%), N	**12**
Clinical Stage 1 (asymptomatic)	5 (41.7)
Clinical Stage 2 (mild symptoms)	6 (50.0)
Clinical Stage 3 (advanced symptoms)	1 (8.3)
Clinical Stage 4 (severe symptoms)	0
Hepatitis B or C Coinfection Status, n (%), N	**12**
Missing	4 (33.3)
Negative	7 (58.3)
Positive	1 (8.3)
Mode of HIV Infection, n (%), N	**12**
Blood transfusion	1 (8.3)
Heterosexual contact	3 (25.0)
Mother to child transmission	5 (41.7)
Other	3 (25.0)
Clade, n (%), N	**12**
A1	2 (16.7)
B	4 (33.3)
C	1 (8.3)
CRF01_AE	2 (16.7)
CRF02_AG	3 (25.0)

N = number of subjects; n = number of observations

10.2 Concomitant Medications

During the trial, for the antiretroviral background regimen, 6 subjects (50%) received zidovudine/lamivudine (AZT/3TC) and 6 subjects (50%) received abacavir/lamivudine (ABC/3TC). Information regarding the non antiretroviral medications that subjects received during the trial is displayed in Table 4. The concomitant medications that were administered in the trial are not anticipated to alter the trial's conclusions.

Table 4-Non antiretroviral medications administered during the trial by more than one subject

Class, n (%)	DRV/rtv 800/100 mg q.d. N = 12
Analgesics	4 (33.3)
Anti-acne preparations	2 (16.7)
Antianemic preparations	3 (25.0)
Antibacterials for systemic use	4 (33.3)
Antibiotics and chemotherapy for dermatologic use	4 (33.3)
Antiemetics and antinauseants	2 (16.7)
Cardiac therapy	2 (16.7)
Laxatives	2 (16.7)
Stomatological preparations	3 (25.0)
Vaccines	2 (16.7)
All other non-therapeutic products	2 (16.7)

N = number of subjects; n = number of observations

10.3 Pharmacokinetic and Statistical Analysis

Table 5-Darunavir pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with ritonavir 100 mg once daily

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	800/100 mg DRV/rtv q.d. + Background Regimen		
n	10[a]		
Week 2			
C_{0h}, ng/mL	2172	±	1096
C_{min}, ng/mL	1589	±	768.2
C_{max}, ng/mL	6721	±	1700
t_{max}, h	3.00 (1.00-6.00)		
AUC_{24h}, ng.h/mL	81880	±	26300
FI, %	158.1	±	46.86
CL/F, L/h	11.28	±	5.776

[a] n = 12 for C_{0h}, C_{max} and t_{max}

Table 6-Median darunavir pharmacokinetic parameters derived using population pharmacokinetic analysis up to week 48 with darunavir 800 mg combined with ritonavir 100 mg once daily

Parameter	AUC_{24h} (µg.h/mL)	C_{0h} (ng/mL)	CL/F (L/h)	$C_{ss, ave}$ (ng/mL)
N	12	12	12	12
Mean	84.4	2141	10.5	3516
SD	23.6	865	4.29	983
Geometric mean	80.7	1930	9.92	3364
CV (%)	28	40	41	28
Median	86.7	2234	9.23	3614
Min	35.5	542	6.49	1480
Max	123	3776	22.5	5139

10.4 Efficacy Analysis

The result of the Week 48 efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL was analyzed by the applicant using two methods: TLOVR and the FDA snapshot. An efficacy analysis was also conducted evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 400 copies/mL using TLOVR. The results are displayed in Tables 7, 8, and 9.

Table 7-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL using TLOVR up to Week 48

	DRV/rtv 800/100 mg q.d.	
Time point	N	n (%)
Week 2	12	0
Week 4	12	1 (8.3)
Week 8	12	3 (25.0)
Week 16	12	9 (75.0)
Week 24	12	11 (91.7)
Week 32	12	11 (91.7)
Week 40	12	10 (83.3)
Week 48	12	10 (83.3)

N = number of subjects; n = number of responders

Table 8-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL using FDA snapshot at week 48

Week 48[e]	
Virologic Success HIV RNA < 50 copies/mL at Week 48	11 (91.7)
Virologic Failure[b]	1 (8.3)[f]
No virologic data at Week 48 - Discontinued due to AE/death[c]	0
No virologic data at Week 48 – Discontinued for other reasons[d]	0

[b] Includes i) subjects who had ≥ 50 copies/mL in the 24/48-week window, ii) subjects who discontinued prior to Week 24/48 for lack or loss of efficacy, iii) subjects who had a switch in their background regimen that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of study medication), and iv) subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable).

[c] Includes subjects who discontinued due to AE or death at any time point from Day 1 through the 24/48-week time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceded by a switch in the background regimen that was not permitted by the protocol).

[d] Includes subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was undetectable).

[e] Visit window; Weeks 44 to 54.

[f] One subject ((b) (6) ID 230-0008) had HIV RNA ≥ 50 copies/mL at Week 48.

Table 9-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 400 copies/mL using TLOVR up to Week 48

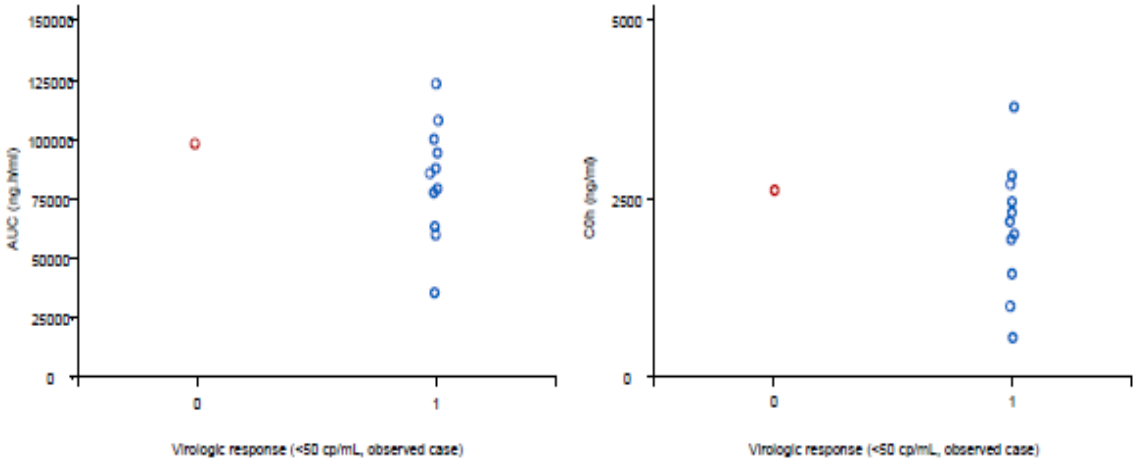
	DRV/rtv 800/100 mg q.d.	
Time Point	N	n (%)
Viral Load < 400 Copies/mL		
Week 2	12	5 (41.7)
Week 4	12	7 (58.3)
Week 8	12	11 (91.7)
Week 16	12	12 (100)
Week 24	12	12 (100)
Week 32	12	12 (100)
Week 40	12	11 (91.7)
Week 48	12	11 (91.7)

N = number of subjects; n = number of responders

10.5 Exposure-Response Analysis

No relationship was observed between the $AUC_{(0\text{-}24h)}$ or C_{0h} of darunavir and virologic response at week 48. Virologic response was defined as a decrease in HIV-1 RNA viral load to less than 50 copies/mL. The results of the exposure-response analysis are displayed in Figure 1.

Figure 1-Exposure response ($AUC_{[0-24h]}$ or C_{0h}) of darunavir compared to the virologic response [HIV-1 RNA viral load less than 50 copies/mL] at week 48)



0 = no virologic response; 1 = virologic response

10.6 Safety Analysis

A summary of the adverse event information for the TMC114-C230 trial is displayed in Table 10. Based on the information, no clinically relevant safety issues were identified for the trial.

Table 10-TMC114-C230 adverse event summary information

n (%)	DRV/rtv 800/100 mg q.d. N = 12
≥ 1 AE	11 (91.7)
≥ 1 grade 3 or 4 AE	3 (25.0)
≥ 1 AE at least possibly related to DRV	2 (16.7)
≥ 1 AE ≥ grade 2 at least possibly related to the DRV	1 (8.3)
≥ 1 SAE	4 (33.3)
AEs leading to discontinuation	0
Deaths	0

N = total number of subjects with data; n = number of observations

11. Discussion and Conclusions

Based on the results from the TMC114-C230 trial, the following conclusions can be made regarding the proposed darunavir/ritonavir pediatric dosage regimen of darunavir/ritonavir 800 mg/100 mg once daily administered with food:

- In adolescents receiving darunavir/ritonavir 800 mg/100 mg once daily, based on a comparison of the population pharmacokinetic parameters, when compared to treatment naïve adults in section 1.3, the median $AUC_{(0\text{-}24h)}$ and C_{0h} was lower by 1% and higher by 9%, respectively. Based on a comparison of the noncompartmental pharmacokinetic parameters, the mean week 2 C_{max} in treatment naïve adolescents was lower by less than 1% versus the week 48 mean C_{max} in treatment naïve adults.
- No clinically relevant exposure-response trends were identified for the trial.
- No clinically relevant safety issues were identified for the trial.

Based on the minimal differences in darunavir exposures that were observed, the results support the conclusion that no clinically relevant efficacy or safety issues related to darunavir expsoures are anticipated for darunavir/ritonavir 800 mg/100 mg once daily in adolescents that are treatment naïve or adolescents with no darunavir resistance associated substitutions.

3.1.2 TMC114-C228 subtrial

Reviewer note: The TMC114-C228 trial was previously reviewed-please see the Clinical Pharmacology review for NDA 202895 for full details of the trial.

1. Title

A substudy of TMC114-C228 to evaluate the pharmacokinetics of darunavir in combination with low-dose ritonavir (darunavir/ritonavir) after once daily dosing in children.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple clinical trial sites in Argentina, Brazil, India, Kenya, and South Africa from September 29, 2009 to August 3, 2010.

3. Objectives

The primary objective of the subtrial was to evaluate the pharmacokinetics and antiviral activity of darunavir when combined with ritonavir in HIV-1 infected pediatric subjects 3 to less than 6 years old with once daily dosing.

4. Trial Design

The TMC114-C228 subtrial enrolled HIV-1 infected pediatric subjects 3 to less than 6 years old weighing between 10 kg and less than 20 kg. Subjects received two weeks of once daily darunavir dosing prior to switching back to twice daily dosing. A minimum of six pediatric subjects were targeted for enrollment in the subtrial. The subtrial was initiated after week 32 of the main trial.

5. Dosage and Administration

Subjects received darunavir 40 mg/kg with ritonavir 7 mg/kg once daily for pediatric subjects weighing less than 15 kg and darunavir/ritonavir 600 mg/100 mg once daily for children weighing at least 15 kg. The doses were administered using darunavir oral suspension and ritonavir oral solution. The actual doses of darunavir/ritonavir that were administered are displayed in Table 1.

Table 1-Once daily doses of darunavir/ritonavir administered to pediatric subjects weighing between 10 kg and less than 20 kg

	DRV		rtv Dose	
Body Weight (kg)	DRV dose (mg q.d.)	Total mL DRV/day	rtv Dose (mg q.d.)	Total mL rtv/day
10 - 10.9	400	4.0	66	0.8
11 - 11.9	440	4.4	72	0.8
12 - 12.9	480	4.8	76	1.0
13 - 13.9	520	5.2	86	1.0
14 - 14.9	560	5.6	92	1.2
15 - 19.9	600	6.0	100	1.2

[a] The DRV oral suspension was administered with a pipette with a 0.8-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band (e.g. subjects in the weight bands 14 - 14.9 kg and 15 -15.9 kg received actually 96 mg rtv q.d.).

[b] The information in Table 1 was provided to the investigators in a separate communication. Note that the total mL rtv solution was rounded to 0.8, 1.0 or 1.2 mL and therefore the actual administered rtv doses are approximations of the calculated rtv doses shown in Table 1.

7. Rationale for Doses Used in the Trial

The dosage regimens of darunavir 40 mg/kg with ritonavir 7 mg/kg once daily for pediatric subjects weighing less than 15 kg and darunavir/ritonavir 600 mg/100 mg once daily for children weighing at least 15 kg were derived using a population pharmacokinetic model. However, the derived dosage regimens were based on simulations that contained an error: the simulations did not include a relative bioavailability factor.

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Darunavir and ritonavir blood samples were obtained at week 2 according to the schedule displayed in Table 2.

Table 2-Week 2 darunavir and ritonavir pharmacokinetic blood sampling schedule

Day	Time (hour) [a]	Blood Sample DRV/rtv	Blood Sample Safety	AE Check + Concomitant Medication [b]	Other
14	Predose	X[c]	X[c,d]	X	Standardized breakfast[e]
	0				DRV/rtv intake in the unit during or within 30 minutes after the standardized breakfast
	1	X			
	3	X			
					Lunch[e]
	6	X			
	12	X			Dinner[e]
15	24	X[c]		X	Breakfast
					Resume b.i.d. dosing regimen[f]

[a] Hospitalization from Day 14 to the morning of Day 15 was recommended to facilitate the pharmacokinetic sampling.
[b] AEs and concomitant medication were monitored on an ongoing basis from signing the ICF onwards until the last study-related visit.
[c] Within 15 minutes before drug intake.
[d] See Time and Events Schedule in Table 3 for details about laboratory safety assessments.
[e] Breakfast, lunch and dinner at Day 14 of DRV/rtv q.d. dosing had to be standardized for all subjects at a specific site (see Food And Nutrition Technical Assistance [FANTA] guidance[11]). Snacks were allowed during the stay in the day clinic/hospital.
[f] On Day 15 subjects resumed their b.i.d. dosing regimen based on body weight as indicated in the protocol of the main study.

Bioanalysis

The darunavir and ritonavir plasma samples for the once daily subtrial were analyzed at the same time as the plasma samples for twice daily dosing in the main trial. Please see the Clinical Pharmacology review for NDA 202895 for information regarding the bioanalysis of the TMC 114-C228 darunavir and ritonavir plasma samples. At the clinical trial sites, samples were stored at -20°C for a maximum of 11 days for the primary samples and at -70°C for a maximum of 7 days for the primary samples. At (b) (4), samples were stored at -20°C for a maximum of 221 days. At the bioanalytical laboratory, samples were stored at -20°C for a maximum of 71 days prior to analysis. The long term stability darunavir and ritonavir data of 1597 days at -20°C generated by (b) (4) and 163 days at both -20°C and -70°C generated by (b) (4) covers the duration of long term stability data necessary for the TMC114-C230 trial.

The FDA Office of Scientific Investigations (OSI) was requested to conduct an inspection of the bioanalytical laboratory that analyzed darunavir and ritonavir plasma samples for the TMC114-C228 trial because the bioanalysis of the darunavir and ritonavir plasma samples from the once daily subtrial was not inspected as part of the bioanalytical inspection for twice daily dosing in the main trial. However, the inspection request was declined by OSI.

Pharmacokinetic Assessments

At week 2, both population pharmacokinetic (PK) and noncompartmental analysis was

performed. For the population PK analysis, the parameters that wee derived included darunavir $AUC_{(0\text{-}12h)}$ and C_{0h}. For the noncompartmental analysis, darunavir and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, C_{0h}, C_{min}, and $AUC_{(0\text{-}24h)}$.

Statistical Analysis

For the noncompartmental analysis, descriptive statistics were calculated for darunavir and ritonavir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values.

10. Results

10.1 Pharmacokinetic and Statistical Analysis

Table 3-Darunavir pharmacokinetic parameters derived using noncompartmental analysis

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**Weight-Based DRV/rtv q.d. Dosing + Background Regimen**		
n	10[a]		
C_{0h}, ng/mL	3670	±	1313
C_{min}, ng/mL	2063	±	1226
C_{max}, ng/mL	10640	±	2881
t_{max}, h	2.92 (0.93 - 11.57)		
AUC_{24h}, ng.h/mL	113900	±	43540
FI, %	203.0	±	110.8
CL/F, L/h	5.741	±	1.835

[a] n = 9 for AUC_{24h} and CL/F

Table 4-Median darunavir pharmacokinetic parameters derived using population pharmacokinetic analysis

Parameter	AUC_{24h} (µg.h/mL)	C_{0h} (ng/mL)	CL/F (L/h)
N	10	10	10
Mean	120	3371	5.39
Geometric mean	115	3029	5.12
SD	40.6	1715	1.69
SE	12.8	542	0.53

Table 5-Statistical analysis of darunavir pharmacokinetic parameters derived using noncompartmental analysis for once daily dosing in pediatric subjects 3 to less than 6 years old compared to treatment naïve adults

Parameter	LS means: TMC114-C211sub: 800/100 mg DRV/rtv q.d. + Background Regimen (TDF/FTC) in Treatment-Naïve HIV-1 Infected Adults[10] (Reference, n = 9)	LS means: TMC114-C228sub: Weight-Based DRV/rtv q.d. Dosing + Background Regimen in Treatment-Experienced HIV-1 Infected Children From 3 to < 6 Years (Test, n = 10)	LS means Ratio	90% CI[b]
C_{min}, ng/mL	1222	1624	1.329	0.7606 - 2.322
C_{max}, ng/mL	5650	10250	1.814	1.443 - 2.280
AUC_{24h}, ng.h/mL[a]	66330	107700	1.623	1.214 - 2.171

[a] n = 9 for for test
[b] 90% CI
TDF: tenofovir disoproxil fumarate
FTC: emtricitabine

10.4 Efficacy Analysis

All subjects that enrolled in the subtrial maintained undetectable HIV-1 RNA viral load (less than 50 copies/mL) after two weeks of darunavir/ritonavir once daily dosing.

11. Discussion and Conclusions

Based on a comparison of the noncompartmental pharmacokinetic parameters, the Cmin, Cmax and $AUC_{(0-24h)}$ were higher by 33%, 81% and 62%, in pediatric subjects 3 to less than 6 years old compared to treatment naïve adults. Appropriate pediatric once daily darunavir/ritonavir dosing recommendations for pediatric patients weighing 10 kg to less than 20 kg were further evaluated as part of the pharmacokinetic modeling and simulation.

For pediatric patients 3 to less than 6 years old, the following once daily dosage regimens are proposed based on on the analyses that were conducted for the review and dicussions with the applicant: darunavir 40 mg/kg with ritonavir 7 mg/kg once daily for pediatric patients weighing 10 kg to less than 15 kg and darunavir 600 mg with ritonavir 100 mg once daily for pediatric patients weighing 15 kg to less than 20 kg,

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 21976/S-28 and S29 & NDA 202895/S-5 and S-6
Submission Number (Date)	3 Aug 2012
Drug Name	Darunavir Once Daily
Proposed Indication	Treatment of HIV-1 infection in pediatric subjects 3 to 18 years old
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 determine whether the proposed once daily dosing regimen for darunavir(DRV)/ritonavir(RTV) in pediatric subjects 3 to < 18 years of age (Table 1, bolded in the right column) is acceptable.

Table 1: Comparison of the approved b.i.d. and proposed q.d. dosing regimen for DRV for pediatric subjects 3 to < 18 years of age

Weight category	DRV b.i.d. regimen*	DRV q.d. regimen
10 to <15 kg	20 mg/kg	(b) (4)
15 to <30 kg	375 mg	**600 mg**
30 to <40 kg	450 mg	**800 mg**
40 kg onward	600 mg	**800 mg**
Adult*	600 mg	800 mg

* Approved.

The review will focus on the following sub-questions.

1.1.1 Does the proposed 800/100 mg DRV/RTV q.d. dosing regimen for adolescents (> 40 kg) have adequate safety support and achieve similar exposures to that of adults receiving the approved 800/100 mg DRV/RTV q.d. dosing regimen?

Yes. The sponsor conducted a clinical trial, study TMC114-C230, using the 800/100 mg DRV/RTV once daily dosing regimen for treatment-naïve HIV-1 infected adolescents weighing > 40 kg. The safety data from the trial supported the proposed dosing regimen. Based on the Week 24 analysis, the geometric mean of individual median DRV AUC_{24h} at steady state in adolescents was 77.8 µg.h/mL, which represents 86.7% of the target geometric mean exposure in treatment-naïve adults from study TMC114-C211 (89.7 µg.h/mL). The geometric mean of individual median DRV trough concentration (C_{0h}) in adolescents was 1819 ng/mL which is also comparable to the 2027 ng/mL in adults from study TMC114-C211. The mean C_{max} of Week 2 measurements in adolescents based on the non-compartment analysis is also comparable to that in adults from study TMC114-C211 (Table 2).

The Week-48 results of study TMC114-C230 were consistent with the Week-24 analyses, where the geometric mean of individual median DRV AUC_{24h} was 80.7 µg.h/mL (90.0% of the target geometric mean exposure in adults).

Table 2: Comparison of DRV exposures in pediatrics at the proposed once daily dosing regimens to those in adults at the approved 800 mg daily dose

Subjects	Parameter	AUCtau (µg.h/mL)	C0h (ng/mL)	Cmax* (ng/mL)
C230** 12-18 yo >40 kg	N	12	12	10
	Mean (SD)	81.9 (25.1)	2041 (910)	6721 (1700)
	Median	87.9	2196	
	Geometric mean	**77.8**	**1819**	
C228 3-6 yo 10-20 kg	N	10	10	10
	Mean (SD)	120 (40.6)	3371 (1715)	10636 (2881)
	Median	107	2981	
	Geometric mean	**115**	**3029**	
Adult	N	335	335	10
	Mean (SD)	93.0 (27.0)	2281 (1168)	6756 (1683)
	Median	87.9	2041	
	Geometric mean	**89.7 (71.8, 117)**	**2027**	

* Based on the NCA

** Study TMC114-C230 was based on Week 24 analysis

1.1.2 Do the proposed DRV q.d. dosing regimens for pediatric subjects (< 40 kg) have adequate safety support and achieve similar exposures to that of adults receiving the approved 800/100 mg DRV/RTV q.d. dosing regimens?

No. An adequate safety trial has not been conducted in pediatric subjects 3 to < 12 years of age (< 40 kg) with the once daily dosing regimens. The safety decision has to rely on the safety data in pediatric subjects 3 to < 12 years of age with the b.i.d. dosing regimens. Therefore, the following considerations need to be taken into account for PK comparison:

- For efficacy, the expected C_{0h} and AUC_{24h} in pediatric patients with q.d. dosing should most closely match C_{0h} and AUC_{24h} values observed in adults receiving DRV/RTV 800mg/100mg q.d. regimen.
- For safety, the expected AUC_{24h}, and C_{max} in pediatric patients with q.d. dosing should not significantly exceed AUC_{24h}, and C_{max} observed in pediatric patients receiving the approved b.i.d. regimens.

Based on the observed data from Study C228 (Table 2), the geometric mean of DRV AUC_{24h} at the steady state in pediatrics 3 to 6 years of age was 115 µg.h/mL, which represents 128% of the target geometric mean exposure in treatment-naïve adults (89.7 µg.h/mL). The mean C_{max} in pediatric subjects 3 to 6 years of age weighing 10 to 20 kg based on the non-compartment analysis is 157% of the mean C_{max} in adults from study TMC114-C211. Comparison the exposure between q.d. and b.i.d. dosing regimens based on PK simulation indicates that C_{max} values in pediatric patients with the proposed q.d. regimens are 137%, 113% and 126% of those in pediatrics with the approved b.i.d. regimens weighing 10 to 15 kg, 15 to 30 kg, and 30 to 40 kg respectively (

Table 3). Because there is limited or no safety data at these higher C_{max} values in the pediatric population, we therefore propose revised q.d. regimens as red-highlighted in Table 3 based on the following reason:

35 mg/kg DRV for subjects weighing 10 to < 15 kg

- There is a possible under exposure of a DRV dose of 30 mg/kg, especially when the subject is close to 10 kg.
- At the 35 mg/kg dose, the expected median DRV AUC_{24h} , C_{0h} and C_{max} are 90 μg.h/mL, 2570 ng/mL and 6641 ng/mL, respectively, which are comparable to those of adults at the approved 800 mg q.d. regimen. In a previous study TMC114-C228, the safety profile with the DRV/RTV 25/3 mg/kg b.i.d. regimen (25% higher DRV exposure compared to the approved 20 mg/kg b.i.d. regimen) for children weighing 10 to15 kg was shown to be acceptable. Therefore, the 20% higher C_{max} with the revised 35 mg/kg q.d. regimen in children weighing 10 to 15 kg compared to that with the approved 20 mg/kg b.i.d. regimen can be justified with the acceptable safety data from DRV/RTV 25/3 mg/kg b.i.d. regimen.

600 mg DRV for subjects weighing 15 to < 30 kg

- Both the 550 mg and 600 mg are expected to produce appropriate pharmacokinetic exposures with the 600 mg dose of DRV producing <10% higher values relative to the 550 mg dose; this difference is within the known inter- and intra-subject pharmacokinetic variability.
- The expected median DRV AUC_{24h}, C_{0h}, and C_{max} are 129 μg.h/mL, 4087 ng/mL and 6947 ng/mL, respectively for children weighing 10 to <15 kg with the DRV/RTV 25/3 mg/kg b.i.d. regimen. These values are higher or comparable to those in children weighing 15 to < 30 kg with the 600 mg DRV q.d. regimen. Although the DRV/RTV 25/3 mg/kg b.i.d. regimen was for subjects weighing 10 to <15 kg, the acceptable safety and tolerability at this regimen still provide additional confidence of the 600 mg DRV dose for children weighing 15 to <30 kg.
- In addition, a DRV dose of 600 mg is considered more convenient for several reasons: 1) a 600-mg tablet is available for patients who can swallow; 2) for patients unable to swallow the tablet(s), a DRV oral suspension (100-mg/mL) is available– the accompanying pipette however is demarked with 0.2 mL gradations thus accurate dosing of 550 mg (i.e. 5.5 mL) may be difficult for some caregivers; 3) outside the United States, many countries in the developing world follow the US Prescribing Information dosing recommendation along with the WHO List of Prequalified Medicinal Products – currently the 75-, 150- and 600-mg darunavir tablets, but not the 400-mg tablet, are on the WHO List of Prequalified Medicinal Products; this may make dosing of 550 mg unavailable in such countries.

675 mg DRV for subjects weighing 30 to < 40 kg

- At the 675 mg dose, the expected median DRV AUC_{24h} , C_{0h} and C_{max} are comparable to those of adults at the approved 800 mg q.d. regimen.
- For safety, the expected AUC_{24h}, and C_{max} with the 675 mg q.d. dosing regimen do not exceed the AUC_{24h}, and C_{max} in subjects receiving the approved 450 mg b.i.d. regimens.

Table 3: Comparison of the expected PK exposures for different regimens per weight group. The bold text corresponds to sponsor's proposed q.d. regimens. The blue text corresponds to the approved b.i.d regimens. The red text corresponds to our recommended q.d. regimens.

Weight Category	Dose	Median C_{0h} (5_{th}-95_{th} percentile) ng/mL	Median AUC_{24h} (5_{th}-95_{th} percentile) µg.h/mL	Median C_{max} (5_{th}-95_{th} percentile) ng/mL
10 to15 kg	30 mg/kg q.d.	2202 (1337 – 4002)	77.2 (52.0 – 125)	5692 (4529 – 7885)
	35 mg/kg q.d.	2570 (1560 – 4669)	90 (60.6 – 146)	6641 (5284 – 9199)
	(b) (4)			
	20 mg/kg b.i.d.	3270 (2035 – 5772)	103 (69.3 – 167)	5557 (4135 – 8234)
15 to 30 kg	475 mg q.d.	1947 (1049 – 4028)	73.9 (50.0 – 129)	5545 (4145 – 8224)
	550 mg q.d.	2255 (1214 – 4664)	85.5 (55.6 – 149)	6420 (4800 – 9522)
	600 mg q.d.	**2460 (1325 – 5088)**	**93.3 (60.6 – 163)**	**7004 (5236 – 10388)**
	375 mg b.i.d.	3547 (2028 – 6944)	117 (75.7 – 203)	6222 (4335 – 10066)
30 to 40 kg	600 mg q.d.	1826 (1056 – 3556)	74.5 (51.2 – 120)	5642 (4455 – 7904)
	675 mg q.d.	2084 (1190 – 4000)	83.8 (57.6 – 135)	6347 (5012 – 8892)
	750 mg q.d.	2316 (1322 – 4445)	93.1 (64.0 – 150)	7052 (5569 – 9880)
	(b) (4)			
	450 mg b.i.d.	3329 (2018 – 6021)	112 (76.8 – 180)	5963 (4397 – 8932)
40 kg onward	**800 mg q.d.**	**1920 (1031 – 3948)**	**81.1 (53.8 – 137)**	**6066 (4615 – 8785)**
	600 mg b.i.d.	3599 (2100 – 6831)	122 (80.7 – 205)	6426 (4559 – 10120)
Adult (TMC114-C211)	800 mg q.d.	2041 (911 – 4632)	87.9 (60.5 – 143)	6756 (1683)*

* Mean (SD) based on the NCA

1.2 Recommendations

The following revised dosing q.d. regimens of DRV/RTV in treatment-naïve HIV-1 infected pediatric subjects 3 to < 12 years of age are recommended:

35 mg/kg DRV/7 mg/kg RTV once daily for pediatric subjects weighing 10 to < 15 kg

600 mg DRV/ 100 mg RTV once daily for pediatric subjects weighing 15 to < 30 kg

675 mg DRV/ 100 mg RTV once daily for pediatric subjects weighing 30 to < 40 kg

800 mg DRV/ 100 mg RTV once daily for pediatric subjects weighing 40 kg onward

2 PERTINENT REGULATORY BACKGROUND

Darunavir (DRV), a HIV protease inhibitor (PI), in combination with low-dose ritonavir (RTV) is currently approved by the FDA for the use in treatment-experienced adults and pediatric subjects aged 3 to < 18 years old as a twice-daily regimen. The once-daily regimen is also approved for use in treatment-naïve adults.

The current submission is to fulfill the Pediatric Written Request for PREZISTA® (DRV) once-daily regimen in HIV-1 infected pediatric subjects aged 3 to < 18 years who are treatment-naïve or treatment-experienced with no DRV resistance-associated mutations. This is based on data from the Phase II study TMC114-C230 in treatment-naïve pediatric subjects aged 12 to < 18 years, a 2-week q.d. substudy of the Phase II study TMC114-C228 in treatment-experienced pediatric subjects aged 3 to < 6 years, results from model-based pharmacokinetic simulations and parameter estimations, and safety data from pediatric clinical studies, along with the data in adults which supported the use of the DRV/rtv q.d. regimen in the adult population (Phase III studies TMC114-C211 and TMC114- C229).

3 SPONSOR'S POPULATION PK ANALYSIS

The sponsor conducted a population pharmacokinetic analysis based on the previously developed model in adults and treatment-experienced pediatric subjects to incorporate new PK data from pediatric subjects with q.d. regimens (Study TMC114-C230 in adolescents as well as the PK substudy of TMC114-C228 in children 3 to 6 years of age, Table 4). The updated model is consistent with the previous models. DRV PK simulations based on the current model were performed to explore different q.d. regimens in each weight group.

Table 4. Summary of Data Included in Model Adjustment

Item	Trial 1	Trial 2		Trial 3	Trials 4 & 5
Trial	TMC114-C230	TMC114-C228 q.d. sub-study	TMC114-C228 b.i.d.	TMC114-C212	TMC125-C206/C216
No. of subjects	12	10	24	41	30
Dose of DRV/rtv	800/100 mg q.d.	40/6.66 mg/kg q.d. for subjects <15 kg 600/100 mg q.d. for subjects ≥15 kg	20/3 mg/kg b.i.d.	300-600/50-100 mg b.i.d.	600/100 mg b.i.d.
Age range (years)	12 - 17	3 - 5	3 - 5	6 - 17	18 - 66
Darunavir formulation(s)	400 mg tablets (F030)	100 mg/mL suspension (F052)	100 mg/mL suspension (F052)	75-mg tablets (F027) 300-mg tablets (F016)	300-mg tablets (F016)
Ritonavir formulation(s)	100 mg capsules	80 mg/mL solution	80 mg/mL solution	80 mg/mL solution	100 mg capsules
Number of samples per subject	6	6	5	5	8
DRV assay LLOQ	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL
rtv assay LLOQ	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL
Time range	0-24 h	0-24 h	0-12 h	0-12 h	0-12 h

Source: Sponsor's tmc114-c230 popPK Week 24 report, Table 2, page 12

Note: For twice daily dosing in the TMC114-C228 trial, the number of subjects included in the analysis is 19 subjects and not 24 subjects.

For details and reviews of model development in adults and older children, please refer to the pharmacometric review of NDA 21-976 by Christine Garnett and NDA 21-976 S009 by Kevin Krudys. Briefly, the model was a two compartment model with the first-order absorption and apparent clearance dependent on AAG concentrations assuming a linear binding and total daily dose. Clearance was described as:

$$CL/F_i = \frac{CL_{int}/F \cdot \left(\frac{1}{1+K_{AFF}\cdot AAG_i}\right)\cdot\left(\frac{WT_i}{70}\right)^{\theta}\cdot e^{\eta_i}}{F_{rel}}$$

Where CL/F_i is the apparent oral clearance of an individual, CL_{int}/F the population estimate of apparent intrinsic clearance, K_{AFF} is the population estimate for the affinity of DRV to α_1-acid glycoprotein (AAG), θ is the influence of the individual weight at baseline (WT_i) on apparent clearance and η_i is the individual random effect. F_{rel} is the population estimate of the relative bioavailability correction for the commercial tablet formulation (F_{rel}=1.18) compared to the clinical trial tablet formulation as determined in the original model in adults.

Final parameter estimates are provided in Table 5. The goodness of fit plots and visual predictive check provided by the sponsor suggest a sufficient model fit and an adequate predictive ability.

Table 5. Pharmacokinetic Parameter Estimates of the Final Adjusted Model

Parameter	Parameter Estimate	Parameter SEE (CV%)	IIV Estimate (CV%)	IIV SEE (CV%)
CL_{int}/F (L/h)	51.0	4.7	28	20
Influence of WT[a] on CL/F	0.504	11		
K_{AFF} of AAG (dL/mg)	0.0304	---		
V2/F (L)	137	21		
Influence of WT[a] on V2/F	0.774	18		
Q/F (L/h)	19.1	16	64	59
V3/F (L)	254	41		
KA (1/h)	0.528	17	50	66
F_{rel}	1.18	---		
Multiplicative residual error	0.0717	12		

a: change in parameter based on body weight (WT)

Source: Sponsor's tmc114-c230 popPK Week 48 report, Table 3, page 7

Reviewer's Comments: The sponsor's population PK analyses are acceptable and are consistent with previous conclusions in adults and children with b.i.d. regimens. Using the population PK model, the typical DRV exposures at steady-state with the dosing regimens in Table 3 were simulated for individuals weighing from 10 to 65 kg and with an AAG concentration value of successively 5th, 50th, and 95th percentile of the AAG concentrations observed in TMC114-C228 and TMC114-C230 trials.

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/s/

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