OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202895	Submission Date: March 30, 2011
NDA: 21976 (SDN 201, S-20)	Submission Date: June 28, 2011
Brand Name	Prezista®
Generic Name	Darunavir
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
Clinical Pharmacology Team Leader	Sarah Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Tibotec, Inc.
Formulation; strength(s) to-be-marketed	Darunavir oral suspension (100 mg/mL)
Currently marketed formulations	Darunavir tablets; 75 mg, 150 mg, 400 mg, 600 mg
Proposed darunavir suspension dosage regimens coadministered with ritonavir solution	Twice daily dosing with food: (b) (4)
Proposed Indication for the Application	Treatment of HIV-1 infection in pediatric patients 3 to less than 6 years old
Review Type(s)	New Drug Application for darunavir suspension formulation, priority review (NDA 202895) Labeling supplement (NDA 21976, SDN 201)

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1 Executive Summary

This review summarizes the clinical pharmacology results for two trials evaluating darunavir oral suspension formulations. Darunavir, an inhibitor of the HIV-1 protease when coadministered with ritonavir, another HIV-1 protease inhibitor, is approved for the treatment of HIV-1 infection. In treatment naive patients 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 recommended dosing for HIV-1 infected children 6 to less than 18 years old that weigh at least 20 kg using darunavir tablets is displayed in Table 1 below. For the current submission that extends dosing to pediatric patients weighing at least 10 kg using the darunavir oral suspension, the proposed dosage regimens are (b) (4)

Table 1-Current darunavir/ritonavir dosing recommendations for HIV-1 infected children 6 to less than 18 years old weighing at least 20 kg (administered with food)

Body Weight		Dose
(kg)	(lbs)	
≥ 20 kg – < 30 kg	≥ 44 lbs – < 66 lbs	375 mg PREZISTA/50 mg ritonavir twice daily
≥ 30 kg – < 40 kg	≥ 66 lbs – < 88 lbs	450 mg PREZISTA/60 mg ritonavir twice daily
≥ 40 kg	≥ 88 lbs	600 mg PREZISTA/100 mg ritonavir twice daily

Note: In Table 1, darunavir tablets are coadministered with ritonavir capsules, tablets, or oral solution

A New Drug Application for the darunavir oral suspension (NDA 202895) was submitted by the applicant to complete the fulfillment of postmarketing study commitments for deferred pediatric studies as required by the Pediatric Research Equity Act (PREA). In addition, a labeling supplement was submitted under the NDA for darunavir tablets (NDA 21976) that included the same proposed changes to the U.S. darunavir prescribing information that were submitted for NDA 202895.

Two trials were submitted as part of the New Drug Application for the darunavir oral suspension. The first trial (TMC114-C169) was a bioequivalence trial comparing a darunavir oral suspension formulation to darunavir tablets in healthy adult subjects. The trial evaluated an experimental darunavir oral suspension that was linked to the darunavir suspension formulation that is proposed for marketing in the United States through a biowaiver. Because the applicant proposed to permit darunavir tablet dosing in HIV-1

infected pediatric patients 15 kg to 20 kg and darunavir suspension dosing in HIV-1 infected adults and children who are not able to swallow darunavir tablets in the proposed revisions to the darunavir U.S. prescribing information, and no other clinical trial data is currently available to support these labeling changes, the TMC114-C169 trial was a pivotal bioequivalence trial. Based on the clinical trial site inspection, the Office of Scientific Investigations recommended that the results of the trial should not be accepted. While a 483 observation was not issued, the recommendation was made because the TMC114-C169 trial did not store reserve samples for the test and reference drug products. The applicant did not retain reserve samples because they did not view the TMC114-C169 trial as a pivotal bioequivalence trial. However, the Office of Clinical Pharmacology determined that it was acceptable to review the pharmacokinetic data from the multiple dosing portion of the TMC114-C169 trial. The inclusion of the additional adult and pediatric dosing recommendations in Tables 3, 4, and 5 as part of the U.S prescribing information for darunavir is supported by the following information:

1) In adults receiving 600 mg darunavir coadministered with ritonavir 100 mg twice daily with food, when the multiple dosing darunavir suspension $AUC_{(0\text{-}12h)}$ value of 58550 ng*hr/mL was compared to historical data for multiple dosing darunavir tablet $AUC_{(0\text{-}12h)}$ values of 46250 ng*hr/mL, 44750 ng*hr/mL, 52310 ng*hr/mL, and 46720 ng*hr/mL from the TMC125-C139 (darunavir-etravirine), TMC114-C123 (darunavir-didanosine), TMC114-C172 (darunavir-carbamazepine), and TMC114-C163 (darunavir-rifabutin) drug-drug interaction trials, the darunavir suspension $AUC_{(0\text{-}12h)}$ was higher by 27%, 31%, 12%, and 25%, respectively. The multiple dosing darunavir tablet values are derived from administration of darunavir/ritonavir by itself.

2) In adults receiving 600 mg darunavir coadministered with ritonavir 100 mg twice daily with food, when the multiple dosing darunavir suspension C_{max} value of 7390 ng/mL was compared to historical data for multiple dosing darunavir tablet C_{max} values of 5460 ng/mL, 5908 ng/mL, 6262 ng/mL, and 5874 ng/mL from the TMC125-C139 (darunavir-etravirine), TMC114-C123 (darunavir-didanosine), TMC114-C172 (darunavir-carbamazepine), and TMC114-C163 (darunavir-rifabutin) drug-drug interaction trials, the darunavir suspension C_{max} was higher by 35%, 25%, 18%, and 26%, respectively. The multiple dosing darunavir tablet values are derived from administration of darunavir/ritonavir by itself.

3) In HIV-1 infected adults, the higher multiple dosing darunavir suspension $AUC_{(0\text{-}12h)}$ and C_{max} values compared to historical data for multiple dosing darunavir tablet $AUC_{(0\text{-}12h)}$ and C_{max} values are not anticipated to result in clinically significant safety or efficacy issues based on the darunavir exposure-response and exposure-safety data.

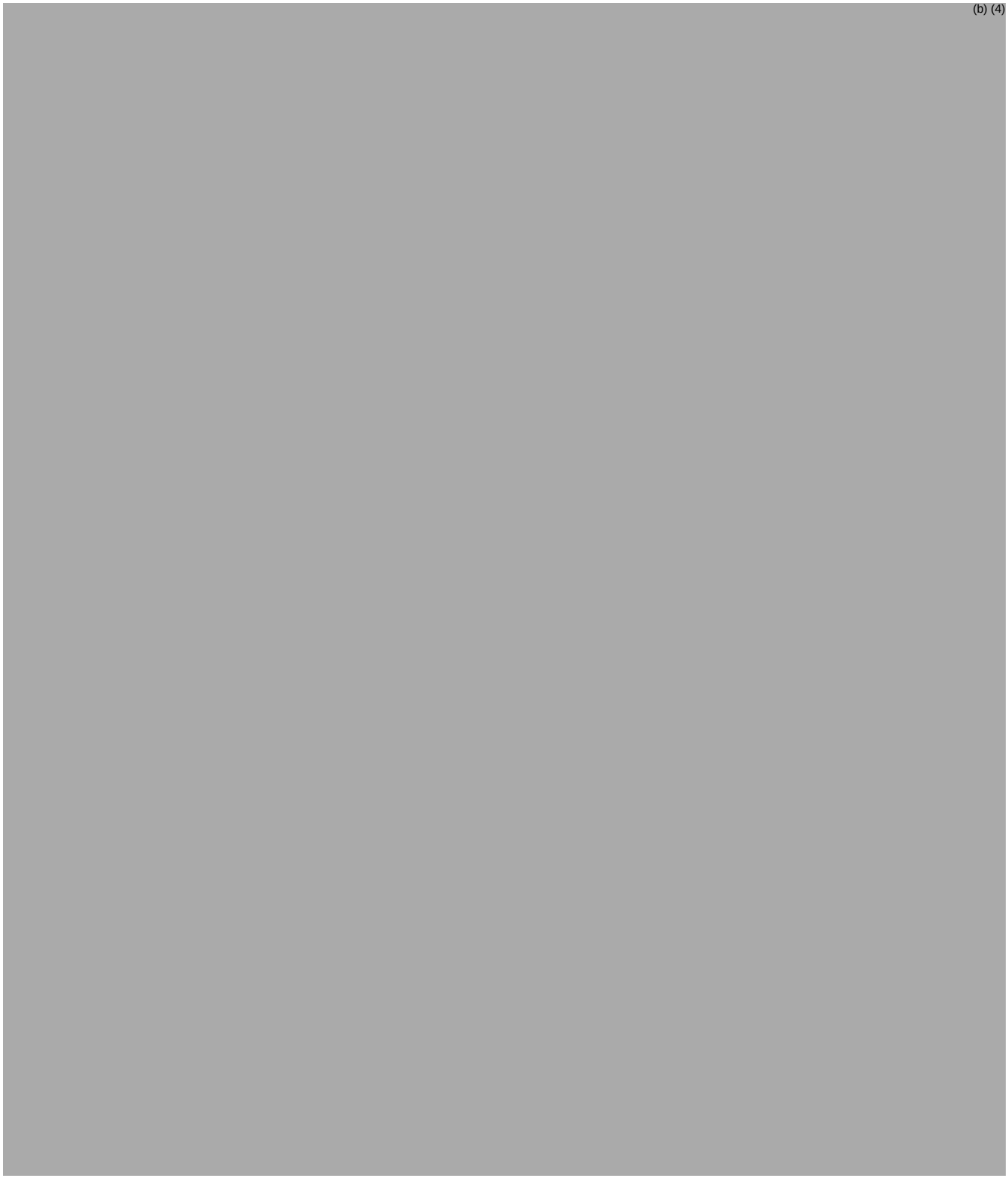
4) In HIV-1 infected pediatric patients, there is no pharmacokinetic data available comparing the darunavir suspension to darunavir tablets in the same weight group. However, the Office of Clinical Pharmacology determined that it was acceptable to apply the results of the multiple dosing analysis in adults to include the pediatric dosing recommendations in Tables 3 and 4 as part of the U.S prescribing information for darunavir. These dosing recommendations are based on the approved dosing recommendation using darunavir tablets with the assumption that the bioavailability of the darunavir suspension is similar to the darunavir tablets within each weight range for which a dosing recommendation exists. Additionally, potential differences in the

ritonavir boosting effects of ritonavir capsules or tablets versus ritonavir solution and the lack of dose proportionality (less than dose proportional increases are observed for darunavir from 400 mg twice daily to 600 mg twice daily) are expected to have a minimal impact based on the darunavir exposure-response and exposure-safety data. The Pharmacometrics review (see section 4) provides additional discussion on this issue.

The second trial (TMC114-C228) evaluated the pharmacokinetics and antiviral activity of twice daily dosage regimens of darunavir administered in combination with ritonavir for the treatment of HIV-1 infection in pediatric subjects 3 to less than 6 years old weighing 10 to less than 20 kg using the darunavir suspension formulation (F052) that is proposed for marketing in the United States.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application. Specifically, the application supports the use of darunavir oral suspension for the treatment of HIV-1 infection in pediatric patients weighing 10 kg to less than 20 kg with the dosage regimens displayed in Table 2 and the additional dosing recommendations for pediatric patients and adults in Tables 3, 4 and 5.



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-C228 trial enrolled HIV-1 infected pediatric subjects 3 to less than 6 years old weighing 10 kg to less than 20 kg at screening. The pediatric subjects that were enrolled were receiving a stable but failing antiretroviral treatment regimen (HIV-1 viral load >1000 copies/mL) that required a modification and had less than three darunavir associated substitutions. For the background regimen, it was recommended that investigators select a minimum of two HIV-1 antiretroviral medications. The initial dosing using a darunavir oral suspension (F052) in combination with ritonavir oral solution is displayed in Table 6 below. The initial dosing regimen was approximately 20 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily.

Table 6-Initial dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

	DRV		rtv	
Body Weight (kg)	Dose of Oral Suspension in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])	Dose of Oral Solution in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])
10 - 10.9	2.0	200 (18.3 - 20.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.2	220 (18.5 - 20.0)	0.4	32 (2.7 - 2.9)
12 - 12.9	2.4	240 (18.6 - 20.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	2.6	260 (18.7 - 20.0)	0.5	48 (3.5 - 3.7)
14 - 14.9	2.8	280 (18.8 - 20.0)	0.6	48 (3.2 - 3.4)
15 - 15.9	3.0	300 (18.9 - 20.0)	0.6	48 (3.0 - 3.2)
16 - 16.9	3.2	320 (18.9 - 20.0)	0.6	48 (2.8 - 3.0)
17 - 17.9	3.4	340 (19.0 - 20.0)	0.6	48 (2.7 - 2.8)
18 - 18.9	3.6	360 (19.0 - 20.0)	0.6	48 (2.5 - 2.7)
19 - 19.9	3.8	380 (19.1 - 20.0)	0.6	48 (2.4 - 2.5)

[a] The DRV oral suspension was administered with a pipette with a 0.2-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.
[b] The actual dose in mg/kg varied given the dose was fixed for each weight band.

After the Week 2 pharmacokinetic data was analyzed using population pharmacokinetic analysis, the applicant determined that a dose adjustment for darunavir was required. The Week 2 population PK parameters are displayed in Table 7.

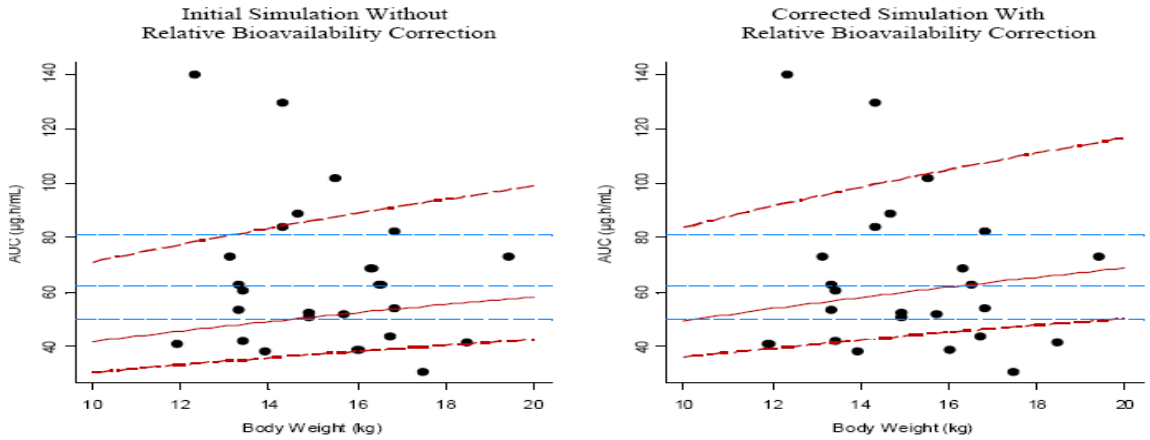
Table 7-Population pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

Weight group	N	Geometric Mean	Mean	SD	5th Percentile	Median	95th Percentile
AUC_{12h} (µg.h/mL)							
All subjects	24	60.7	65.4	27.8	38.8	57.6	125
10 - < 15 kg	13	65.0	70.7	32.3	40.2	61.0	133
15 - < 20 kg	11	56.0	59.3	21.0	35.3	54.2	91.9
C_{0h} (ng/mL)							
All subjects	24	3433	3927	2188	1662	3460	8779
10 - < 15 kg	13	3680	4289	2621	1950	3533	9411
15 - < 20 kg	11	3164	3500	1583	1607	3387	5897

While the $AUC_{(0\text{-}12h)}$ data in Table 4 indicates that the darunavir exposure for both the 10 kg to less than 15 kg and the 15 kg to less than 20 kg groups were within 80% to 130% of the target $AUC_{(0\text{-}12h)}$ of 62.3 µg*hr/mL, the applicant's rationale for increasing the darunavir dose was based on the simulations. The simulations are presented in Figure 1.

The simulations that were conducted did not include a relative bioavailability factor for the difference in darunavir bioavailability for the Phase 2 and the marketed tablet. The applicant repeated the simulations with the relative bioavailability factor included.

Figure 1-Predicted darunavir exposure for 3 to less than 6 year olds receiving darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily



Expected DRV AUC_{12h} for the 5th, 50th and 95th percentile of AAG are presented in red; 80%, 100%, and 130% of the mean adult target exposure are presented in blue; the model-based estimates after 2 weeks treatment are presented as black dots.

The simulations suggested the exposure with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily was low compared to the target exposure range and lower darunavir exposure with lower body weights was also observed in the simulations. When the applicant repeated the simulations with the relative bioavailability factor included, it was concluded that the rationale for adjusting the darunavir dose was still valid (see Figure 1).

The adjusted dosage regimens are displayed in Table 8. The adjusted dosage regimens were approximately 25 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily for pediatric subjects weighing between 10 kg to less than 15 kg and 375 mg of darunavir combined with approximately 50 mg of ritonavir administered twice daily for pediatric subjects weighing between 15 kg to less than 20 kg.

Table 8-Adjusted dosing of darunavir oral suspension in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])	Dose of Oral Solution in mL b.i.d.[b]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])
10 - 10.9	2.6	260 (23.8 - 26.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.8	280 (23.5 - 25.5)	0.4	32 (2.7 - 2.9)
12 - 12.9	3.0	300 (23.3 - 25.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	3.4	340 (24.5 - 26.1)	0.5	40 (2.9 - 3.1)
14 - 14.9	3.6	360 (24.2 - 25.7)	0.6	48 (3.2 - 3.4)
15 - 19.9	3.8	380	0.6	48

[a] The DRV oral suspension was administered with a pipette with a 0.2-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.
[b] The actual dose in mg/kg varied given the dose was fixed for each weight band.

Subsequent to the dosage adjustment, the population PK analysis was repeated two weeks after dosage adjustment. It was concluded that the trial could proceed using the adjusted darunavir dosage regimens. The data is presented in the individual trial review for TMC114-C228 (see section 3). Comparative results of the mean darunavir $AUC_{(0\text{-}12h)}$ values with the initial and adjusted darunavir dosage regimens to the mean target adult exposure of 62.3 µg/mL*hr in adults are presented in Table 9 below.

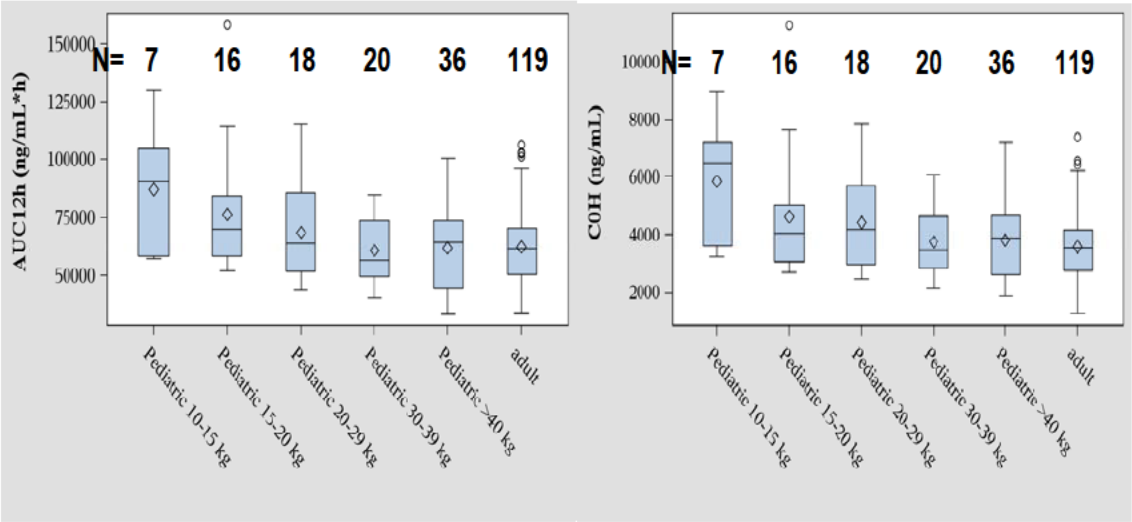
Table 9-Comparison of the mean darunavir $AUC_{(0\text{-}12h)}$ values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

For the initial darunavir dosage regimens (before dosage adjustment), the darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0\text{-}12h)}$ for pediatric subjects weighing 10 kg to < 15 kg or 15 kg to < 20 kg. After the darunavir dosage regimens were adjusted, the darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0\text{-}12h)}$ for pediatric subjects weighing 15 kg to < 20 kg but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg. The 40% higher $AUC_{(0\text{-}12h)}$ for pediatric subjects weighing 10 kg to < 15 kg compared to the target adult exposure is not expected to result in any safety issues based on the exposure-safety information for darunavir.

A comparison of the darunavir exposure after dosage adjustment for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults is displayed in Figure 2.

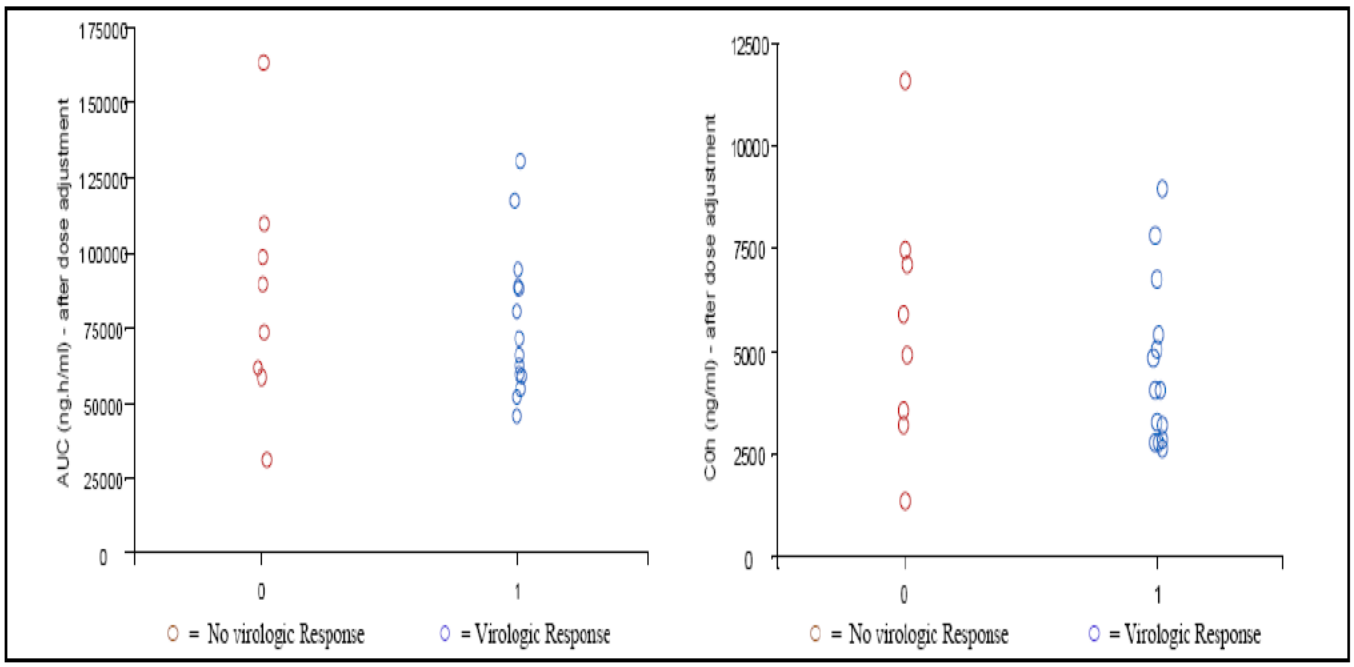
Figure 2-Darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} after dosage adjustment in 3 to < 6 year olds (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults



The comparison of the darunavir exposure after dosage adjustment for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults indicates that the range of $AUC_{(0\text{-}24h)}$ and C_{0h} values were generally similar with the exception of the 10 kg to <15 kg group.

The exposure response analysis conducted by the applicant compared the range of darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} values (for the adjusted darunavir dosage regimens) for subjects achieving virologic response to subjects that did not achieve virologic response (HIV-1 RNA less than 50 copies/mL (see Figure 3).

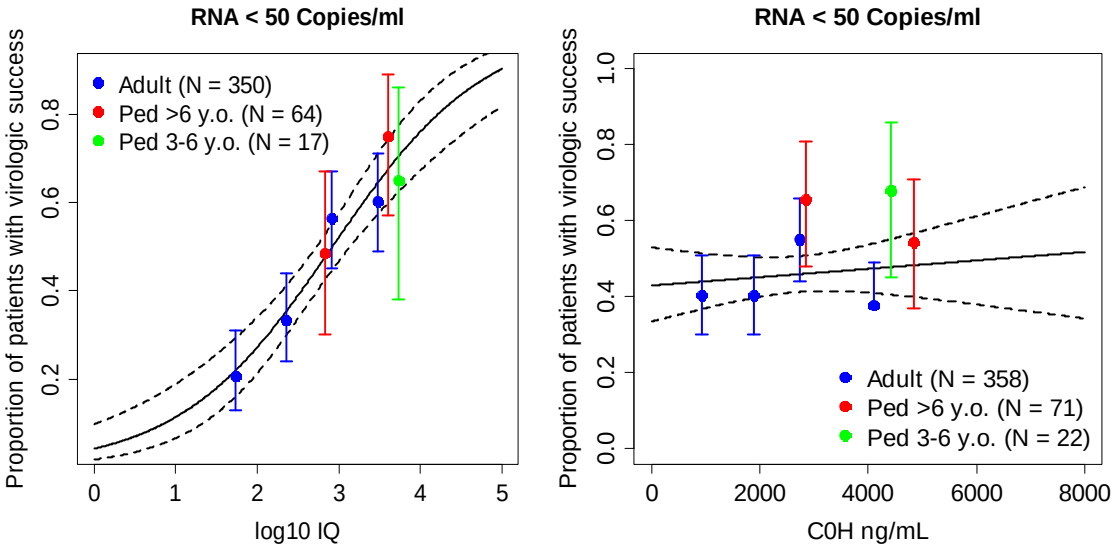
Figure 3-Comparison of $AUC_{(0\text{-}12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Based on the results displayed in Figure 3, the range of darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} values were similar for the two groups.

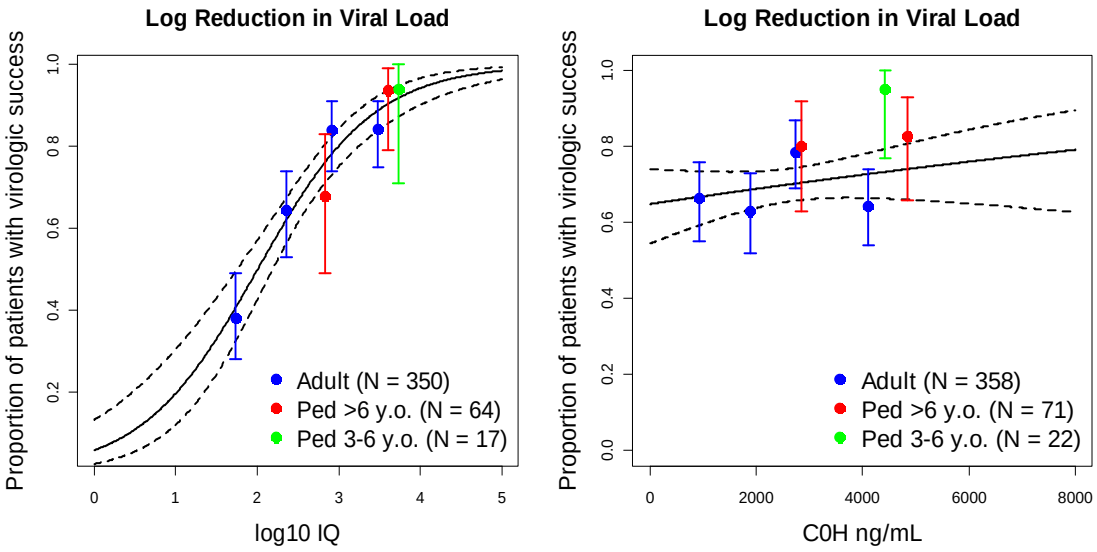
The Pharmacometrics reviewer conducted additional darunavir exposure-response analyses. The additional analyses evaluated the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL and IQ and the proportion of subjects achieving a one log reduction in viral load. For the analyses that was conducted for the review, the IQ was defined as the ratio of the darunavir C_{0h} (exposure) values after dosage adjustment at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus). In addition, the analysis was compared to the results that were previously obtained in older pediatric subjects (6 to less than 18 years old) and adults. The results are displayed in Figures 4 and 5.

Figure 4-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset.

Figure 5-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (one log reduction in viral load)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset.

The data for pediatric subjects 3 to less than 6 years old were not broken down into multiple groups and therefore the relationship between the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL or IQ and a one log reduction in viral load could not be evaluated. In Figures 4 and 5, each vertical bar in the plots represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset. For pediatric subjects 3 to less than 6 years old, the vertical bar was generally consistent with the vertical bars from older pediatric subjects (6 to less than 18 years old) and adults.

Based on the conclusion that the reported adverse events for the trial did not warrant further exposure response analysis, there were no additional exposure-safety analyses that were conducted by the FDA for pediatric subjects 3 to less than 6 years old. No relevant trends were identified for the exposure safety analyses that were conducted by the applicant.

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 trial. The results are discussed in the individual trial review (see section 3).

The following conclusions from the TMC114-C228 trial support the proposed darunavir/ritonavir doses in Table 2:

- The darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean

adult $AUC_{(0\text{-}12h)}$ of 62.3 µg*hr/mL for pediatric subjects weighing 15 kg to < 20 kg (22% higher) but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg (the 40% higher exposure is not expected to result in any safety issues).

- When compared to 6 to <18 years olds (20 kg to > 40 kg) and adults, the darunavir $AUC_{(0\text{-}24h)}$ and C_{0h} values for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg), were generally similar with the exception of the 10 kg to <15 kg group.
- When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} values were similar.
- When the proportion of subjects with virologic success (<50 copies/mL or one log reduction in viral load) at the median value (log_{10} IQ ratio or darunavir C_{0h}) were evaluated, the results for pediatric subjects 3 to < 6 years old were generally consistent with the previous results from older pediatric subjects (6 to less than 18 years old) and adults.

2 Labeling Recommendations

The labeling changes below as of September 2011 include the proposed revisions for relevant clinical pharmacology sections of the darunavir/ritonavir U.S. prescribing information.

Section 2-Dosage and Administration

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

3 Appendices

3.1 Individual Trial Reviews

3.1.1 TMC114-C169 trial

Reviewer note: the Office of Clinical Pharmacology did not accept the results from the TMC114-C169 trial pertaining to the bioequivalence analysis comparing darunavir suspension to darunavir tablets based on the recommendation from the Office of Scientific Investigations that the results of the TMC114-C169 trial should not be accepted-see section 9 (Bioanalysis) for further details.

1. Title

A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir

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

The trial was conducted at Kendle International B.V., Clinical Pharmacology unit, Bolognalaan 40, 3584 CJ Utrecht, the Netherlands from April 15, 2008 to August 18, 2008.

3. Objectives

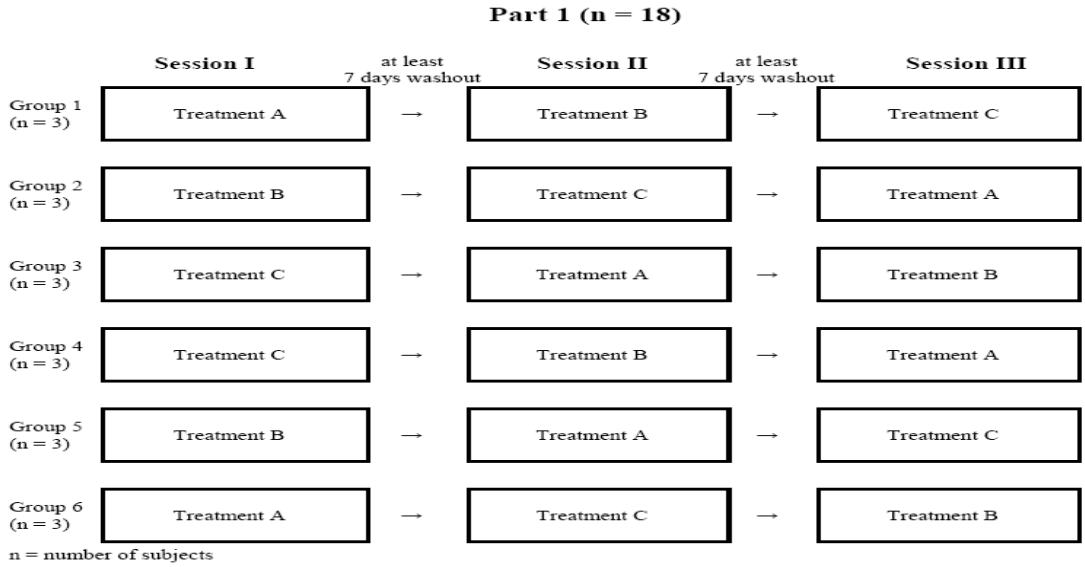
The primary objectives of the trial were to evaluate the single dose bioavailability under fed or fasted conditions of a darunavir suspension formulation (F051) coadministered with ritonavir capsules compared to a darunavir tablet formulation under fed conditions and to evaluate the single dose bioavailability of a darunavir suspension formulation (F051) under fed and fasted conditions. In addition, the multiple dosing pharmacokinetics of the darunavir suspension formulation was to be evaluated either under fasted or fed conditions.

4. Trial Design

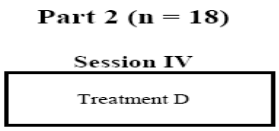
TMC114-C169 was a Phase I open label, randomized, crossover clinical trial that enrolled healthy male and female subjects between 18 and 55 years old. The washout period was a minimum of 7 days after each dose of darunavir/ritonavir was administered. The trial design is displayed in Figure 1. The trial was divided into two parts. In Part 1, the pharmacokinetics of single doses of the darunavir oral suspension or darunavir tablets combined with ritonavir capsules under fed conditions was evaluated. In Part 2, the pharmacokinetics of multiple doses of the darunavir oral suspension coadministered with ritonavir capsules under fasted or fed conditions was evaluated. The treatments that were

administered are listed in Table 1 and the treatment sequences are displayed in Table 2.

Figure 1-TMC114-C169 trial design



Results from Part 1 were evaluated before the start of Part 2 of the trial.



Preferably, the subjects participating in Part 1 of the trial were the same as those in Part 2, but additional subjects could be entered in case of dropout.

Table 1-Treatments administered for the TMC114-C169 trial

Part	Number of subjects	Treatment	Volume
1	18	**Treatment A:** **DRV:** single dose of 600 mg on Day 3 (fed) **Ritonavir:** 100 mg b.i.d. on Days 1-5	2 tablets of F016 (DRV eq. 300 mg/tablet) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
1	18	**Treatment B:** **DRV:** single dose of 600 mg on Day 3 (fasted) **Ritonavir:** 100 mg b.i.d. on Days 1-5	6 mL of suspension F051 (DRV eq. 100 mg/mL) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
1	18	**Treatment C:** **DRV:** single dose of 600 mg on Day 3 (fed) **Ritonavir:** 100 mg b.i.d. on Days 1-5	6 mL of suspension F051 (DRV eq. 100 mg/mL) 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)
2	18	**Treatment D:** **DRV:** 600 mg b.i.d. on Days 1-6 and a 600 mg morning dose on Day 7 (fed)[a] **Ritonavir:** 100 mg b.i.d. on Days 1-9	6 mL of suspension F051 per intake (DRV eq. 100 mg/mL)[a] 1 capsule of ritonavir (Norvir®) per intake (ritonavir eq. 100 mg/capsule)

[a] DRV dose, volume of suspension per intake and food recommendations for DRV/rtv intake for Part 2 (Treatment D) were determined based on the results of Part 1 (Treatments A, B and C) of the trial.

Table 2-Treatment sequences for the TMC114-C169 trial

Number of subjects	Treatment sequence
3	ABC
3	BCA
3	CAB
3	CBA
3	BAC
3	ACB

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of acetaminophen, hormone replacement therapy, and hormonal contraceptives was permitted during the trial. All other medications, including nonprescription and natural medicines, were to be discontinued a minimum of 14 days before the first dose of trial medication.

Other restrictions during the trial included prohibiting the use of beverages containing alcohol or quinine from 24 hours before the first dose of trial medication until the collection of the last pharmacokinetic (PK) blood sample in each session. In both Parts 1 and 2, grapefruit and grapefruit juice was prohibited from 7 days before the first dose of trial medication until the collection of the last pharmacokinetic (PK) blood sample in either Part 1 or 2.

In the event of an adverse event, the following medications were permitted:
A) Rash or an allergic reaction: cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents (specific medications were not included in the trial report)
B) Nausea: antiemetics (specific medications were not included in the trial report)
C) Diarrhea: loperamide

6. Dosage and Administration

When darunavir was administered as a suspension, the dose was administered in a bottle that was shaken extensively and then rinsed with water that the subject had to drink.

In Part 1, for treatments A and C, ritonavir was administered within ten minutes after completing a meal, and on Day 3, darunavir was administered within 5 minutes after ritonavir. For treatment B, ritonavir was administered within ten minutes after completing a meal, except on Day 3 when both darunavir and ritonavir were administered under fasted conditions and darunavir was administered within 5 minutes after ritonavir. For treatments A, B, and C, subjects fasted overnight for a minimum of ten hours for Day 3 dosing. Additionally, with the exception of water (e.g. 200 mL) that was administered with a dose, water was not permitted from 2 hours before to 2 hours after darunavir/ritonavir administration.

In Part 2, ritonavir was administered within ten minutes after completing a meal. When darunavir was combined with ritonavir, darunavir was administered within 5 minutes

after ritonavir. Subjects fasted overnight for a minimum of ten hours for Day 7 dosing. Additionally, with the exception of water (e.g. 200 mL) that was administered with a dose, water was not permitted from 2 hours before to 2 hours after darunavir/ritonavir administration.

When darunavir/ritonavir was administered with food in both Parts 1 and 2, in response to an information request, the applicant clarified that the meal provided approximately 21 grams of fat (189 kcal), 67 grams of carbohydrates (268 kcal), and 19 grams of protein (76 kcal), and in total, the meal provided approximately 533 kcal.

7. Rationale for Doses Used in the Trial

Currently, twice daily dosing with food of darunavir 600 mg coadministered with ritonavir 100 mg, is the currently approved treatment regimen for treatment experienced adult patients with at least one darunavir resistance associated substitution.

8. Drugs Used in the Trial

The darunavir suspension that was administered in the trial (F051) is an experimental darunavir suspension formulation. A different darunavir suspension formulation (F052) is proposed for marketing in the United States. However, the Office of New Drug Quality Assessment (ONDQA) determined that based on the results of the TMC114-C169 trial, the use of the F052 formulation in the pediatric 3 to < 6 years old clinical trial (TMC114-C228), and the in vitro dissolution results comparing the F051 and F052 darunavir suspension formulations, a comparison of the bioavailability of the two formulations in a clinical trial was not necessary and therefore, a biowaiver could be granted (please refer to the biopharmaceutics review for IND 62477, supporting document number 1247).

The darunavir 300 mg tablets (F016) that were administered in the trial are no longer commercially marketed in the United States. However, based on the results from a clinical trial (TMC114-C162), the 300 mg tablets (F016) administered as two 300 mg tablets are bioequivalent under fasted conditions to the currently U.S. marketed 600 mg tablets (F032) [please refer to the Clinical Pharmacology review for NDA 21-976, supporting document number 40]. In addition, ONDQA has approved biowaivers for the other U.S. marketed darunavir tablet strengths: 75 mg (F029), 150 mg (F050), and 400 mg (F030).

Ritonavir capsules were administered in the trial. The trial does not reflect the clinical use of ritonavir oral solution with darunavir oral suspension. In addition, the ritonavir capsules that were administered are the European marketed ritonavir capsules. The applicant states that based on information provided by Abbott Laboratories (the manufacturer of ritonavir capsules, tablets, and oral solution) there are no differences in either the composition or bioavailability of the U.S. and European marketed ritonavir capsules, tablets, and oral solution. The inhibitory effects of ritonavir on darunavir exposure have not been directly compared for ritonavir capsules (or ritonavir tablets)

versus ritonavir oral solution. However, the differences in ritonavir bioavailability between the different ritonavir formulations are not expected to result in any clinically significant differences in darunavir exposure when coadministered with ritonavir capsules, tablets or oral solution.

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

Sample Collection

In Part 1, ritonavir blood samples were obtained on Day 1 (within 2 hours of administration of trial medication) and darunavir and ritonavir blood samples were obtained on Day 3 at predose and up to 12 hours postdose, and at 24, 48, and 72 hours postdose on Days 4, 5, and 6, respectively. In Part 2, darunavir and ritonavir blood samples were obtained on Day 1, 5, 6, and 7 immediately prior to administration of trial medication, on Day 7 at predose and up to 12 hours postdose, and at 24, 48, and 72 hours postdose on Days 8, 9, and 10, respectively.

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) . The blood samples for analysis of darunavir and ritonavir were collected in tubes containing lithium heparin as an anticoagulant. For darunavir, the lower limit of quantification 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. For the TMC114-C169 trial, precision and accuracy were evaluated using plasma darunavir QC samples at three concentration levels: 13.6 ng/mL, 240 ng/mL, and 7680 ng/mL. The corresponding darunavir inter-run accuracy values were 0% for 13.6 ng/mL, -4.6% for 240 ng/mL, and -7.7% for 7680 ng/mL. The darunavir inter-run precision values were 6.5% for 13.6 ng/mL, 6.4% for 240 ng/mL, and 5.7% for 7680 ng/mL. For ritonavir, the lower limit of quantification 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-C169 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at three concentration levels: 13.6 ng/mL, 240 ng/mL, and 7680 ng/mL. The corresponding ritonavir inter-run accuracy values were 1.5% for 13.6 ng/mL, -2.9% for 240 ng/mL, and -3.4% for 7680 ng/mL. The ritonavir inter-run precision values were 7% for 13.6 ng/mL, 4.6% for 240 ng/mL, and 5.1% for 7680 ng/mL.

For the TMC114-C169 trial, the darunavir and ritonavir plasma samples were stored at -20°C at both at the clinical trial site and at the bioanalytical laboratory. The long term stability darunavir and ritonavir data of 1597 days covers the duration of long term stability data necessary for the TMC114-C169 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 and the clinical trial site for the TMC114-C169 trial. The clinical trial site is currently not operated by Kendle. There was one 483 observation issued to the bioanalytical laboratory [redacted] (b) (4) The 483 observation was issued because of the failure to use fresh calibration standards during the 5 day reinjection stability experiment during method validation. The experiment was repeated and the submitted data was acceptable. For the clinical trial site inspection, the Office of Scientific Investigations recommended that the results of the trial should not be accepted. While a 483 observation was not issued, the recommendation was made because reserve samples were not stored for the test and reference drug products. The applicant did not retain reserve sample because they did not view the TMC114-C169 trial as a pivotal bioequivalence trial. However, because the applicant proposed to permit darunavir tablet dosing in HIV-1 infected pediatric patients 15 kg to 20 kg and darunavir suspension dosing in HIV-1 infected adults and children who are not able to swallow darunavir tablets in the proposed revisions to the darunavir U.S. prescribing information, and no other clinical trial data is currently available to support these labeling changes, the TMC114-C169 trial is a pivotal bioequivalence trial. The Office of Clinical Pharmacology subsequently determined that it was acceptable to review the pharmacokinetic data from the multiple dosing portion of the TMC114-C169 trial and include the pediatric and adult dosing recommendations that are displayed in section 1, Tables 3, 4, and 5.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate darunavir and ritonavir plasma pharmacokinetic parameters. In Part 1, on Day 3, the pharmacokinetic parameters that were derived included C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ for darunavir, and C_{max}, C_{0h}, C_{min}, and $AUC_{(0\text{-}12h)}$ for ritonavir. In Part 2, on Day 7, the pharmacokinetic parameters that were derived included C_{max}, C_{0h}, C_{min}, and $AUC_{(0\text{-}12h)}$ for both darunavir and ritonavir. If a major difference (> 10.00% deviation from the scheduled time) was observed for a subject during a specific treatment arm, the actual sampling time was used instead of the scheduled sampling time.

Statistical 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 in both Parts 1 and 2.

In Part 1, the statistical analysis for darunavir involved the following comparisons for the log transformed C_{max}, $AUC_{0\text{-}inf)}$, and $AUC_{0\text{-}inf)}$ parameters: a) treatment B (test arm) to treatment A (reference arm), b) treatment C (test arm) to treatment A (reference arm), and c) treatment C (test arm) to treatment B (reference arm). Using a linear mixed effects model, least squares means were calculated and 90% confidence intervals were derived.

For the 90% confidence interval, the applicant did not provide a predefined range (lower and upper limit) for achieving bioequivalence in exposure for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. For the purposes of this review, 90% confidence interval limits of 80%-125% will be used as the criteria for achieving bioequivalence in exposure.

In Part 1, for ritonavir, the predose concentrations on Days 3, 4, 5, and 6 were graphically evaluated to determine if steady state for ritonavir was achieved by Day 3.

In Part 2, for a darunavir/ritonavir 600 mg/100 mg twice daily dosage regimen, the darunavir and ritonavir multiple dose pharmacokinetic parameters for the suspension were compared to historical data for darunavir and ritonavir multiple dose pharmacokinetic parameters for the 300 mg tablet formulation (F016). The historical data was from the following clinical trials: TMC114-C123, TMC114-C163, and TMC114-C171. For ritonavir, the predose concentrations on Days 5, 6, 7, 8, 9, and 10 were graphically evaluated to determine if steady state for ritonavir was achieved by Day 7. For darunavir, the predose concentrations on Days 5, 6, and 7, were graphically evaluated to determine if steady state for ritonavir was achieved by Day 7.

10. Results

Reviewer note: The results section will not discuss the ritonavir single or multiple dose pharmacokinetic data or the comparison of the darunavir exposure under fasted conditions with the darunavir suspension (test arm) to the darunavir exposure under fed conditions with darunavir tablets (reference arm).

10.1 Subject Demographics and Disposition

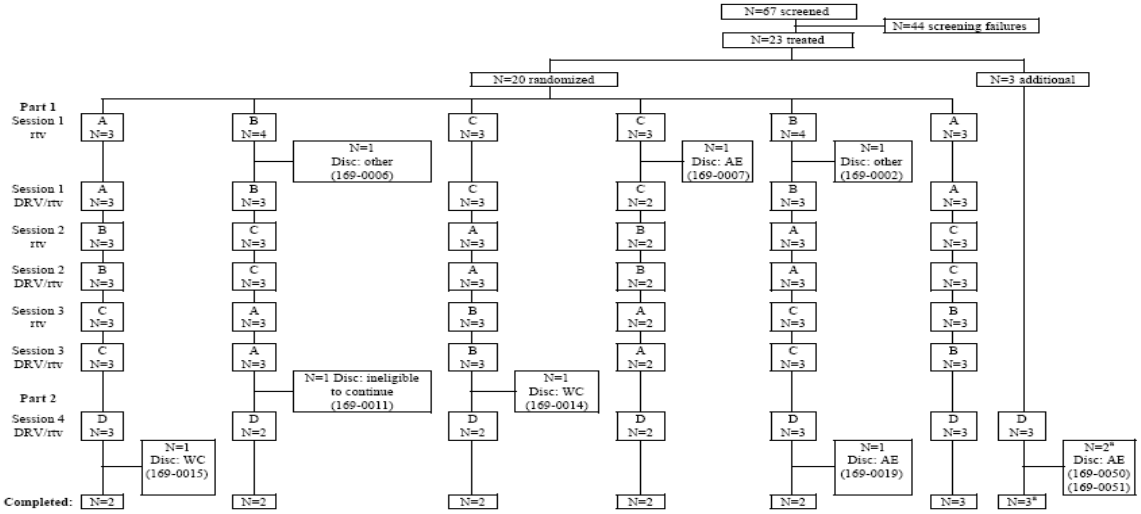
Table 3-TMC114-C169 subject demographics

Parameter	All Subjects N = 23
Age, years Median (range)	30.0 (20-53)
Height, cm Median (range)	178.0 (159-198)
Weight, kg Median (range)	80.0 (53-95)
BMI, kg/m^2 Median (range)	23.90 (19.5-28.7)
Gender, n (%) Male Female	 18 (78.3) 5 (21.7)
Ethnic Origin, n (%) Caucasian/White Black Other	 20 (87.0) 1 (4.3) 2 (8.7)[a]

N = number of subjects, n = number of subjects with that observation

[a] One subject was Asian Pacific and one subject was of mixed Asian/Caucasian origin.

Figure 2-TMC114-C169 subject disposition



10.2 Prior and Concomitant Medications

Eight subjects administered concurrent medications during the trial (including follow up). Four subjects administered acetaminophen. Other medications that were administered to a maximum of one subject included amoxicillin/clavulanate, cetirizine, desogestrel, dimenhydrinate, fluticasone propionate, ibuprofen, and xylometazoline. Based on the currently available information, the concomitant medications are not expected to impact the reported plasma concentration data for darunavir or ritonavir.

10.3 Pharmacokinetic and Statistical Analysis

On Day 3, five subjects each in Treatments A, B, and C that received single doses of darunavir (combined with ritonavir dosing that was initiated on Day 1) in either Period 2 or Period 3 had quantifiable predose darunavir concentrations. However, these concentrations were 5% or less of the subject's C_{max} for the period, and no adjustments were necessary for the pharmacokinetic analyses. There were no subjects with quantifiable predose darunavir concentrations in Period 1.

10.3.1 Pharmacokinetic and Statistical Analysis

Part 1-darunavir (DRV)

Table 4-Pharmacokinetic parameters for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as 300 mg tablets under fed conditions (treatment A) or as an oral suspension under fasted conditions (treatment B) or fed conditions (treatment C)

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)
n	17[a]	17	17
C_{max}, ng/mL	5654 ± 1478	5176 ± 1411	5885 ± 1724
t_{max}, h	3.0 (2.5-5.0)	2.0 (1.0-3.0)	4.0 (1.5-4.0)
AUC_{last}, ng.h/mL	85240 ± 38020	83510 ± 33540	88410 ± 32590
AUC_{∞}, ng.h/mL	87330 ± 40890	88520 ± 35570	92270 ± 33540
$t_{1/2term}$, h	15.04 ± 7.884	16.08 ± 7.236	15.36 ± 6.438

[a] n=16 for AUC_{∞} and $t_{1/2\ term}$, Trt = treatment

Table 5-Statistical analysis for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as an oral suspension under fed conditions (treatment C-test arm) or as 300 mg tablets under fed conditions (treatment A-reference arm)

Parameter	LSmeans [a] 600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)	LSmeans [a] 600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)	LSmeans ratio, %	90% CI,% [c]	p-value Period	p-value Sequence
C_{max}, ng/mL	5434	5676	104.4	99.38 - 109.8	0.0036*	0.4093
AUC_{last}, ng.h/mL	77480	83320	107.5	101.1 - 114.4	0.0011*	0.5269
AUC_{∞}, ng.h/mL[b]	81270	86940	107.0	100.3 - 114.1	0.0036*	0.5592
Parameter	**Median[a] 600 mg DRV tablet + 100 mg rtv b.i.d. (fed) (Trt A, reference)**	**Median[a] 600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)**	**Treatment difference median**	**90% CI,% [c]**	**p-value Period**	**p-value Sequence**
t_{max}, h	3.0	4.0	0.00	(-0.75) - (0.50)	0.7326	0.3023

Trt = treatment
[a] n= 17 for reference and test
[b] n = 16 for reference
[c] 90% confidence intervals.
* Statistically significant difference

Statistical analyses were conducted for 600 mg single doses of darunavir comparing a darunavir oral suspension administered under fed conditions (test arm) to darunavir 300 mg tablets administered under fed conditions (reference arm). The 90% confidence interval for darunavir C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ were within 80%-125%.

For the darunavir oral suspension, the trial did not evaluate the effect of food with high fat meals compared to fasted conditions. The trial did compare the effect of the meal that was administered to subjects in the trial (which included 21 grams of fat [189 kcal] and in

total, approximately 533 kcal) compared to fasted conditions for the darunavir oral suspension. The results are displayed in Table 6.

Table 6-Statistical analysis for a single 600 mg dose of darunavir (combined with 100 mg twice daily of ritonavir) administered as an oral suspension under fed conditions (treatment C-test arm) or fasted conditions (treatment B-reference arm)

	LSmeans [a]				p-value	
Parameter	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension + 100 mg rtv b.i.d. (fed) (Trt C, test 2)	LSmeans ratio, %	90% CI,% [b]	Period	Sequence
C_{max}, ng/mL	4954	5662	114.3	105.9 - 123.3	0.0931	0.2335
AUC_{last}, ng.h/mL	77590	82920	106.9	100.1 - 114.1	0.0057*	0.1612
AUC_{∞}, ng.h/mL	81900	86590	105.7	98.66 - 113.3	0.0153*	0.2190
	Median[a]				p-value	
Parameter	600 mg DRV suspension + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)	600 mg DRV suspension 1 + 100 mg rtv b.i.d. (fed) (Trt C, test 2)	Treatment difference median	90% CI,% [b]	Period	Sequence
t_{max}, h	2.0	4.0	1.13	(0.76) - (1.50)	0.4007	0.5916

Trt = treatment
[a] n= 17 for reference and test
[b] 90% confidence intervals.
* Statistically significant difference

When the darunavir exposure under fed conditions with the darunavir suspension (test arm) was compared to the darunavir exposure under fasted conditions with the darunavir suspension (reference arm), the 90% confidence interval for darunavir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

Part 2- darunavir (DRV)

The applicant evaluated the multiple dose pharmacokinetics of the darunavir oral suspension under fed conditions. The applicant did not conduct any statistical analyses using the multiple dosing darunavir pharmacokinetic data. Based on a review of the individual profiles of the darunavir C_{0h} values on Days 5 and 6, and 7, darunavir steady state appeared to have been achieved by Day 7 in most subjects.

Table 7-Pharmacokinetic parameters for 600 mg twice daily of darunavir oral suspension (combined with ritonavir 100 mg twice daily) and historical data for darunavir tablets from the TMC114-C171, TMC114-C123, and TMC114-C163 trials

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	600 mg DRV suspension b.i.d. + 100 mg rtv b.i.d. (fed) (Treatment D)		
n	17		
C_{0h}, ng/mL	4029 ± 1677		
C_{min}, ng/mL	3345 ± 1172		
C_{max}, ng/mL	7390 ± 1540		
t_{max}, h	3.0 (2.0-4.0)		
AUC_{12h}, ng.h/mL	58550 ± 17570		
Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C171)**	**600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C123)**	**600/100 mg DRV/rtv b.i.d. (Historical data: TMC114-C163)**
n	17	17	16[a]
C_{0h}, ng/mL	3450 ± 944.1	2742 ± 625.0	2768 ± 1077
C_{min}, ng/mL	3132 ± 1006	2353 ± 744.2	2349 ± 1006
C_{max}, ng/mL	6894 ± 1654	5908 ± 916.8	5874 ± 1637
t_{max}, h	3.0 (1.0 - 5.0)	3.0 (2.0 - 5.0)	4.0 (1.0 - 9.0)
AUC_{12h}, ng.h/mL	58550 ± 17200	44750 ± 7773	46720 ± 15430

[a] n = 15 for C_{0h}

There are no clinically significant differences observed based on evaluating the multiple dose data for darunavir or ritonavir C_{max} and $AUC_{(0-12h)}$ for the oral suspension and the data for darunavir tablets using historical data that was selected by the applicant from the TMC114-C171, TMC114-C123, and TMC114-C163 trials.

Reviewer note: The results of the TMC114-C171 trial were not included in the multiple dosing analysis that is discussed in section 1 because the results were obtained with administration of buprenorphine/naloxone in combination with darunavir/ritonavir.

11. Discussion and Conclusions

Based on the results from the TMC114-C169 trial, the following conclusions for darunavir can be made based on the applicant's analysis:

- Under fed conditions, when 600 mg single doses of darunavir were administered as oral suspension compared to 300 mg tablets, the darunavir C_{max}, $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ ratios were increased by 4%, 8%, and 7%, respectively. The 90% confidence interval for darunavir C_{max}, $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ were within 80%-125%.
- When 600 mg single doses of darunavir were administered as an oral suspension under fed conditions compared to fasted conditions, the darunavir C_{max}, $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ ratios were increased by 4%, 7% and 6%, respectively. The 90% confidence interval for darunavir C_{max}, $AUC_{(0-last)}$, and $AUC_{(0-inf)}$ were within 80%-125%.
- With multiple dosing, clinically significant differences were not observed based on evaluating the multiple dose data for darunavir C_{max} and $AUC_{(0-12h)}$ for the oral suspension and the data for darunavir tablets using historical data from the TMC114-C171, TMC114-C123, and TMC114-C163 trials.

The applicant did not evaluate 600 mg single doses of darunavir for the darunavir suspension compared to darunavir tablets under fasted conditions. This is the standard bioequivalence trial design for immediate release products evaluating formulation differences. However, based on the current or proposed darunavir US prescribing information, both darunavir tablets and darunavir suspension are recommended to be administered with food, and the evaluation of 600 mg single doses of darunavir for the darunavir suspension compared to darunavir tablets under fed conditions is a reasonable alternative.

There were multiple issues that were reviewed in evaluating whether the results of the TMC114-C169 trial are applicable to the darunavir suspension formulation (F052) that is proposed for marketing in the United States. The following issues are not anticipated to affect the applicability of the TMC114-C169 trial results to the proposed US marketed darunavir suspension: a) the darunavir suspension that was administered in the trial (F051) is an experimental darunavir suspension formulation, b) the ritonavir capsules that were administered are the European marketed ritonavir capsules, and c) ritonavir capsules instead of ritonavir oral solution were used in combination with darunavir oral suspension. The results of the trial are also expected to be applicable to the current US marketed darunavir tablet strengths (75 mg, 150 mg, 400 mg, and 600 mg) based either on the results of a bioequivalence trial (for the 600 mg tablet strength) or through the approval of biowaivers.

3.1.2 TMC114-C228 trial

1. Title

A Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low-dose ritonavir (DRV/rtv) in treatment-experienced HIV-1 infected children from 3 to < 6 years of age. Week-24 Primary analysis. (Additional applicant information: This trial is referred to as ARIEL.)

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 trial 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 and to develop darunavir/ritonavir dosing recommendations for the 3 to less than 6 years old age group.

4. Trial Design

TMC114-C228 was an open label, clinical trial that enrolled HIV-1 infected pediatric subjects 3 to less than 6 years old weighing 10 kg to less than 20 kg at screening. The trial design included enrolling approximately 24 male and female HIV-1 infected pediatric subjects that were currently receiving a stable but failing antiretroviral treatment regimen (HIV-1 viral load >1000 copies/mL) that required a modification and had less than three darunavir associated substitutions. The subjects were to be categorized into two weight bands: 10 kg to < 15 kg and 15 kg to <20 kg. The initial dosing using a darunavir oral suspension (F052) in combination with ritonavir oral solution is displayed in Table 1 below. The initial dosing regimen was approximately 20 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily. The options available for trial investigators in choosing a background regimen are displayed in Table 2 (it was recommended that investigators select a minimum of two HIV-1 antiretroviral medications).

Table 1-Initial dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

Body Weight (kg)	DRV		rtv	
	Dose of Oral Suspension in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])	Dose of Oral Solution in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])
10 - 10.9	2.0	200 (18.3 - 20.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.2	220 (18.5 - 20.0)	0.4	32 (2.7 - 2.9)
12 - 12.9	2.4	240 (18.6 - 20.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	2.6	260 (18.7 - 20.0)	0.5	48 (3.5 - 3.7)
14 - 14.9	2.8	280 (18.8 - 20.0)	0.6	48 (3.2 - 3.4)
15 - 15.9	3.0	300 (18.9 - 20.0)	0.6	48 (3.0 - 3.2)
16 - 16.9	3.2	320 (18.9 - 20.0)	0.6	48 (2.8 - 3.0)
17 - 17.9	3.4	340 (19.0 - 20.0)	0.6	48 (2.7 - 2.8)
18 - 18.9	3.6	360 (19.0 - 20.0)	0.6	48 (2.5 - 2.7)
19 - 19.9	3.8	380 (19.1 - 20.0)	0.6	48 (2.4 - 2.5)

[a] The DRV oral suspension was administered with a pipette with a 0.2-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.

[b] The actual dose in mg/kg varied given the dose was fixed for each weight band.

Table 2-List of permitted and prohibited HIV-1 antiretroviral medications for the TMC114-C228 trial

ARV Class	Allowed	Disallowed
PIs	DRV/rtv	All other PIs
NRTIs	All NRTIs with available pediatric dose recommendations	-
NNRTIs	nevirapine efavirenz	Investigational NNRTI etravirine[a] delavirdine
Entry inhibitors (including fusion inhibitor)	-	maraviroc[a], enfuvirtide[a]
Integrase inhibitors	-	raltegravir[a]

[a] Once there were sufficient safety data on this ARV and there were dose recommendations for children between 3 and < 6 years, the ARV was allowed as part of the OBR.

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Other than the prohibited HIV-1 antiretroviral medications listed in Table 2, use of CYP 3A inducers was not permitted from 14 days before the first administration of trial medication until the end of the treatment period and CYP 3A substrates with a narrow therapeutic index was not permitted from the first administration of trial medication until the end of the treatment period.

Other restrictions during the trial included prohibiting the use of liquids containing quinine or intake of grapefruit and grapefruit juice from 24 hours before the first administration of trial medication until Day 15.

6. Dosage and Administration

Darunavir oral suspension and ritonavir oral suspension were administered within 30

minutes after the end of a meal on a twice daily (every 12 hours) schedule. There were no restrictions on the type of meal that could be administered. The darunavir suspension was shaken prior to dose administration. Both the darunavir oral suspension and ritonavir oral suspension were administered using a syringe. The syringe for the darunavir oral suspension displayed measurements of 0.2 mL and the syringe for the ritonavir oral solution displayed measurements of 0.1 mL.

7. Rationale for Doses Used in the Trial

The initial darunavir doses (approximately 20 mg/kg) administered twice directly were based on the highest darunavir mg/kg dose (18.75 mg/kg) that was administered in the pediatric TMC114-C212 trial that evaluated the pharmacokinetics of darunavir/ritonavir in older pediatric subjects 6 to less than 18 years old. The highest darunavir dose of 18.75 mg/kg was selected in anticipation of preventing underdosing because of potential increased clearance in younger pediatric patients. The ritonavir doses (approximately 3 mg/kg) administered twice daily were designed to minimize the differences in the darunavir to ritonavir ratios between the different weight bands. For the ritonavir doses that were administered in the trial, the initial darunavir to ritonavir ratios ranged from 6:1 to 7.6:1.

After the Week 2 pharmacokinetic data was analyzed using population pharmacokinetic analysis, the applicant determined that a dose adjustment for darunavir was required. The adjusted dosage regimens are displayed in Table 3. The rationale for the dosage adjustment and the results of the population pharmacokinetic analysis are discussed in section 10. The adjusted dosage regimens were approximately 25 mg/kg of darunavir combined with approximately 3 mg/kg of ritonavir administered twice daily for pediatric subjects weighing between 10 kg to less than 15 kg and 375 mg of darunavir combined with approximately 50 mg of ritonavir administered twice daily for pediatric subjects weighing between 15 kg to less than 20 kg. The reasons for selecting these adjusted dosage regimens included limiting the need for weight based dosing to pediatric patients weighing less than 15 kg, and allowing interchangeability between darunavir tablets and darunavir oral suspension for pediatric patients weighing between 15 kg to less than 20 kg.

Table 3-Adjusted dosing of darunavir oral suspension (F052) in combination with ritonavir oral solution in TMC114-C228

	DRV		rtv	
Body Weight (kg)	Dose of Oral Suspension in mL b.i.d.[a]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])	Dose of Oral Solution in mL b.i.d.[b]	Actual Dose in mg b.i.d.[a] (Range in mg/kg[b])
10 - 10.9	2.6	260 (23.8 - 26.0)	0.4	32 (2.9 - 3.2)
11 - 11.9	2.8	280 (23.5 - 25.5)	0.4	32 (2.7 - 2.9)
12 - 12.9	3.0	300 (23.3 - 25.0)	0.5	40 (3.1 - 3.3)
13 - 13.9	3.4	340 (24.5 - 26.1)	0.5	40 (2.9 - 3.1)
14 - 14.9	3.6	360 (24.2 - 25.7)	0.6	48 (3.2 - 3.4)
15 - 19.9	3.8	380	0.6	48

[a] The DRV oral suspension was administered with a pipette with a 0.2-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.

[b] The actual dose in mg/kg varied given the dose was fixed for each weight band.

8. Drugs Used in the Trial

Information regarding the darunvair and ritonavir formulations that were administered in the trial is displayed in Table 4. The darunavir oral suspension that was administered in the trial (F052) is the formulation that is proposed for marketing in the United States.

Table 4-Information on the darunavir and ritonavir formulations administered in the TMC114-C228 trial

Treatment	DRV suspension	Rtv solution	DRV tablet[a]
Concentration	100 mg/mL	80 mg/mL	75-mg tablet
Formulation Number	F052	-	F029
Usage	Oral	Oral	Oral
Batch Numbers	361887: (b) (4) 362473: 363405:	-	362432: (b) (4)

[a] After the Week-24 analysis, upon guidance of the DSMB, children weighing ≥ 20 kg, and able and willing to swallow tablets, could switch to the DRV tablet formulation.

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 12 hours postdose. At weeks 4, 24, and 48 and for the visit two weeks after dose adjustment, two darunavir and ritonavir blood samples were obtained with the first sample collected prior to dose administration and the second sample collected a minimum of one hour or later after the first blood sample.

Reviewer note: the blood sampling for weeks 2 and 4 occurred with the initial darunavir dosage regimens and the blood sampling 2 weeks after dosage adjustment and at week 24 occurred with the adjusted darunavir dosage regimens.

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 sodium heparin as an anticoagulant. An experiment 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-C228 plasma samples that were analyzed for this submission that included data for the Week 24 analysis, for darunavir, the lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 5000 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-C228 trial, precision and accuracy were evaluated using plasma darunavir QC samples at four concentration levels: 15 ng/mL, 250 ng/mL, 1500 ng/mL (for runs 6 to 12 only), and 4000 ng/mL (in response to an information request, it was clarified that the 1500 ng/mL darunavir and ritonavir QC samples was added because the reported concentrations were at the upper end of the calibration curve range). The corresponding darunavir inter-run accuracy values were 12% for 15 ng/mL, -1.2% for 250 ng/mL, -4% for 1500 ng/mL and -4% for 4000 ng/mL. The darunavir inter-run precision values were 55.5% for 15 ng/mL, 5.8% for 250 ng/mL, 4% for 1500 ng/mL, and 3% for 4000 ng/mL. For the low darunavir QC, in each analytical run that was accepted, at least one of the two analyzed low QC samples met acceptance criteria. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the TMC114-C228 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at 15 ng/mL, 250 ng/mL, 1500 ng/mL (for runs 6 to 12 only), and 4000 ng/mL. The corresponding ritonavir inter-run accuracy values were -2.7% for 15 ng/mL, -3.2% for 250 ng/mL, -9.3% for 1500 ng/mL and -0.3% for 4000 ng/mL. The ritonavir inter-run precision values were 4.8% for 15 ng/mL, 2.5% for 250 ng/mL, 3.5% for 1500 ng/mL, and 1.8% for 4000 ng/mL.

For the TMC114-C228 trial, the darunavir and ritonavir plasma samples were stored at -20°C at both at the clinical trial site and at the bioanalytical laboratory. The long term stability darunavir and ritonavir data of 1597 days covers the duration of long term stability data necessary for the TMC114-C228 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. Three 483 observations were issued, however the Office of Scientific Investigations does not believe that the 483 observations impact the trial results:

1) Failure to use fresh calibration standards in evaluating autosampler stability during method validation.
2) Lack of maintaining relevant documentation:
-Failure to investigate the cause of a failed 21 hour autosampler stability experiment
-Not tracking whether the multiple use calibration standard and quality control samples used for the bioanalysis of the TMC114-C228 samples were used within the established number of freeze thaw stability cycles.

3) Failure to maintain the audit trial for the initial data processing results for the darunavir and ritonavir samples analyzed for the TMC114-C228 trial.

To address the first 483 observation, (b) (4) will conduct an additional autosampler stability method validation experiment using freshly prepared calibration standards. The results of the second autosampler stability method validation experiment were acceptable. To address the second 483 observation related to the failure to

investigate the cause of a failed 21 hour autosampler stability experiment, a procedure was implemented mandating an investigation for failed validation experiment and a retroactive investigation concluded that contamination was the most likely reason for the failed experiment. To address the second 483 observation related to not tracking whether the multiple use calibration standard and quality control samples used for the bioanalysis of the TMC114-C228 samples were used within the established number of freeze thaw stability cycles, in the future, (b) (4) will label the calibration standard and quality control samples with identifiers that will be documented in the laboratory notebook. To address the third 483 observation related to the failure to maintain the audit trial for the initial data processing results for the darunavir and ritonavir samples analyzed for the TMC114-C228 trial, a new procedure was implemented and the data was reprocessed for the TMC114-C228 trial. The plasma concentration results were similar for both procedures.

Pharmacokinetic Assessments

Prior to dosage adjustment, at week 2, both population pharmacokinetic (PK) and noncompartmental analysis was performed. For the population PK analysis, darunavir $AUC_{(0\text{-}l2h)}$ and C_{0h} were derived. For the noncompartmental analysis, darunavir and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, C_{0h}, C_{min}, and $AUC_{(0\text{-}12h)}$.

After dosage adjustment, based on the pharmacokinetic data obtained two weeks after dosage adjustment, darunavir $AUC_{(0\text{-}l2h)}$ and C_{0h} were derived using population PK analysis.

A population PK analysis was also performed to derive $AUC_{(0\text{-}l2h)}$ and C_{0h}values for the initial and adjusted darunavir dosage regimens.

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.

The criterion to determine whether the darunavir dosage regimens provided sufficient darunavir exposure compared to adults receiving darunavir/ritonavir 600 mg/100 mg twice daily was based on evaluating the $AUC_{(0\text{-}l2h)}$ that was derived using population PK analysis. If the $AUC_{(0\text{-}l2h)}$ was less than 80% or greater than 130% of the target $AUC_{(0\text{-}l2h)}$ of 62.3 µg*hr/mL, a dosage adjustment could be implemented.

10. Results

10.1 Subject Demographics and Disposition

Table 5-TMC114-C228 subject demographics

Demographic Parameter	DRV/rtv
Sex, n (%), N	**27**
Female	12 (44.4)
Male	15 (55.6)
Age (years), N	**27**
Mean (SE)	4.6 (0.17)
Median (range)	4.5 (3.1; 5.8)
Race, n (%), N	**27**
Asian	1 (3.7)
Black or African American	18 (66.7)
Black or African American/White	2 (7.4)
White	6 (22.2)
Ethnicity, n (%), N	**27**
Hispanic or Latino	10 (37.0)
Not Hispanic or Latino	17 (63.0)
Height (cm), N	**27**
Mean (SE)	101.2 (1.43)
Median (range)	102.0 (90.0; 117.0)
Weight (kg), N	**27**
Overall Mean (SE)	15.3 (0.40)
Overall Median (range)	14.9 (11.9; 19.8)
BMI (kg/m^2), N	**27**
Mean (SE)	14.9 (0.29)
Median (range)	14.7 (10.9; 18.3)
Z-Score for height, N	**27**
Mean (SE)	-1.4 (0.20)
Median (range)	-1.4 (-3.9; 0.6)
Z-Score for weight, N	**27**
Mean (SE)	-1.1 (0.18)
Median (range)	-1.1 (-3.6; 1.7)
Z-Score for BMI, N	**27**
Mean (SE)	-0.4 (0.24)
Median (range)	-0.4 (-4.4; 1.9)

N = number of subjects; n = number of observations

Table 6-Baseline HIV-1 infection information

Baseline Characteristic	DRV/rtv
Log_{10} viral load (copies/mL), N	**27**
Mean (SE)	4.43 (0.150)
Median (Range)	4.51 (2.85; 5.74)
Viral load (copies/mL), n (%), N	**27**
< 20,000	11 (40.7)
20,000 - < 50,000	5 (18.5)
50,000 - < 100,000	4 (14.8)
≥ 100,000	7 (25.9)
CD4+ Percentage, N	**21**
Mean (SE)	30.1 (2.19)
Median (Range)	27.7 (15.6; 51.1)
CD4+ Percentage, N	**21**
≥ 25%	14 (66.7)
< 25%	7 (33.3)
CD4+ cell count (x 10^6/L), N	**21**
Mean (SE)	1091 (131.6)
Median (Range)	927 (209 - 2429)
CD4+ cell count (x 10^6/L), n (%), N	**27**
Missing	6 (22.2)
≥ 200	21 (77.8)
Known duration of HIV infection (years)	**27**
Mean (SE)	3.5 (0.25)
Median (range)	3.8 (0.1; 5.4)
DRV FC, n (%), N	**22**
Mean	0.55
Median (range)	0.5 (0.2; 2.3)
WHO Clinical Stage of HIV infection[19], n (%), N	**27**
Clinical Stage 1 (asymptomatic)	6 (22.2)
Clinical Stage 2 (mild symptoms)	5 (18.5)
Clinical Stage 3 (advanced symptoms)	12 (44.4)
Clinical Stage 4 (severe symptoms)	4 (14.8)
Mode of HIV infection, n (%), N	**27**
Mother-to-child transmission	27 (100)
Clade, n (%), N	**27**
A1	5 (18.5)
B	5 (18.5)
C	11 (40.7)
CRF12_BF	4 (14.8)
D	1 (3.7)
F1	1 (3.7)
Hepatitis B or C coinfection status, n (%), N	**27**
Negative	12 (44.4)
Missing	15 (55.6)

N = number of subjects; n = number of observations

Table 7-TMC114-C228 subject disposition

n (%)	DRV/rtv
ITT Population	
N screened	42
N treated	27
N not treated	15
Discontinuations - Reason, n (%)	**1 (3.7)**
AE	1 (3.7)
Ongoing	**26 (96.3)**

N = number of subjects; n = number of observations

10.2 Prior and Concomitant Medications

Information regarding the antiretroviral medications that HIV-1 infected pediatric subjects were receiving at screening and the initial antiretroviral medications that HIV-1 infected pediatric subjects were receiving on Day 7 or, for subjects that discontinued, the last treatment day during the first seven days is displayed in Tables 8 and 9. Information regarding the non antiretroviral medications that subjects received during the trial is displayed in Table 10. The concomitant medications that were administered in the trial are not anticipated to alter the trial's conclusions.

Table 8-Antiretroviral medications at screening

ARV, n (%)	DRV/rtv
Number of ARVs Used at Screening	
PIs, N	**27**
0	14 (51.9)
1	13 (48.1)
NRTIs, N	**27**
1	2 (7.4)
2	22 (81.5)
3	3 (11.1)
NNRTIs, N	**27**
0	19 (70.4)
1	8 (29.6)
ARVs Used at Screening	
PIs	**13**
Lopinavir	12 (44.4)
Nelfinavir	1 (3.7)
NRTIs	**27**
Abacavir	6 (22.2)
Didanosine	2 (7.4)
Lamivudine	23 (85.2)
Stavudine	11 (40.7)
Zidovudine	13 (48.1)
NNRTIs	**8**
Efavirenz	3 (11.1)
Nevirapine	5 (18.5)

N = number of subjects; n = number of observations

Table 9-Initial antiretroviral background medications

ARVs, n (%)	DRV/rtv
Number of ARVs in the Initial OBR	
NRTIs, N	**27**
2	25 (92.6)
3	2 (7.4)
ARVs Used in the Initial OBR	
NRTIs, N	**27**
Abacavir	14 (51.9)
Didanosine	5 (18.5)
Lamivudine	14 (51.9)
Stavudine	8 (29.6)
Tenofovir disoproxil fumarate	1 (3.7)
Zidovudine	14 (51.9)
NRTI Combinations in the Initial OBR, N	**27**
Abacavir + didanosine	4 (14.8)
Abacavir + lamivudine	1 (3.7)
Abacavir + lamivudine + zidovudine	1 (3.7)
Abacavir + stavudine	4 (14.8)
Abacavir + zidovudine	4 (14.8)
Didanosine + zidovudine	1 (3.7)
Lamivudine + stavudine	4 (14.8)
Lamivudine + tenofovir disoproxil fumarate + zidovudine	1 (3.7)
Lamivudine + zidovudine	7 (25.9)

N = number of subjects; n = number of observations

Table 10-Non antiretroviral medications administered during the trial in > 10% of subjects

Class, n (%)	DRV/rtv N = 27
Analgesics	11 (40.7)
Antianemic preparations	3 (11.1)
Antibacterials for systemic use	20 (74.1)
Antibiotics and chemotherapy for dermatological use	5 (18.5)
Antidiarr., intest. antiinfl./antiinfect. agents	6 (22.2)
Antifungals for dermatological use	5 (18.5)
Antihistamines for systemic use	4 (14.8)
Nasal preparations	3 (11.1)
Stomatological preparations	10 (37.0)
Vaccines	3 (11.1)
Vitamins	5 (18.5)

N = number of subjects; n = number of observations

10.3 Pharmacokinetic and Statistical Analysis

Table 11-Subjects with protocol deviations related to incorrect darunavir or ritonavir dose administration

CRF ID	Details on Dosing Error[a]	Dosing Error in mg[b]	Duration	Time Point(s)
Incorrect dose of DRV				
228-0005[c]	93% of DRV dose[d]: 2.6 ISO 2.8 mL b.i.d.	260 ISO 280 mg b.i.d.	6 weeks	Week 8 to dose switch
	95% of DRV dose: 3.6 ISO 3.8 mL b.i.d.	360 ISO 380 mg b.i.d.	5 weeks	Dose switch to cut-off
228-0010	94% of DRV dose: 3.2 ISO 3.4 mL b.i.d.	320 ISO 340 mg b.i.d.	5.5 weeks	Week 8 to dose switch
228-0014[c]	94% of DRV dose: 3.0 ISO 3.2 mL b.i.d.	300 ISO 320 mg b.i.d.	6 weeks	Week 8 to dose switch
	79% of DRV dose: 3.0 ISO 3.8 mL b.i.d.	300 ISO 380 mg b.i.d.	2 weeks	Dose switch to dose-switch follow-up
228-0018[c]	175% of DRV dose: 4.2 ISO 2.4 mL b.i.d.	420 ISO 240 mg b.i.d.	2 weeks	Baseline to Week 2
228-0025	103% of DRV dose: 3.3 ISO 3.2 mL b.i.d.	330 ISO 320 mg b.i.d.	11 weeks	Baseline to dose switch
228-0033	88% of DRV dose: 3.0 ISO 3.4 mL b.i.d.	300 ISO 340 mg b.i.d.	16 weeks	Weeks 16 to 32
228-0038	94% of DRV dose: 3.4 ISO 3.6 mL b.i.d.	340 ISO 360 mg b.i.d.	8 weeks	Weeks 16 to 24
Incorrect dose of rtv				
228-0005[c]	83% of rtv dose[e]: 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	4 weeks	Weeks 8 to 12
228-0038	83% of rtv dose: 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	8 weeks	Weeks 16 to 24
228-0042	83% of rtv dose: 0.5 ISO 0.6 mL b.i.d.	40 ISO 48 mg b.i.d.	4 weeks	Baseline to Week 4

ISO = instead of; '-' = missing data
[a] Verbatim as on the CRF.
[b] Equivalent of dosing in mg.
[c] For this subject, see also Section 4.2.1.2.
[d] DRV dose according to body weight following Table 1 or Table 20
[e] Rtv dose according to body weight following Table 1 or Table 20

The applicant states in the TMC114-C228 trial report that the protocol deviations in Table 11 did not affect the trial's efficacy or safety results. The subjects listed in Table 11 that were excluded from one or more of the pharmacokinetic analyses displayed in 10.3A to 10.3E were as follows: 5, 10, 14, 18, 33, 38, and 42. The reasons for excluding specific subjects are discussed below.

A) Pre dose adjustment week 2 population PK analysis

Three subjects were excluded from the pre dose adjustment week 2 population PK analysis:

1) Subject 30 was excluded because the ritonavir plasma concentrations were all below the lower limit of quantification.
2) Subject 42 did not have blood samples drawn for pharmacokinetic analysis at week 2.
3) Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis at week 2.

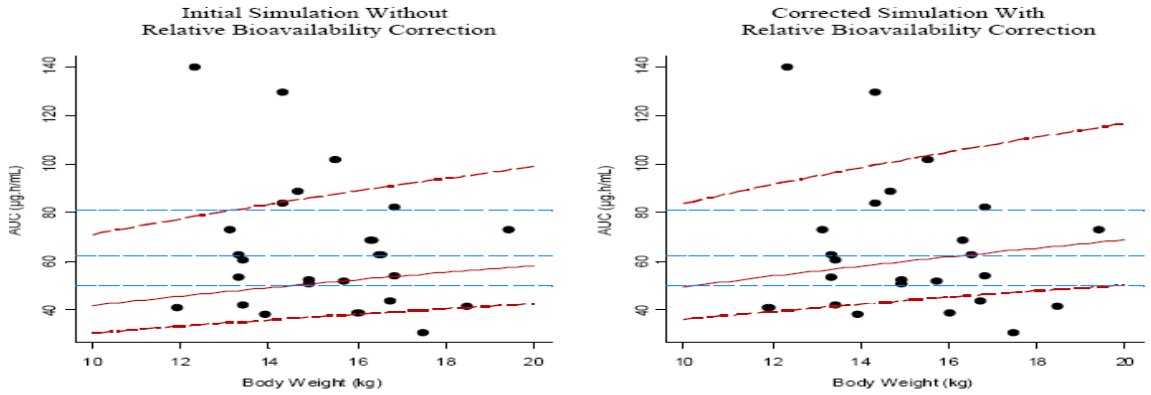
Table 12-Population pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

Weight group	N	Geometric Mean	Mean	SD	5th Percentile	Median	95th Percentile
AUC_{12h} (µg.h/mL)							
All subjects	24	60.7	65.4	27.8	38.8	57.6	125
10 - < 15 kg	13	65.0	70.7	32.3	40.2	61.0	133
15 - < 20 kg	11	56.0	59.3	21.0	35.3	54.2	91.9
C_{0h} (ng/mL)							
All subjects	24	3433	3927	2188	1662	3460	8779
10 - < 15 kg	13	3680	4289	2621	1950	3533	9411
15 - < 20 kg	11	3164	3500	1583	1607	3387	5897

The $AUC_{(0\text{-}12h)}$ data in Table 12 indicates that the darunavir exposure for both the 10 kg to < 15 kg and the 15 kg to < 20 kg groups were within 80% to 130% of the target $AUC_{(0\text{-}12h)}$ of 62.3 µg*hr/mL. The applicant's rationale for increasing the darunavir dose was based on the simulations that suggested the exposure with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily was low compared to the target exposure range. Lower darunavir exposure with lower body weights was also predicted based on the simulations.

However, the simulations that were conducted did not include a relative bioavailability factor for the difference in darunavir bioavailability for the Phase 2 and the marketed tablet. The applicant subsequently conducted an analysis with the relative bioavailability factor included and concluded that the rationale for adjusting the darunavir dose was still valid (see Figure 1).

Figure 1-Predicted darunavir exposure for 3 to less than 6 year olds receiving darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily



Expected DRV AUC_{12h} for the 5th, 50th and 95th percentile of AAG are presented in red; 80%, 100%, and 130% of the mean adult target exposure are presented in blue; the model-based estimates after 2 weeks treatment are presented as black dots.

B) Pre dose adjustment week 2 noncompartmental PK analysis

Table 13-Noncompartmental pharmacokinetic parameters at Week 2 with darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily

Pharmacokinetics of DRV at Week 2 (mean [SD], t_{max}: median [range])	**DRV/rtv 20/3 mg/kg b.i.d.**
n	22[a]
C_{0h} (ng/mL)	4321 (2955)
C_{min} (ng/mL)	2568 (1706)
C_{max} (ng/mL)	8196 (3284)
t_{max} (h)	3.00 (0.87 - 6.00)
AUC_{12h} (ng.h/mL)	60100 (25520)
FI (%)	112 (44.2)

[a] n = 23 for C_{0h}, C_{max} and t_{max}

Pharmacokinetics of rtv at Week 2 (mean [SD], t_{max}: median [range])	**DRV/rtv 20/3 mg/kg b.i.d.**
n	22[a]
C_{0h} (ng/mL)	646 (805)
C_{min} (ng/mL)	213 (140)
C_{max} (ng/mL)	1178 (842)
t_{max} (h)	3.08 (0.87-6.05)
AUC_{12h} (ng.h/mL)	8085 (4741)
FI (%)	149 (50.7)

[a] n = 23 for C_{0h}, C_{max} and t_{max}

The subjects that were excluded from the noncompartmental analysis were as follows: 30 (discontinued prior to week 2), 42 (outlier for patient randomization date [no further explanation was provided]), 18 (received 175% of the darunavir dose), and 33 (suspected nonadherence). One subject (10) did not have darunavir and ritonavir C_{min}, $AUC_{(0\text{-}12h)}$, and fluctuation index values calculated because the 12 hour sample at week 2 was taken postdose.

The applicant did not provide a comparison of the data in Table 12 to the adult

pharmacokinetic data in subjects receiving 600 mg of darunavir combined with 100 mg of ritonavir twice daily. However, based on evaluating the $AUC_{(0\text{-}12h)}$ data in Table 13, the darunavir exposure was within 80% to 130% of the target $AUC_{(0\text{-}l2h)}$ of 62.3 µg*hr/mL. The same conclusion was reached using the population PK analysis in Table 12.

C) Post dose adjustment (2 weeks after dose adjustment) population PK analysis

Nine subjects were excluded from the post dose adjustment (2 weeks after dose adjustment) population PK analysis. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and the following additional eight subjects were excluded:

Table 14-Subjects excluded from the post dose adjustment (2 weeks after dose adjustment) population PK analysis

Subject Number	Reason for exclusion
05	AAG measured in local lab, not central lab
10	AAG measured in local lab, not central lab
14	AAG measured in local lab, not central lab
18	AAG measured in local lab, not central lab
26	No ritonavir exposure in sample
33	No ritonavir exposure in sample
38	AAG measured in local lab, not central lab
42	AAG measured in local lab, not central lab, no PK sample available at Week 2

Reviewer's note: The information provided by the applicant in Table 15 differs from the information presented as part of the Data Safety Monitoring Board meeting minutes for June 30, 2010. The $AUC_{(0\text{-}12h)}$ pharmacokinetic data that were included in the meeting minutes was as follows: a) Overall mean: 77.3 µg*hr/mL (n=18), b) Mean (< 15 kg): 88.4 µg*hr/mL [n=8], and c) Mean: ≥ 15 kg: 68.3 µg*hr/mL [n=10].

Table 15-Darunavir population PK analysis results derived from the Week 24 analysis for the adjusted dosage regimen 2 weeks after dose adjustment (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 375 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Weight group	N	Geometric Mean	Mean	SD	5th Percentile	Median	95th Percentile
AUC_{12h} (µg.h/mL)							
All subjects	18	82.3	87.6	33.1	53.8	81.4	144
10 to <15 kg	4	117	118	19.1	97.2	119	137
15 to <20 kg	14	74.5	79.0	31.4	53.0	68.6	127
C_{0h} (ng/mL)							
All subjects	18	5061	5636	2737	2774	5168	10147
10 to <15 kg	4	8313	8394	1326	6924	8522	9686
15 to <20 kg	14	4392	4848	2526	2771	4365	8744

Based on the pharmacokinetic data that was presented to the Data Safety Monitoring

Board, it was concluded that the trial could proceed using the adjusted darunavir dosage regimens.

Reviewer note: For the analysis in "D", the data includes the population PK parameters for weeks 2 and 4 with the initial darunavir dosage regimens and for the analysis in "E", the data includes the population PK parameters for 2 weeks after dosage adjustment and at week 24 with the adjusted darunavir dosage regimens.

D) Population PK analysis for the initial dosage regimens

Eight subjects were excluded from the population PK analysis for the initial dosage regimens. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and the following additional seven subjects were excluded:

Table 16-Subjects excluded from the population PK analysis for the initial dosage regimens

Subject Number	Visit number	Time post dose (h)	Reason for exclusion
05	3, 4	All	AAG measured in local lab, not central lab
10	3, 4	All	AAG measured in local lab, not central lab
14	3, 4	All	AAG measured in local lab, not central lab
18	3, 4	All	AAG measured in local lab, not central lab
33	3, 4	All	No ritonavir exposure in sample
38	3, 4	All	AAG measured in local lab, not central lab
42	4	All	AAG measured in local lab, not central lab, no PK sample available at Visit 3

Visit 3 corresponds to Week 2, Visit 4 corresponds to Week 4.
Note: Subject 42 also did not have blood samples drawn for pharmacokinetic analysis at week 2

Table 17-Darunavir population PK analysis results for the initial dosage regimen (darunavir 20 mg/kg combined with ritonavir 3 mg/kg twice daily)

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC_{12h} (ng.h/mL)	All	19	66.9	62.4	6.0	26.1	55.1 - 78.7	27.1	35.4	50.0	61.8	80.5	114	132
	10 - < 15 kg	10	68.9	65.6	8.1	25.5	53.0 - 84.8	46.7	47.1	52.8	61.8	71.4	113	132
	15 - < 20 kg	9	64.7	59.1	9.4	28.1	46.3 - 83.1	27.1	30.8	49.0	53.5	86.9	104	112
C_{0h} (ng/mL)	All	19	4220	3749	477	2081	3285 - 5155	1057	1783	2761	3773	5432	7642	9498
	10 - < 15 kg	10	4445	4117	651	2059	3169 - 5721	2607	2682	3126	4025	4695	7943	9498
	15 - < 20 kg	9	3969	3379	733	2200	2532 - 5406	1057	1380	2588	3306	6124	6956	7435
$C_{ss,ave}$ (ng/mL)	All	19	5575	5201	499	2175	4597 - 6553	2256	2951	4168	5151	6709	9514	10956
	10 - < 15 kg	10	5740	5463	671	2123	4425 - 7055	3889	3924	4402	5153	5951	9385	10956
	15 - < 20 kg	9	5391	4924	782	2345	3858 - 6924	2256	2565	4083	4460	7243	8667	9354
CL/F (L/h)	All	19	5.15	4.76	0.53	2.31	4.11 - 6.19	2.13	3.03	3.76	4.23	6.06	9.15	12.26
	10 - < 15 kg	10	4.23	4.09	0.35	1.10	3.54 - 4.92	2.13	2.58	3.89	4.22	4.78	5.72	6.13
	15 - < 20 kg	9	6.17	5.64	0.97	2.91	4.27 - 8.07	3.63	3.63	3.68	5.98	7.01	10.88	12.26

Notes:
1) The units in the table should be µg/mL*hr for $AUC_{(0-12h)}$.
2) The population PK analysis includes the pharmacokinetic data from weeks 2 and 4.

E) Population PK analysis for the adjusted dosage regimens

Four subjects were excluded from the population PK analysis for the initial dosage regimens. Subject 30 discontinued from the trial and did not have blood samples drawn for pharmacokinetic analysis and three additional subjects were excluded (26, 33, and 38) that are included in Table 18 below:

Table 18-Subjects excluded from the population PK analysis for the adjusted dosage regimens

Subject Number	Visit number	Time post dose (h)	Reason for exclusion
05	105	All	AAG measured in local lab, not central lab
10	105	All	AAG measured in local lab, not central lab
14	105	All	AAG measured in local lab, not central lab, Protocol deviation : >20% difference in DRV dose
18	105	All	AAG measured in local lab, not central lab
26	105, 8	All	No ritonavir exposure in sample
33	105, 8	All	No ritonavir exposure in sample
38	105, 8	All	AAG measured in local lab, not central lab
42	105	All	AAG measured in local lab, not central lab

Visit 105 corresponds to post-dose adjustment visit, Visit 8 corresponds to Week 24.

Table 19-Darunavir population PK analysis results for the adjusted dosage regimen (darunavir 25 mg/kg combined with ritonavir 3 mg/kg twice daily [10 kg to <15 kg and 375 mg of darunavir combined with 50 mg of ritonavir twice daily [15 to < 20 kg])

Parameter	Weight	N	Mean	Geometric Mean	SE	SD	95% CI	Minimum	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Maximum
AUC_{12h} (ng.h/mL)	All	23	79.6	75.9	5.7	27.1	68.4 - 90.8	52.0	52.8	59.0	71.4	89.1	128	158
	10 - < 15 kg	7	87.1	83.6	10.2	26.9	67.1 - 107	57.1	57.5	64.0	90.7	102	122	130
	15 - < 20 kg	16	76.3	72.8	6.8	27.4	63.0 - 89.6	52.0	52.6	59.0	70.0	83.7	125	158
C_{0h} (ng/mL)	All	23	4993	4600	463	2220	4086 - 5900	2708	2749	3221	4227	6121	8842	11270
	10 - < 15 kg	7	5833	5474	816	2158	4234 - 7432	3251	3358	3917	6488	7144	8442	8974
	15 - < 20 kg	16	4626	4263	553	2212	3542 - 5710	2708	2727	3050	4031	4955	8555	11270
$C_{ss,ave}$ (ng/mL)	All	23	6634	6326	471	2258	5711 - 7557	4331	4404	4920	5953	7429	10706	13190
	10 - < 15 kg	7	7260	6963	848	2244	5598 - 8922	4759	4788	5330	7555	8506	10197	10835
	15 - < 20 kg	16	6360	6066	570	2281	5243 - 7477	4331	4379	4917	5836	6979	10451	13190
CL/F (L/h)	All	23	5.08	4.86	0.30	1.45	4.49 - 5.67	2.41	2.80	4.29	5.17	6.21	7.19	7.32
	10 - < 15 kg	7	4.26	4.09	0.48	1.28	3.32 - 5.20	2.79	2.82	3.17	4.24	5.16	5.84	6.13
	15 - < 20 kg	16	5.44	5.24	0.35	1.41	4.75 - 6.13	2.41	3.11	4.48	5.43	6.48	7.23	7.32

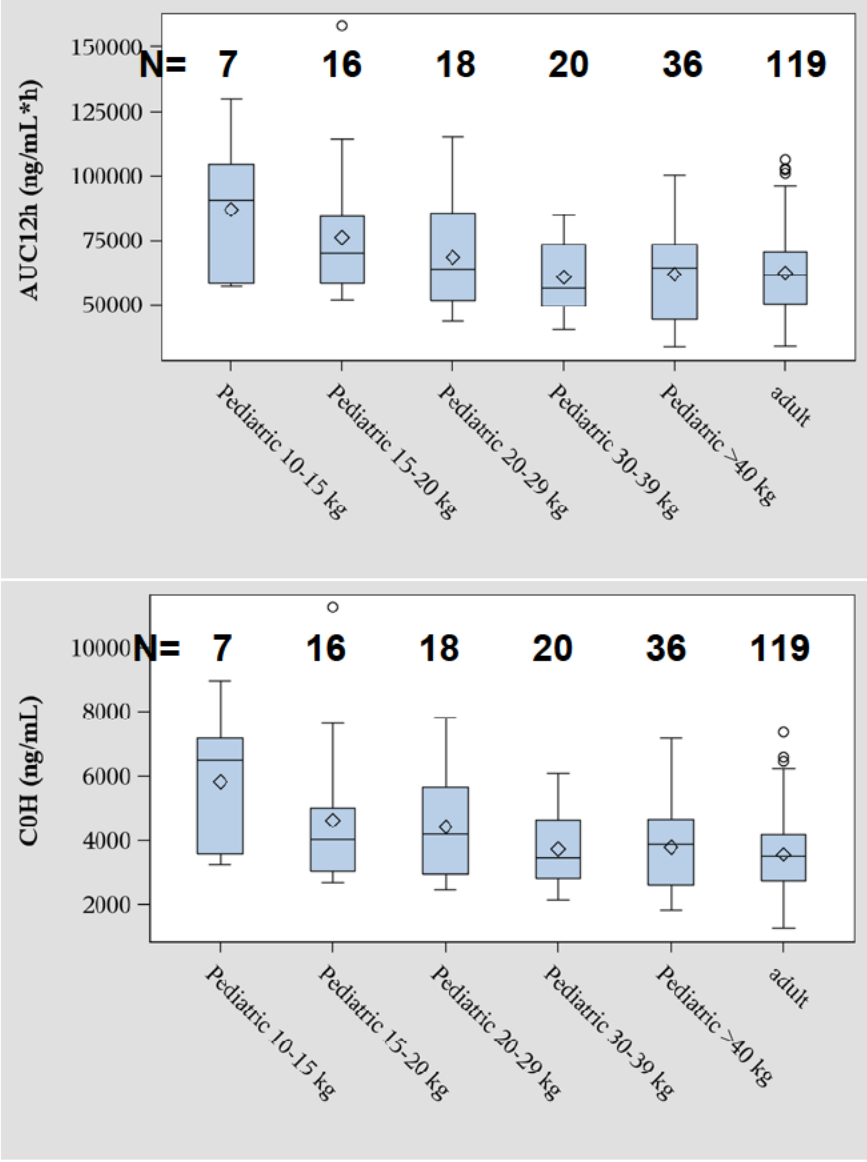
Notes:
1) The units in the table should be µg/mL*hr for $AUC_{(0\text{-}12h)}$.
2) The population PK analysis includes the pharmacokinetic data from 2 weeks after dosage adjustment and week 24.

Table 20-Comparison of the mean darunavir $AUC_{(0\text{-}12h)}$ values prior to and subsequent to the adjustment of the darunavir dosage regimens to the mean target adult exposure

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

Note:
1) The mean $AUC_{(0\text{-}12h)}$ values in Tables 14 and 15 are compared to the mean adult target exposure of 62.3 µg/mL*hr.

Figure 2-Darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} after dosage adjustment in 3 to < 6 year olds (10 kg to < 20 kg) compared to 6 to <18 year olds (20 kg to > 40 kg) and adults



For the initial darunavir dosage regimens, the darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0\text{-}l2h)}$ of 62.3 µg*hr/mL for pediatric subjects weighing 10 kg to less than 15 kg or 15 kg to less than 20 kg. For the adjusted darunavir dosage regimens, the darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0\text{-}l2h)}$ of 62.3 µg*hr/mL for pediatric subjects weighing 15 kg to less than 20 kg but was greater than 130% for pediatric subjects weighing 10 kg to less than 15 kg. The 40% higher $AUC_{(0\text{-}12h)}$ for pediatric subjects weighing 10 kg to less than 15 kg compared to the target adult exposure is not expected to result in any safety issues based on the exposure-safety information for darunavir (see section 10.6). When the darunavir exposure after dosage adjustment for pediatric subjects 3 to less than 6 years old (10 kg to < 20 kg) was compared to 6 to less than 18 year olds (20 kg to greater than 40 kg) and adults, the range of $AUC_{(0\text{-}24h)}$ and C_{0h} values were generally similar with the exception of the 10 kg to less than 15 kg group.

In prior darunavir Clinical Pharmacology reviews, based on the population PK modeling, lower darunavir exposure were observed in subjects with lower baseline AAG concentration. Consistent with these results, in the current trial, lower $AUC_{(0\text{-}12h)}$ values were observed in subjects with lower AAG concentrations. In the Clinical Pharmacology review evaluating the pharmacokinetics of darunavir in older HIV-1 infected subjects 6 to less than 18 years old (NDA 21976-supplement 9), a slight trend was observed of greater changes in viral load from baseline for subjects with higher baseline AAG concentrations. An analysis was not conducted by the applicant to determine if a similar trend is observed in HIV-1 infected pediatric subjects 3 to less than 6 years old. However, in older HIV-1 infected subjects, it was concluded an increase in the darunavir dose was not warranted in pediatric subjects with lower baseline AAG concentrations.

10.4 Efficacy Analysis

The result of the Week 24 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 21, 22, and 23.

Table 21-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 50 copies/mL using TLOVR at Week 24

	DRV/rtv	
Analysis	N	n (%)
TLOVR	27	15 (55.6)
Observed Case	25	16 (64.0)
NC = F	27	16 (59.3)
TLOVR non-VF censored	26	15 (57.7)

N = number of subjects; n = number of responders

Table 22-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 24[a]

n (%)	DRV/rtv N = 27
Virologic success (< 50 copies/mL) at Week 24	16 (59.3)
Virologic failure[b]	9 (33.3)
No virologic data at Week 24 - Discontinued due to AE/death[c]	1 (3.7)
Missing data at Week 24	1 (3.7)

N = number of subjects; n = number of responders

[a] Visit window; Week 20 to 28.

[b] Includes a) subjects who had ≥ 50 copies/mL in the Week-24 window, b) subjects who discontinued prior to Week 24 for lack or loss of efficacy, c) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication), and d) 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 Week-24 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 OBR that was not permitted by the protocol).

Table 23-Efficacy analysis evaluating the percentage of HIV-1 infected subjects with HIV-1 RNA viral load less than 400 copies/mL using TLOVR

	DRV/rtv	
Time Point	N	n (%)
Viral Load < 400 Copies/mL		
Week 2	27	9 (33.3)
Week 4	27	12 (44.4)
Week 8	27	19 (70.4)
Week 16	27	24 (88.9)
Week 24	27	24 (88.9)

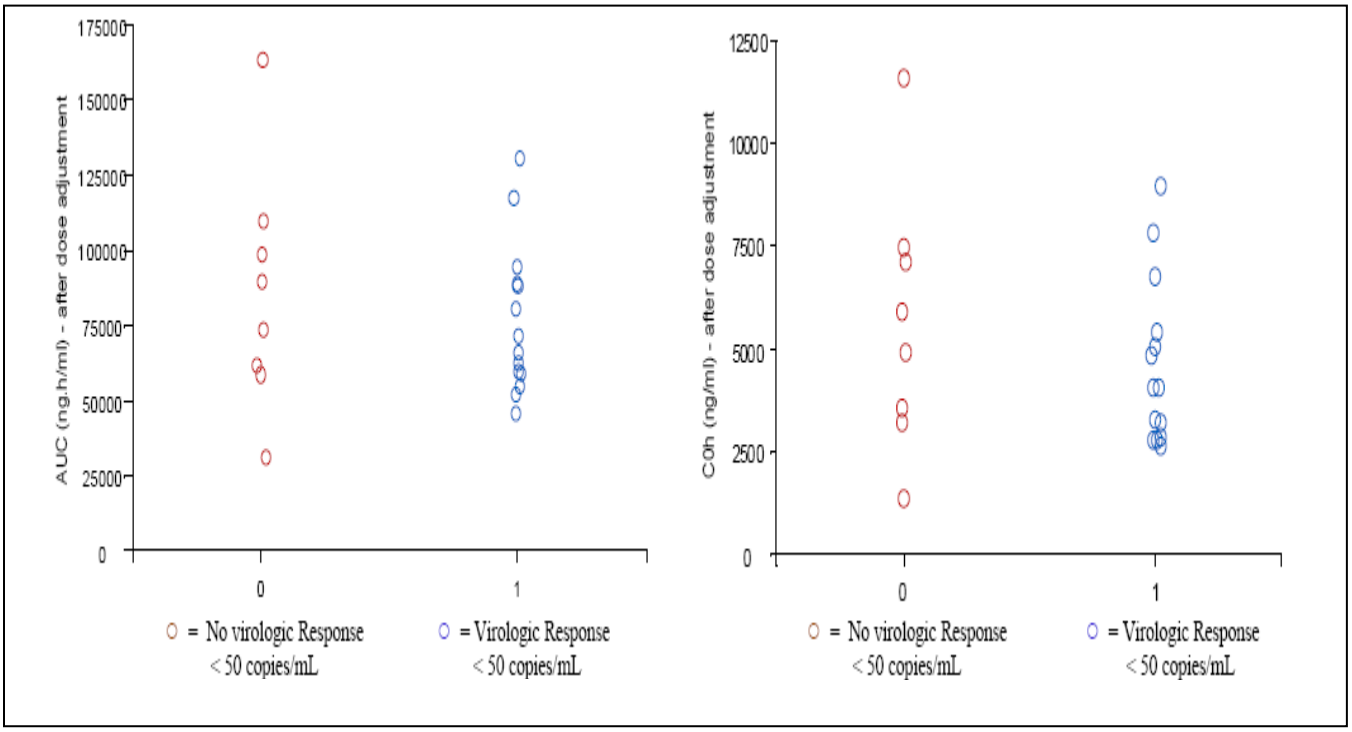
N = number of subjects; n = number of responders

10.5 Exposure-Response Analysis

10.5.1 Applicant Exposure-Response Analysis

In Figure 3, the applicant compared the range of darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects achieving virologic response to subjects that did not achieve virologic response (HIV-1 RNA less than 50 copies/mL).

Figure 3-Comparison of $AUC_{(0-12h)}$ and C_{0h} (for the adjusted darunavir dosage regimens) for subjects either achieving virologic response or not achieving virologic response (HIV-1 RNA less than 50 copies/mL)

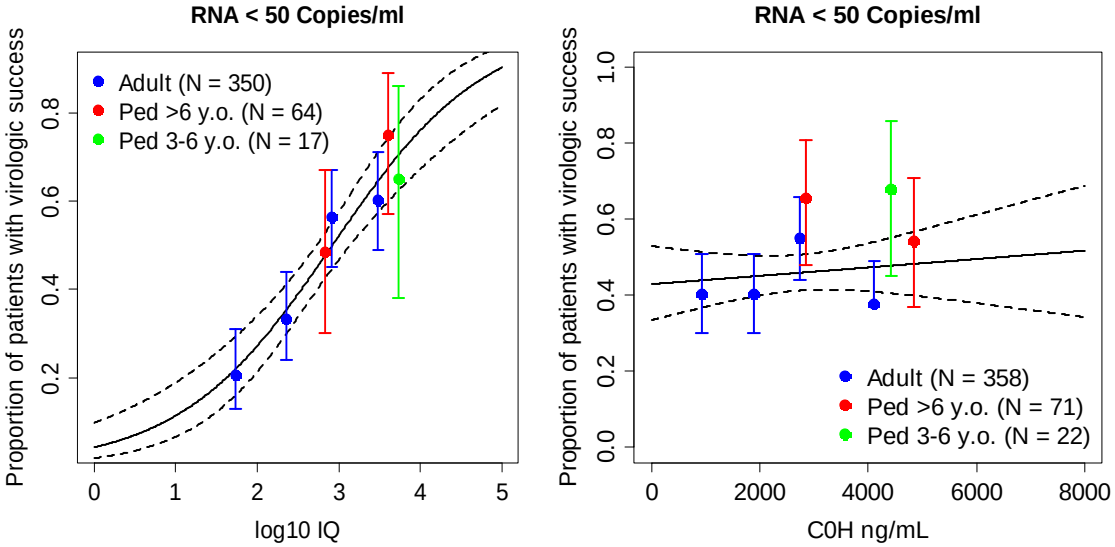


When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir $AUC_{(0-12h)}$ and C_{0h} values were similar.

10.5.2 FDA Exposure-Response Analysis

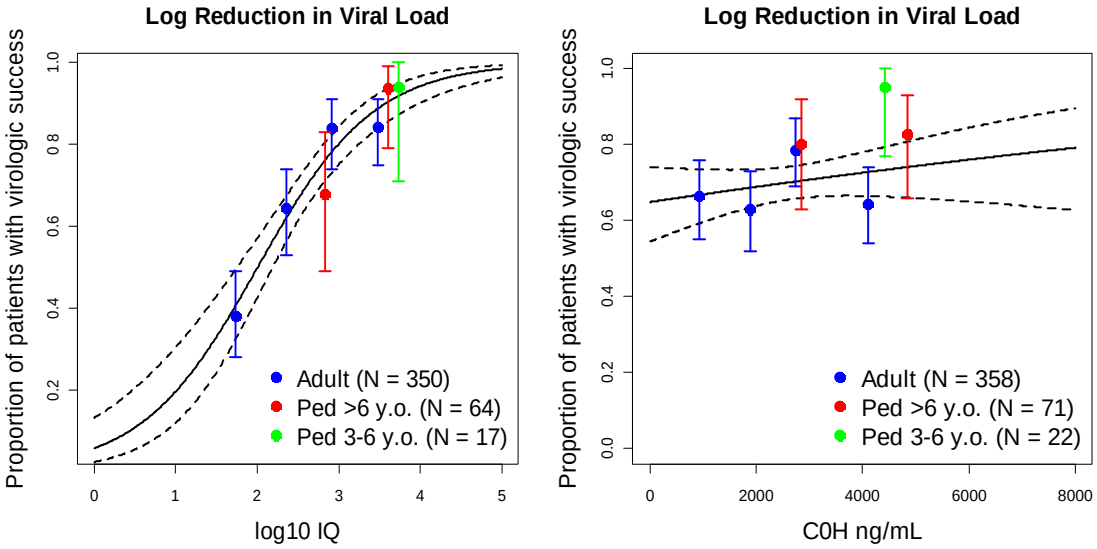
The Pharmacometrics reviewer conducted additional darunavir exposure-response analyses that included an evaluation of the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL and IQ and the proportion of subjects achieving a one log reduction in viral load. For the analysis that was conducted for the review, the IQ was defined as the ratio of darunavir C_{0h} (exposure) at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus). The C_{0h} concentrations reflect the values obtained after adjustment of the darunavir dosage regimens. In addition, the analysis was compared to the results that were previously obtained in older pediatric subjects (6 to less than 18 years old) and adults. The analyses are displayed in Figures 4 and 5.

Figure 4-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (HIV-1 RNA less than 50 copies/mL)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset.

Figure 5-Evaluation of IQ and darunavir C_{0h} (for the adjusted darunavir dosage regimens) and the proportion of subjects achieving virologic response (one log reduction in viral load)



Note: Each vertical bar represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset.

The data for pediatric subjects 3 to less than 6 years old were not broken down into multiple groups (the data for older pediatric subjects 6 to less than 18 years old was divided into two quantiles and the adult data was divided into quartiles). Therefore, for pediatric subjects 3 to less than 6 years old, the relationship between the inhibitory quotient (IQ) and the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL or IQ or a one log reduction in viral load could not be evaluated. In Figures 4 and 5, each vertical bar in the plots represents the proportion of subjects with virologic success (and the 95% confidence interval) at the median value (log_{10} IQ ratio or darunavir C_{0h}) for a given dataset. For pediatric subjects 3 to less than 6 years old, the vertical bar was generally consistent with the vertical bars from older pediatric subjects (6 to less than 18 years old) and adults.

10.6 Safety Analysis

Adverse event information for the TMC114-C228 trial is displayed in Tables 24 and 25.

Table 24-TMC114-C228 adverse event summary information

n (%)	DRV/rtv Overall N = 27	DRV/rtv Before Dose Adjustment N = 27	DRV/rtv After Dose Adjustment N = 26
Mean Exposure (Weeks)	*30.5*	*12.8*	*18.4*
≥ 1 AE	23 (85.2)	19 (70.4)	17 (65.4)
≥ 1 grade 3 or 4 AE	5 (18.5)	4 (14.8)	1 (3.8)
≥ 1 AE at least possibly related to DRV	5 (18.5)	3 (11.1)	2 (7.7)
≥ 1 AE ≥ grade 2 and at least possibly related to DRV	2 (7.4)	1 (3.7)	1 (3.8)
≥ 1 SAE	3 (11.1)	2 (7.4)	1 (3.8)
≥ 1 AE leading to permanent discontinuation	1 (3.7)	1 (3.7)	0

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

Note: Because subjects can have different AEs before compared to after dose adjustment, the sum of the incidences before and after dose adjustment can be greater than the incidence for the overall treatment period.

Table 25-TMC114-C228 adverse events reported in greater than one subject (regardless of severity or causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv Overall N = 27	DRV/rtv Before Dose Adjustment N = 27	DRV/rtv After Dose Adjustment N = 26
Mean Exposure (Weeks)	*30.5*	*12.8*	*18.4*
Any AE	*23 (85.2)*	*19 (70.4)*	*17 (65.4)*
Blood and Lymphatic System Disorders	**3 (11.1)**	**3 (11.1)**	**0**
Neutropenia	2 (7.4)	2 (7.4)	0
Cardiac Disorders	**2 (7.4)**	**2 (7.4)**	**0**
Tachycardia	2 (7.4)	2 (7.4)	0
Eye Disorders	**2 (7.4)**		
Gastrointestinal Disorders	**12 (44.4)**	**11 (40.7)**	**1 (3.8)**
Diarrhea	8 (29.6)	8 (29.6)	0
Vomiting	3 (11.1)	3 (11.1)	0
General Disorders and Administration Site Conditions	**3 (11.1)**	**2 (7.4)**	**1 (3.8)**
Pyrexia	3 (11.1)	2 (7.4)	1 (3.8)
Infections and Infestations	**20 (74.1)**	**12 (44.4)**	**12 (46.2)**
Impetigo	2 (7.4)	2 (7.4)	0
Nasopharyngitis	4 (14.8)	0	4 (15.4)
Otitis media acute	2 (7.4)	1 (3.7)	1 (3.8)
Otitis media chronic	2 (7.4)	1 (3.7)	1 (3.8)
Pharyngitis	2 (7.4)	1 (3.7)	1 (3.8)
Pneumonia	2 (7.4)	1 (3.7)	1 (3.8)
Rhinitis	3 (11.1)	3 (11.1)	0
Tinea capitis	2 (7.4)	1 (3.7)	1 (3.8)
Upper respiratory tract infection	9 (33.3)	7 (25.9)	2 (7.7)
Injury, Poisoning and Procedural Complications	**3 (11.1)**	**1 (3.7)**	**2 (7.7)**
Investigations	**6 (22.2)**	**3 (11.1)**	**4 (15.4)**
Metabolism and Nutrition Disorders	**6 (22.2)**	**6 (22.2)**	**0**
Acidosis	3 (11.1)	3 (11.1)	0
Alkalosis	4 (14.8)	4 (14.8)	0
Hypokalemia	5 (18.5)	5 (18.5)	0
Hyponatremia	2 (7.4)	2 (7.4)	0
Respiratory, Thoracic and Mediastinal Disorders	**5 (18.5)**	**5 (18.5)**	**2 (7.7)**
Cough	4 (14.8)	4 (14.8)	-
Nasal congestion	2 (7.4)	1 (3.7)	1 (3.8)
Rhinorrhea	2 (7.4)	1 (3.7)	1 (3.8)
Skin and Subcutaneous Tissue Disorders	**5 (18.5)**	**3 (11.1)**	**3 (11.5)**

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

10.7 Exposure-Safety Analysis

There were no additional exposure-safety analyses that were conducted by the FDA for pediatric subjects 3 to less than 6 years old. The adverse events that were reported for the trial did not warrant further exposure response analysis (see Tables 20 and 21). No

relevant trends were identified for the exposure-safety analyses that were conducted by the applicant.

11. Discussion and Conclusions

Based on the results from the TMC114-C228 trial, the following conclusions can be made regarding the proposed darunavir/ritonavir pediatric dosage regimens in pediatric patients (b) (4)

- The darunavir mean $AUC_{(0\text{-}12h)}$ value was within 80% to 130% of the target mean adult $AUC_{(0\text{-}12h)}$ of 62.3 µg*hr/mL for pediatric subjects weighing 15 kg to < 20 kg (22% higher) but was greater than 130% for pediatric subjects weighing 10 kg to < 15 kg (40% higher).
- The 40% higher $AUC_{(0\text{-}12h)}$ value for pediatric subjects weighing 10 kg to < 15 kg compared to the target adult exposure is not expected to result in any safety issues.
- When compared to 6 to <18 years olds (20 kg to > 40 kg) and adults, the darunavir $AUC_{(0\text{-}24h)}$ and C_{0h} values for pediatric subjects 3 to < 6 years old (10 kg to < 20 kg), were generally similar with the exception of the 10 kg to <15 kg group.
- When pediatric subjects achieving HIV-1 RNA less than 50 copies/mL were compared to pediatric subjects that did not achieve HIV-1 RNA less than 50 copies/mL, the range of darunavir $AUC_{(0\text{-}12h)}$ and C_{0h} values were similar.
- When the proportion of subjects with virologic success (<50 copies/mL or one log reduction in viral load) at the median value (log_{10} IQ ratio or darunavir C_{0h}) were evaluated, the results for pediatric subjects 3 to < 6 years old were generally consistent with the previous results from older pediatric subjects (6 to less than 18 years old) and adults.
- No relevant exposure-safety trends were identified for the trial.

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 202895
Submission Number (Date)	23 Nov 2010
Drug Name	Darunavir
Proposed Indication	Treatment of HIV-1 infection in pediatric subjects 3 to 6 years old
Clinical Division	DAVP
Primary CP Reviewer	Stanley Au, Pharm.D., BCPS
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Sarah Robertson, Pharm.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Applicant	Tibotec, Inc.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The main purpose of this review is to determine whether the proposed dosing regimen for darunavir(DRV)/ritonavir(RTV) in pediatric subjects 3 to < 6 years of age (Table 1) is acceptable.

Table 1. Proposed Dosing Regimen for DRV Oral Suspension in Combination with RTV for Pediatric Subjects 3 to < 6 Years of Age

Body Weight		Dose
(kg)	**(lbs)**	**(twice daily)**
		(b) (4)

The review will focus on the following sub-questions.

1.1.1 Does the proposed DRV/RTV dosing regimen in pediatric subjects 3 to < 6 years of age (10-20 kg) achieve similar exposures to that of other pediatric subjects (>20 kg) and adults receiving the approved dosing regimens?

The proposed DRV/RTV dosing regimen (Table 1) in pediatric subjects 3 to < 6 years of age achieve higher exposures compared to exposures in other pediatric subjects (>20 kg) and adults receiving the approved dosing regimen. The pharmacokinetic data were

derived from subjects weighing 10-<15 kg (N=7) and 15-<20 kg N=16) after DRV oral suspension doses were adjusted in the TMC114-C228 trial. The results showed that the mean DRV exposure (AUC_{12} and C_{0h}) was about 40% and 20% higher in the 10-<15 kg and 15-<20 kg weight groups after receiving DRV oral suspension compared to exposures in adults at the approved 600 mg DRV/100 mg RTV b.i.d. tablets (TMC114-C202 and TMC114-C213 trials) (Figure 1 and Figure 2). The AUC_{12} and C_{0h} in other pediatric subjects (≥ 20 kg from TMC114-C212) at the approved twice daily regimen were within the exposures observed in adults and pediatric subjects weighing 10- <20 kg.

Figure 1. DRV AUC_{12} (ng*h/mL) in adult and pediatric subjects at the proposed dosing regimen

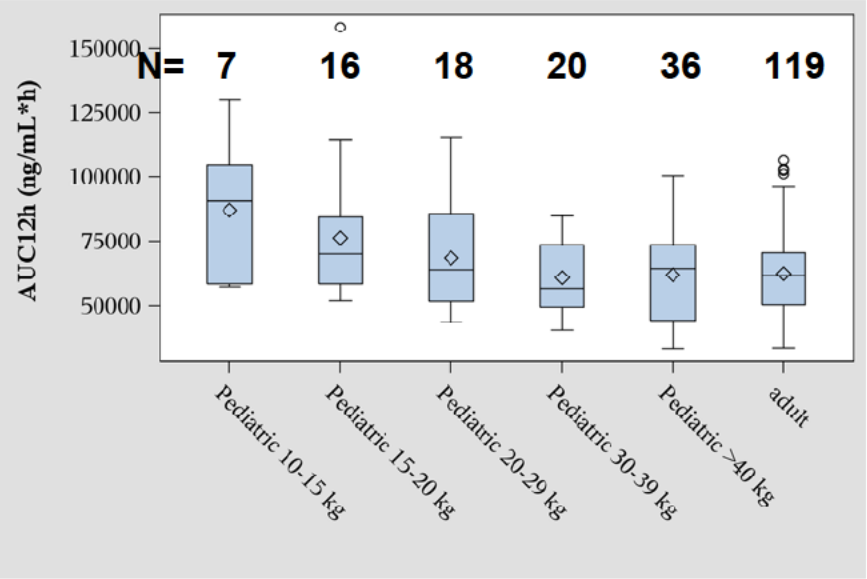
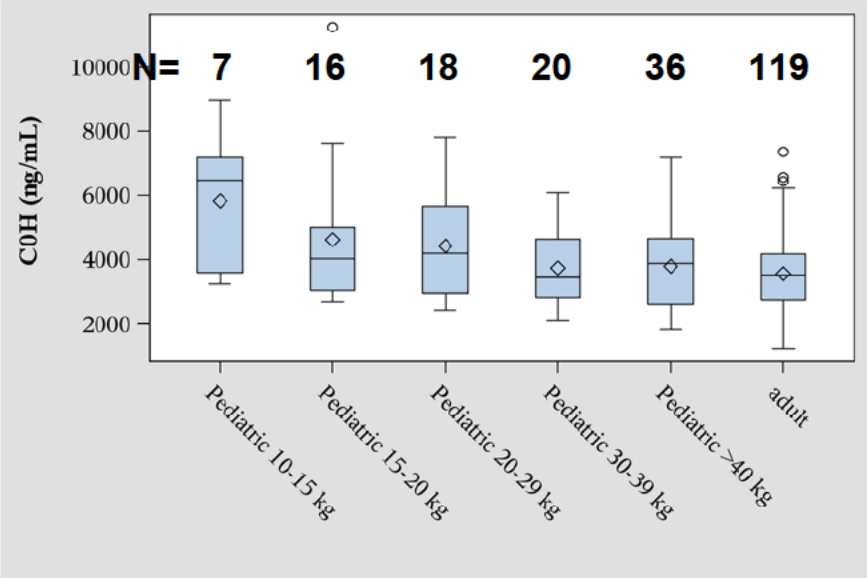


Figure 2. DRV C_{0h} (ng/mL) in adult and pediatric subjects at the proposed dose



1.1.2 Is the inhibitory quotient (IQ)-response relationship for efficacy in pediatric subjects 3 to < 6 years of age consistent with that of other pediatric subjects (6 to <18 years) and adults?

The IQ-response relationship in pediatric subjects 3 to <6 years of age was consistent with the relationship observed in other pediatric subjects (6 to < 18 years old) and adults. The inhibitory quotient (IQ) is the ratio of steady-state trough concentration (C_{0h}) and the baseline IC_{50} value. The IQ combines the drug concentration and the susceptibility of the virus to DRV. As observed in other pediatric subjects and adults, the fold-change (FC) resistance is the primary driver of the virologic success in pediatric subjects 3 to <6 years of age. The pharmacometric review of DRV for the treatment-experienced adults from the TMC114-C202 and TMC114-C213 trials and for pediatric subjects 6 to < 18 years of age from the TMC114-C212 trial demonstrated that the probability of virologic response or success (measured as HIV-1 RNA <50 copies/mL or 1 log reduction in viral load by week 24) was strongly related to increasing IQ values. On the other hand, the relationship between C0h and the probability of virologic response or success was shallow. The data in pediatric subjects 3 to <6 years of age from the study TMC114-C228 was consistent with the previously observed relationships between IQ and C_{0h} (Figure 3 and Figure 4). For those subjects 3 to <6 years of age with complete IQ and viral load data at week 24, 68% of subjects had a viral load < 50 copies/ml and 95% of subjects experienced at least a one log drop decrease in plasma viral load.

Figure 3. Relationship between IQ (left) or C_{0h} (right) and the Probability of Virologic Success (HIV-1 RNA < 50 copies/mL at Week 24) in Adults and Pediatric Subjects. The solid line represents the logistic regression model fit for the data in adults. The dotted lines represent the 95% confidence interval.

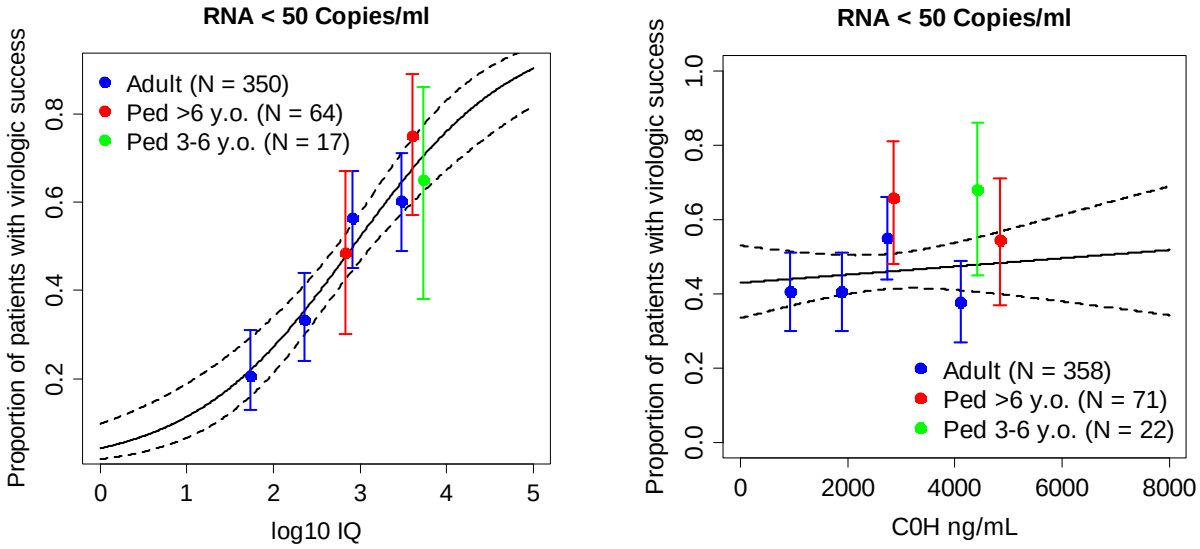
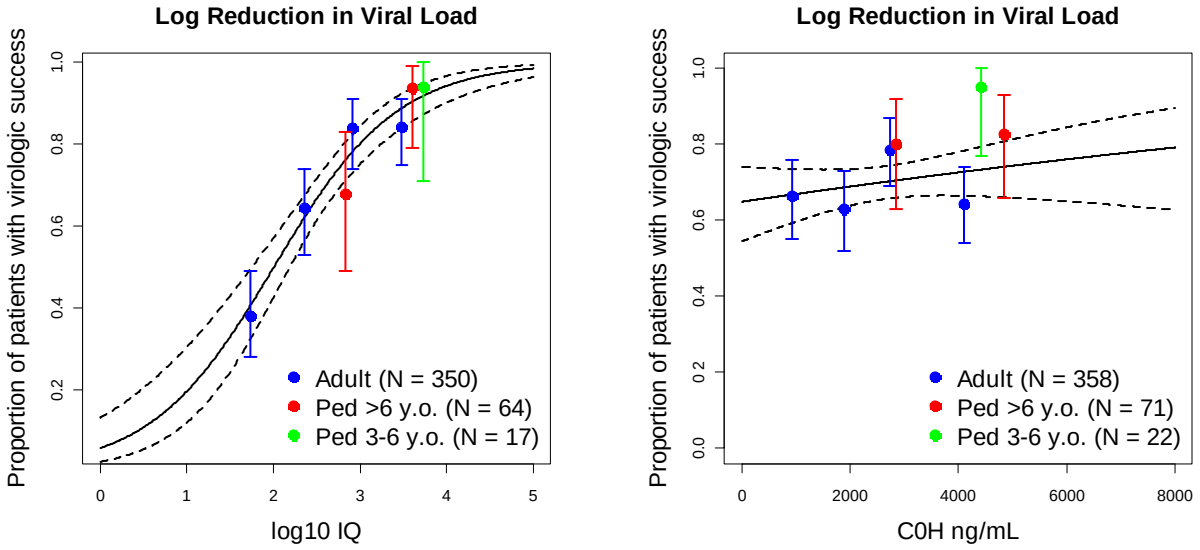


Figure 4. Relationship between IQ (left) or C_{0h} (right) and the Probability of 1 Log Reduction in Viral Load at Week 24 in Adults and Pediatric Subjects. The solid line represents the logistic regression model fit for the data adult. The dotted lines represent the 95% confidence interval.



1.1.3 What are the characteristics of the exposure-safety relationship in pediatric subjects 3 to < 6 years of age?

Twenty-seven subjects (15 males and 12 females) were enrolled in the trial and only one subject prematurely discontinued (due to vomiting, grade 2 that was considered to be not related to DRV). The initial dose of DRV was 20 mg/kg in combination with RTV (3 mg/kg) to target DRV exposure between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL that was achieved with DRV/RTV 600/100 mg twice daily. The initial dose was adjusted to DRV/RTV 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg based on the applicant's interim simulation.

Most of the adverse events were not considered related to DRV. According to the medical reviewer, "*the Applicant demonstrated an acceptable safety profile for darunavir co-administered with ritonavir in combination with other antiretroviral drugs*." Adverse events considered at least possibly related to DRV were in Table 2. Three events occurred before the dose adjustment and two events occurred after the dose adjustment. Therefore, it appears there is no clear exposure-safety relationship which is also consistent with the observations in the adults and pediatric subjects 6 to < 18 years of age.

Table 2. Adverse Events Considered at Least Possibly Related to DRV During the Treatment Period – TMC114-C228

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv Overall N = 27	DRV/rtv Before Dose Adjustment N = 27	DRV/rtv After Dose Adjustment N = 26
Mean Exposure (Weeks)	*30.5*	*12.8*	*18.4*
Any AE at Least Possibly Related to DRV	*5 (18.5)*	*3 (11.1)*	*2 (7.7)*
Gastrointestinal Disorders	**2 (7.4)**	**2 (7.4)**	**0**
Diarrhea	2 (7.4)	2 (7.4)	0
Infections and Infestations	**1 (3.7)**	**1 (3.7)**	**0**
Rash pustular	1 (3.7)	1 (3.7)	0
Investigations	**3 (11.1)**	**1 (3.7)**	**2 (7.7)**
AST increased	1 (3.7)	1 (3.7)	0
Blood cholesterol increased	1 (3.7)	0	1 (3.8)
ECG QT prolonged	1 (3.7)	0	1 (3.8)
Skin and Subcutaneous Tissue Disorders	**1 (3.7)**	**0**	**1 (3.8)**
Rash papular	1 (3.7)	0	1 (3.8)

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

Source: Sponsor's Summary of Clinical Safety report, Table 8, page 25

Due to the lack of any major safety signal, the higher exposures in pediatric subjects 3 to <6 years of age are acceptable. These higher exposures also ensure that the coverage for efficacy is sufficient.

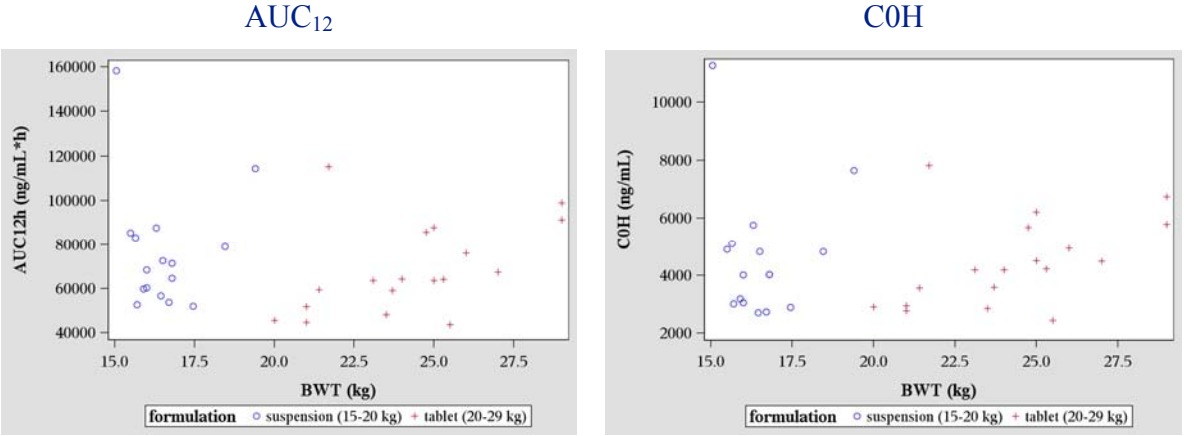
1.1.4 Does the clinical evidence support using DRV suspension in pediatrics weighing > 20 kg and adults and DRV tablet in pediatrics weighing 15 to 20 kg who can swallow?

Yes. The use of DRV suspension in pediatrics weighing > 20 kg and adults and using DRV tablet in pediatrics weighing 15 to 20 kg are acceptable.

The sponsor conducted a relative BA/BE study (TMC114-C169) in healthy subjects to compare the suspension formulation to that of the commercial 300 mg tablet formulation in the presence of low-dose RTV. Coadministration of a single 600 mg dose of DRV with low-dose ritonavir resulted in comparable Cmax, AUClast, and AUC∞ values of DRV following administration of an oral suspension and commercial tablet with 90% confidence intervals within the limits of bioequivalence. However, OSI recommended that the C169 data should not be accepted based on the regulatory compliance issue (Tibotec did not maintain reserve samples of either reference or test drug for the C169 trial).

The DRV exposures (AUC_{12} and C0H) for pediatric subjects who received 380 mg of DRV suspension (rounding due to the dosing pipette) in Study TMC114-C228 and 375 mg tablets in Study TMC114-C21 were compared. As shown in Figure 5, the DRV exposure values were comparable between these groups. To derive the ratio between the exposures after two formulations, AUC_{12} was normalized for 20 kg of body weight and was adjusted for the AAG level by using SAS "proc glm lsmeans" method for log transformed AUC_{12_WT20} (both body weight and AAG were significant covariates for CL in population PK analysis). The ratio of DRV AUC_{12} geometric means (normalized at 20 kg and adjusted for AAG) between the suspension and tablet was found to be 97% (with 90% CI: 80% - 118%). Based on these data, the suspension and tablet formulations yield comparable exposures at 375 mg DRV dose in combination with RTV.

Figure 5. DRV exposure in pediatric subjects with 380 mg DRV suspension or 375 mg DRV tablet (by body weight)



There are no data on interchangeability of these formulations at doses higher than 375 mg. DRV exposures for tablet formulation increase in less than dose-proportional manner

(increasing the dose from 400 to 600 (1.5 fold) results in 1.18 to 1.29 fold increase in DRV exposures). Therefore, dose proportionality of the suspension formulation cannot be derived from the lower dose strength. However, the exposures at the 450 mg (pediatric subjects weighing 30 to 39 kg) or 600 mg (pediatric subjects weighing >40 kg and adults) doses are comparable to the exposure of that of 375 mg dose in the subjects weighing 15 to 29 kg. Therefore, the concerns about the potential nonlinearity PK are less important. On the other hand, the exposure-response for both efficacy and safety is shallow. The viral response and safety profiles in the first quartile of exposure (median AUC=25071 ng*h/mL or Ctrough=934 ng/mL) in adults were comparable to those in the last quartile (median AUC=68813 ng*h/mL or Ctrough=4113 ng/mL). Therefore, if the change in exposures after suspension formulation is slightly different from those observed with the tablet formulation, the shallow exposure-response relationship supports *the use of either the oral suspension or the commercial tablets.*

1.2 Recommendations

The proposed dosing recommendation of DRV/RTV in pediatric subjects 3 to < 6 years of age (Table 1) is acceptable.

2 PERTINENT REGULATORY BACKGROUND

Darunavir (DRV), a HIV protease inhibitor (PI), in combination with the low-dose ritonavir (RTV) is currently approved by the FDA for the use in treatment-experienced pediatric subjects aged 6 years to < 18 years old. The current approved dose is shown in Table 3.

Table 3. Currently Approved Dose of DRV/RTV for Subjects 6 Years to < 18 Years Old

Body Weight		Dose
(kg)	**(lbs)**	(twice daily)
> 20 kg - < 30 kg	> 44 lbs - < 66 lbs	375 mg DRV/50 mg RTV
≥ 30 kg - < 40 kg	≥ 66 lbs - < 88 lbs	450 mg DRV/60 mg RTV
≥ 40 kg	≥ 88 lbs	600 mg DRV/100 mg RTV

The currently NDA 202-895 is submitted to fulfill the remaining requirements for the Pediatric Written Request for PREZISTA® (DRV). The new open-label Phase 2 trial, TMC114-C228, provides pharmacokinetic, safety, tolerability and virologic success data that supports the weight-based dosing recommendations of DRV in combination with RTV for the treatment of HIV-1 treatment-experienced pediatric subjects ages 3 to < 6 years and weighing between 10 and 20 kilograms. Twenty-seven subjects were enrolled in the study and were stratified by weight (≥10 - < 15kg, ≥ 15- < 20 kg). The initial dose of DRV was 20 mg/kg in combination with RTV (3 mg/kg) to target DRV exposure between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL achieved with DRV/r

600/100 mg twice daily). The initial dose was adjusted to DRV/RTV 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg based on the sponsor's interim simulation. The sponsor is seeking an approval of the adjusted dosing regimen (b) (4)

3 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted a population pharmacokinetic analysis based on the previously developed model in the treatment-experienced adults and pediatric subjects 6 to < 18 years of age to incorporate data from pediatric subjects aged 3 to <6 years from the TMC114-C228 trial. The resulting model was then used to predict the individual pharmacokinetic parameters at Week 24, which were subsequently used for the description of DRV exposures and the evaluation of exposure-response relationships.

The dataset used for the initial model adjustment consisted of 555 plasma DRV concentrations from 95 subjects from the TMC125-C206 and TMC125-C216 trials for adults and TMC114-C212 for pediatric subject aged 6 and above and Week 2 data from the study TMC114-C228 for pediatric subjects aged 3 to <6 years (Table 4). The data from the two studies in adult subjects was chosen to provide a similar richness of pharmacokinetic sampling and a balance between the number of adults and children included in the analysis.

Table 4. Summary of Data Included in Model Adjustment

Item	Trial 1	Trial 2	Trial 3	Trial 4
Trial	TMC114-C228	TMC114-C212	TMC125-C206	TMC125-C216
No. of subjects	24	41	11	19
Administration routes and dose of DRV/rtv	20/3 mg/kg b.i.d.	300-600/50-100 mg b.i.d.	600/100 mg b.i.d.	600/100 mg b.i.d.
Darunavir formulation(s)	100 mg/mL suspension	75-mg tablets (F027) 300-mg tablets (F016)	300-mg tablets (F016)	300-mg tablets (F016)
Ritonavir formulation(s)	80 mg/mL solution	80 mg/mL solution	100-mg capsules	100-mg capsules
Number of samples per subject	5	5	8	8
Assay LOQ	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL	5.00 ng/mL
Time range	0-12 h	0-12 h	0-12 h	0-12 h

Source: Sponsor's tmc114-c228 popPK report, Table 1, page 12

For details and reviews of model development in adults and older kids, 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. Considerable shrinkage to the mean is apparent in individual estimates of V2, Q and V3, but to a smaller extent for CL_{INT} and KA. 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)	51.4	5.6	29	19
Influence of WT[a]	0.524	12		
K_{AFF} of AAG (dL/mg)	0.0304	---		
V2/F (L)	131	11	48[2]	103
Influence of WT[b]	0.867	16		
Q/F (L/h)	15.0	---	65	---
V3/F (L)	84.3	---	56	---
KA (1/h)	0.455	---	77[2]	32
F_{rel}	1.18	---		
Residual Error	0.0623	10		

[a] Change in parameter based on body weight (WT)
[b] Correlation between the variance estimates of apparent central volume and absorption rate constant estimated at 0.67

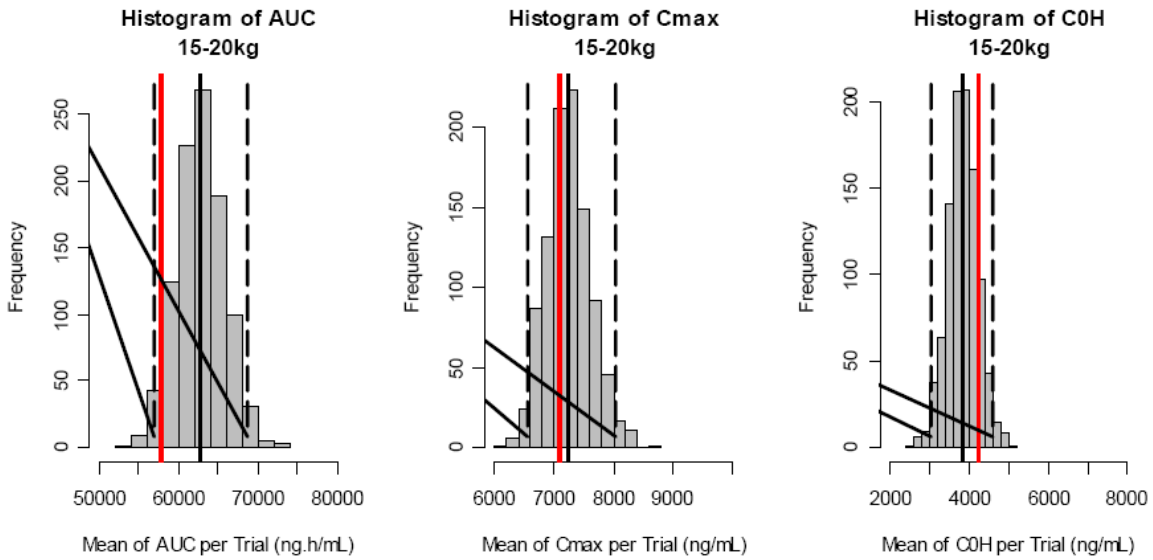
Source: Sponsor's tmc114-c228 popPK report, Table 5, page 18

The dataset used for prediction of DRV pharmacokinetic parameters in pediatric subjects at Week 24 combined richly sampled profiles from 19 subjects at Week 2 and sparse data from 24 subjects. It consisted of a total of 298 plasma DRV measurements from the TMC114-C212 trial. To obtain individual pharmacokinetic parameters, empirical Bayes estimation was performed using NONMEM V with the MAXEVAL=0 option in the $ESTIMATION record. Simulation records were added to the NONMEM dataset to obtain prediction of C_{0h} at each visit. The area under the model-predicted DRV concentration curve (AUC_{tau}) was calculated as Dose/(CL/F).

Reviewer's Comments: The sponsor's population PK analyses are acceptable and are consistent with previous conclusions in older kids and adults.

The actual observed pharmacokinetics (PK) (AUC_{tau}, C_{max} and C_{0h}) of darunavir (DRV) after administration of an oral suspension formulation from Study C228 were compared with the expected pharmacokinetics obtained through simulation after administration of the commercial tablet. The population PK model that describes the PK of DRV in children >20 kg and treated twice daily with the commercial tablet (see Dr. Kevin Krudys' previous PM review) was used to simulate concentrations in a selected pediatric population weighing 15 to <20 kg in Study C228. As shown in Figure 6, the observed PK means (AUC_{tau}, C_{max} and C_{0h}) of the TMC114-C228 study are contained within the 95th prediction interval of the simulated PK means.

Figure 6: Predicted mean distribution of AUCtau, Cmax and C0h calculated from the simulations in 15 to <20 kg children treated b.i.d. with the commercial tablet. The solid red line represents the observed trial mean, as obtained in study TMC114-C228, the solid black line represents the mean of the simulated trial means, and the dashed black lines represent the 95th prediction interval of the simulated trial means.



Source: Sponsor's simulation report responding to the teleconference held with the Division on 22 Aug 2011 regarding clinical pharmacology aspects of the oral suspension formulation, Figure 1, page 9.

*Reviewer's Comments: The sponsor's simulation is reasonable and the results suggest that the administration of the DRV oral suspension and the commercial tablet results in similar exposure (AUCtau, Cmax and C0h) in HIV-1 infected children weighing 15 to <20 kg. Although the observed mean AUCtau after the DRV oral suspension (~58000 ng*h/mL) is 8% lower than the predicted AUCtau after tablet (~63000 ng*h/mL), this*

difference should not be a clinical concern considering that the exposure-response for both efficacy and safety is shallow. Therefore, the available information supports the use of either the oral suspension or the commercial tablets.

4 LISTING OF ANALYSES DATA SETS, CODES AND OUTPUT FILES

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
TMC114-C202 and TMC114-C213	xpk.xpt	\\Cdsesub1\evsprod\NDA021976\0006\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\tmc114-c926\datasets\analysis
TMC114-C212	expsaf.xpt	\\Cdsesub1\evsprod\NDA021976\0069\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hiv-1-infection\5352-stud-rep-uncontr\tmc114-c212\datasets\analysis
TMC114-C228	pcad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\
TMC114-C228	ppad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\ppad.xpt
TMC114-C228	ptad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\ptad.xpt
TMC114-C228	vlad.xpt	\\Cdsesub1\evsprod\NDA202895\0000\m5\datasets\tmc114-c228\analysis\datasets\vlad.xpt
TMC114-C228 (WK 2 NONMEM data)	modeldataset-dat.xpt	\\Cdsesub1\evsprod\NDA202895\0006\m5\datasets\tmc114-tidp29-c228\pharmacokinetics\week2-model-app-c
TMC114-C228 (WK 24 NONMEM data)	modeldataset20101021.xpt	\\Cdsesub1\evsprod\NDA202895\0006\m5\datasets\tmc114-tidp29-c228\pharmacokinetics\week24-model-app-d

Table 7. Analysis Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
eff_analysis_1log.R	IQ – 1 log reduction in viral load exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_1log_C0H.R	C_{0h} – 1 log reduction in viral load exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_RNA_50.R	IQ – < 50 copies/ml RNA exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
eff_analysis_RNA_C0H_50.R	C_{0h}– < 50 copies/ml RNA exposure-response analysis	Darunavir_NDA202895_JL\ER Analyses
PKPD_darunavir.sas	Comparing DRV exposure between pediatircs and adults	Darunavir_NDA202895_JL\ER Analyses
week2.ctl	Sponsor's final model (NONMEM control file)	Darunavir_NDA202895_JL\PPK Analyses\week2-model-app-c
week2.lst	Sponsor's final model (NONMEM output file)	Darunavir_NDA202895_JL\PPK Analyses\week2-model-app-c
week24.ctl	Sponsor's model of Week 24 PK parameters (NONMEM control file)	Darunavir_NDA202895_JL\PPK Analyses\week24-model-app-d
week24.lst	Sponsor's model of Week 24 PK parameters (NONMEM output file)	Darunavir_NDA202895_JL\PPK Analyses\week24-model-app-d

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/s/

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Concur with pharmacometrics review

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