CLINICAL REVIEW

Application Type	NDA 21-976
Submission Number	009
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Letter Date	June 20, 2008
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Reviewer Name	Yodit Belew, M.D.
Review Completion Date	November 29, 2008
Established Name	Darunavir
(Proposed) Trade Name	PREZISTA
Therapeutic Class	Protease Inhibitor
Applicant	Tibotec
Priority Designation	P
Formulation	Oral Tablet (75 mg, 300mg)
Dosing Regimen	Twice daily (BID)
Indication	Treatment of HIV-1 Infection
Intended Population	Pediatric Population 6 -<18 years of Age

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1 RECOMMENATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

The supplement to NDA (b) (4) (009) containing interim 24 week data from the ongoing pediatric clinical trial TMC114-c112 supports the use of Prezista (darunavir, DRV) co-administered with ritonavir in combination with other antiretroviral drugs for the treatment of HIV infection in treatment-experienced subjects ages 6 - < 18 years of age. This reviewer recommends the approval of this supplemental NDA (sNDA). Darunavir co-administered with ritonavir, in combination with other drugs, resulted in DRV plasma exposures comparable or slightly higher than the exposures in adults and resulted in HIV-1 viral load reductions and increases in CD4 cell counts over the 24 week study period across all ages.

No deficiencies were identified in the sNDA that would preclude the approval. Darunavir/ritonavir (DRV/r) was studied in one phase 1/2a, open-label, randomized study. Subjects were stratified according to weight (≥20- <30 kg, ≥30- <40 kg, ≥40 kg) and randomized to one of the 3 doses of darunavir/ritonavir: 375 mg DRV/50 mg ritonavir twice daily, 450 mg DRV/60 mg ritonavir twice daily, or 600 mg DRV/100 mg ritonavir twice daily, respectively with an optimized background antiretroviral (ARV) therapy. In addition, the Applicant submitted dissolution profiles to support new 75 mg tablet strength for use in pediatric subjects.

Two doses of darunavir/ritonavir were studied during Part 1 of the study. Part 1 was designed to provide dose recommendations of DRV/rtv in HIV-1 infected, treatment-experienced pediatric subjects weighing 20 to 50 kg. A total of 44 subjects were enrolled and randomized in a 1:1 ratio to receive either the adult equivalent dose of DRV with low-dose ritonavir b.i.d. (Dose Group A) or a 20 to 33% higher dose of DRV with low-dose ritonavir b.i.d. (Dose Group B) in combination with ARV agents. Results from the Week 2 pharmacokinetic, efficacy and safety analysis showed both groups met the protocol specified criteria for target plasma exposures based on the overall mean results; however, based on the individual pharmacokinetic data as well as the favorable efficacy, safety and tolerability profile seen with Group B, the higher dose was selected for Part 2. All subjects from Part 1 were switched to the selected dose at the next visit and subjects subsequently continued to the second part of the trial.

Eighty subjects were enrolled for Part 2 of the study. Subjects were stratified by weight and received DRV/rtv according to the weight band:

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

Overall, the virologic response defined as the percentage of subjects with a confirmed virologic response (plasma viral load < 400 copies/mL) was 66%. The proportion of subjects with virologic response was higher in the younger age group (6-12 years) when compared to the older

age group (12-18 years), 92% vs. 55%, respectively. The response was also higher in the lower weight groups: 75% in the 20-39kg group vs. 54% in the 40-49kg group vs. 58% in the >50kg group. These differences are likely due to the extent of treatment experience in older (and higher weight) groups compared to younger subjects with less treatment experience.

The Applicant demonstrated an acceptable safety profile for darunavir co-administered with ritonavir in combination with other antiretroviral drugs. While adverse events were common (85%), significantly less were serious in nature (10%) and only one subject discontinued treatment prior to week 24 due to an adverse event. Many of the adverse events were related to common childhood illnesses or conditions. Five subjects (6%) experienced liver related adverse events and 5 subjects (6%) experienced rash or maculopapular rash. Clinically significant laboratory abnormalities were also relatively uncommon and did not lead to treatment discontinuation.

No exposure-safety relationship was demonstrated for neither hepatic adverse events nor for rash adverse events.

The applicant will submit a full 48 week study report when available.

Similar to many other pediatric studies which evaluate safety and effectiveness of ARVs, this study did not contain a control group and was not powered to detect safety or efficacy differences between groups. Descriptive statistical methods were used to describe the findings.

1.2 Risk Benefit Assessment

Darunavir/ritonavir in combination with other antiretroviral drugs has been shown to be effective in treating HIV-1 infected treatment experienced adults. Virologic activity and immunologic benefit was also demonstrated in all the studied pediatric age groups. More children weighing <40 kg (most of whom were younger than 12 years of age) achieved and maintained HIV RNA < 400 and < 50 copies/mL compared to children who weigh >40 kg. The most likely explanation for the observed difference in virologic response is the history of previous ARV treatment. Most of the subjects acquired HIV via vertical transmission. Therefore subjects who weighed >40 kg tended to be older and with more treatment experience.

The observed risks for darunavir are well known and the type and rate of adverse events were similar to adults with few exceptions. Risks identified with the use of darunavir/ritonavir in adults include hepatotoxicity (including drug-induced hepatotoxicity), which are displayed under the Warnings and Precautions section in the current darunavir label. The risk of darunavir induced (i.e. drug induced) liver toxicity was added to the darunavir label in March, 2008 after review of case reports and Periodic Safety Update Reports.

At the Week 24 study analysis in the adult trials (TMC114-C213 and TMC114-C202, randomized; TMC-C213 and TMC114-C202, non-randomized), 5-10% of the subjects had Grade 2 or higher elevation in AST, 7% had ≥ Grade 2 elevation in ALT and 3-5% of the subjects had ≥ Grade 2 elevation in alkaline phosphatase.

Similar to adults, 3% pediatric subjects (n=2) developed Grade 2 or greater elevation in AST, ALT and/or alkaline phosphatase. Only one subject had Grade 4 increase in ALT and no subject had Grade 4 increases in AST or alkaline phosphatase.

There are currently a limited number of protease inhibitors available for use in pediatric patients. Darunavir would provide an alternative treatment option for HIV-1 infected treatment-experienced pediatric patients. Given no apparent increase in clinically significant adverse events, including hepatotoxicity, the virologic and immunologic benefit demonstrated in all age groups outweighs the observed and potential risks.

Of note, the DSMB responsible for review of this pediatric study was also in support of the selection of the high dose to be used during Part 2 of the study. The DSMB also acknowledged that the successful treatment of HIV-1 infection outweighed the potential for adverse events.

I also concur with the CMC and Clinical Pharmacology review and support approval for the 75 mg tablet formulation.

1.3 Recommendations for Postmarketing Risk Management Activities

The Applicant will continue to follow pediatric subjects who have enrolled into the study until week 48. In addition, the Applicant will submit periodic safety reports for review.

No additional pediatric postmarketing risk management activities are planned.

1.4 Recommendations for other Post Marketing Study Commitments

Additional pediatric post marketing study commitments have already been issued (see Section 2.5). No new PMC for pediatric population will be issued at this time.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Established name:	Darunavir (DRV)
Trade name:	Prezista™
Molecular formula:	$C_{27}H_{37}N_3O_7S$
Chemical:	[(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester monoethanolate
Class:	Protease Inhibitor
Proposed indication:	Treatment of HIV-1 infection in pediatric population age 6 to <18 years of age.

Dose and regimen:

- Pediatric Patients 6 to < 18 years of age

Recommended Dose for Pediatric Patients (6 to < 18 years of age) for PREZISTA® Tablets with ritonavir		
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

*≥ 20 – < 30 kg: 375 mg DRV/50 mg ritonavir b.i.d.
[(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.625 mL ritonavir]

≥ 30 – < 40 kg: 450 mg DRV/60 mg ritonavir b.i.d.
[(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV) + (0.75 mL ritonavir)]

≥ 40 – < 50 kg: 600 mg DRV/100 mg ritonavir b.i.d.
[(8 tablets of 75 mg **or** 2 tablets of 300 mg DRV) + (one 100 mg capsule ritonavir)]

- Pediatric Patients < 6 years of age:
    - The safety and efficacy of PREZISTA®/rtv in pediatric patients 3 to < 6 years of age has not been established.
    - Do not administer PREZISTA®/rtv in pediatric patients below 3 years of age.
    - Do not administer PREZISTA®/rtv once daily in pediatric patients.

Dosage form: Approved: 600mg, 400mg and 300mg tablets; Proposed: 75 mg tablet

Darunavir (DRV) is a protease inhibitor (PI) and selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells. Darunavir was first approved in 2006 for treatment of HIV-1 infection in treatment experienced adults.

2.2 Tables of Currently Available Treatments for Proposed Indications

Protease inhibitors have become the mainstay of highly active antiretroviral therapy when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combination antiretroviral drugs therapy are now the standard of care. Despite the great progress in treatment of HIV infection, a number of challenges remain, including the development of resistance to currently existing drugs and the significant adverse effects associated with these drugs. A need for new drugs with improved resistance profiles and better tolerability and toxicity profiles remains critical.

Table 1: Currently approved pediatric ARV drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine	Viramune®
	Efavirenz	Sustiva®
PI	Ritonavir	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Atazanavir	Reyataz®
	Tipranavir	Aptivus®
Fusion Inhibitor	Enfuvirtide (T20)	Fuzeon®

2.3 Availability of Proposed Active Ingredient in the United States

Darunavir is currently marketed in the United States under the trade name Prezista. The proposed API for the treatment of HIV-1 infected pediatric subjects remains the same as the approved darunavir. The same tablet formulation that is currently on market will be accessed by pediatric subjects. In addition, a dose proportional 75 mg tablet has been developed for used in pediatric subjects. **(b) (4)**

2.4 Important Safety Issues with Consideration to Related Drugs

General safety issues associated with PIs include side effects such as hyperglycemia and diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia and bleeding diathesis in hemophiliac subjects. PIs also have potential for multiple drug-drug interactions, especially when boosted with ritonavir. Section 7 further discusses the adverse events associated with darunavir when administered to pediatric population.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Darunavir was first submitted to the Agency on December 19, 2002 under IND 62,477. A Fast Track designation was granted in November 2004. In February 2005, all subjects in the phase 2 studies were converted to the recommended dose of DRV/rtv 600/100 mg BID. The clinical

section of the NDA was submitted in September 2005 and accelerated approval was granted in June 2006. The traditional approval of darunavir occurred in October 2008.

At the time of the accelerated approval, among the postmarketing commitments (PMC) and Pediatric Research Equity Act (PREA) requirements were to conduct study(ies) in pediatric subjects with HIV-1 infection:

- Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 6 to 17 years. Please assess the pharmacokinetics, safety, tolerability and antiviral activity in two alternative doses of a suitable pediatric formulation in combination with ritonavir, in treatment-experienced pediatric children and adolescents between 6 and 17 years of age.
    - Protocol Submission: Completed
    - Final Report Submission: June 2008

- Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients less than 6 years. Tibotec Inc will evaluate dose requirements and safety in pediatric patients <6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year of children in trial TMC114-C112 with the Division of Antiviral Products (DAVP).
    - Protocol submission: By December 2008
    - Final Report Submission: By June 2011

In addition to PREA requirements, a Pediatric Written Request (PWR) was also issued in November 2006, which required the study to be conducted in pediatric subjects from 1 month of age to <18 years.

Furthermore, in October 2008, approval was granted for treatment of HIV-1 infection in treatment naïve adults. In accordance, a new PMC was issued at the time of the approval.

- Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.
    - Submission of final protocol: June, 2009
    - Submission of final study report: July, 2012

- Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 3 to <12 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety over 48 weeks.
    - Submission of final protocol: March, 2011
    - Submission of final study report: March, 2015

The currently submitted pediatric study provides an interim study report to one of the 4 PMC. The Applicant plans to submit a 48 week safety and efficacy data.

Please refer to Appendix (sections 9.1 and 9.2) for review of the complete PWR and PREA.

2.6 Other Relevant Background Information

In juvenile rats, single (20 mg/kg to 160 mg/kg at ages 5-11 days) and multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. In some animals, deaths were associated with convulsions. The exposures in plasma, liver and brain for these juvenile rats were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. The exposures and toxicity profile in the older animals (day 23 or day 26) were comparable to those observed in adult rats. A 12 days old juvenile rat is roughly equivalent to a two year old human. In humans, the activity of drug-metabolizing enzymes approaches adult values by 3 years of age.

Due to the juvenile rat study results, pediatric studies will not be conducted in children under 3 years of age. “Less than 3 years of age” was selected as the minimum age cut off for two reasons: 1) in humans, the activity of drug-metabolizing enzymes approaches adult values by 3 years of age and, 2) although the observed toxicity was in up to 12-day old juvenile rats (which are equivalent to a 2-year old human child, a minimum age of 3 was selected to add an additional 1-year safety margin.

Both the PREA (PMC) and the PWR have been amended to reflect the minimum age of 3.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The sNDA was submitted as an electronic document. The submission was well organized and easily navigated using appropriate software (EDR). Datasets were easy to open and manipulate.

3.2 Compliance with Good Clinical Practices

The Applicant states that the study was conducted according to accepted ethical standards based on the principles established by the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. The studies were written to conform to accepted ethical standards and were reviewed by Institutional Review Boards overseeing individual sites. A copy of a sample Informed Consent Form is included in the submission.

Two clinical sites were chosen for DSI investigation based on the number of subjects enrolled. The investigation did not discover deficiencies. Please refer to the DSI investigation report for further detail.

3.3 Financial Disclosures

The Applicant submitted financial disclosure information and this was reviewed in the original NDA package. Updated financial disclosure information was submitted with this pediatric study report.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

No issues have been identified. Please refer to the CMC review for full detail.

4.2 Clinical Microbiology

Please refer to Dr. Lisa Naegar's Microbiology Review for details.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology study report was submitted with this pediatric sNDA. Please refer to Dr. Wendy Carter's and Dr. Peyton Myer's review of the traditional approval for darunavir.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

4.4.2 Pharmacodynamics

Please refer to Dr. Kevin Krudys's pharmacometrics review. Briefly, the pharmacometrics (and pharmacokinetics) review focused on 3 main questions:

1. Does the exposure from the selected pediatric dose reasonably match the adult exposure?

The pediatric exposures reasonably matched the adult exposure at 600mg/100mg BID.

2. Is there an exposure-virologic success relationship for DRV?

Inhibitory Quotient (IQ), calculated by dividing geometric mean DRV plasma trough concentration (Cmin) by IC_{50}, was found to be one of the major predictors of virologic success (proportion of subjects with viral load below 400 copies/mL and 50 copies/mL) at week 24.

3. Is there exposure-safety relationship for DRV?

The analysis of safety and exposure conducted focused on rash and liver enzyme tests (LFT). There was no apparent relationship shown between rash or LFT increases and exposure increases.

4.4.3 Pharmacokinetics

Please refer to Dr. Stanely Au's Clinical Pharmacology review of this sNDA. Briefly, the pediatric exposures at the selected doses were slightly higher than the adult exposure at 600mg/100mg BID.

5 SOURCES OF CLINCAL DATA

This submission contains data from a single randomized pediatric study, Study TMC114-C112. The study was conducted by the Applicant and utilized 28 investigators, 12 clinical sites, in 7 countries.

This submission contains electronic materials documenting the study results and Tibotec's conclusions regarding Study C112, a 24-Week Interim Study Report. An additional study report summary has also been submitted which contains a 48 week safety report for those subjects who have reached Week 48. In addition, copies of the CRTs and CRFs have been submitted as a reviewer's aid. Datasets (as SAS transport files) of demographic, safety and efficacy data have also been submitted.

5.1 Tables of Clinical Studies

Table 2 summarizes the studies included in this review. Table 3 summarizes the subjects enrolled in Study C112 by country and site.

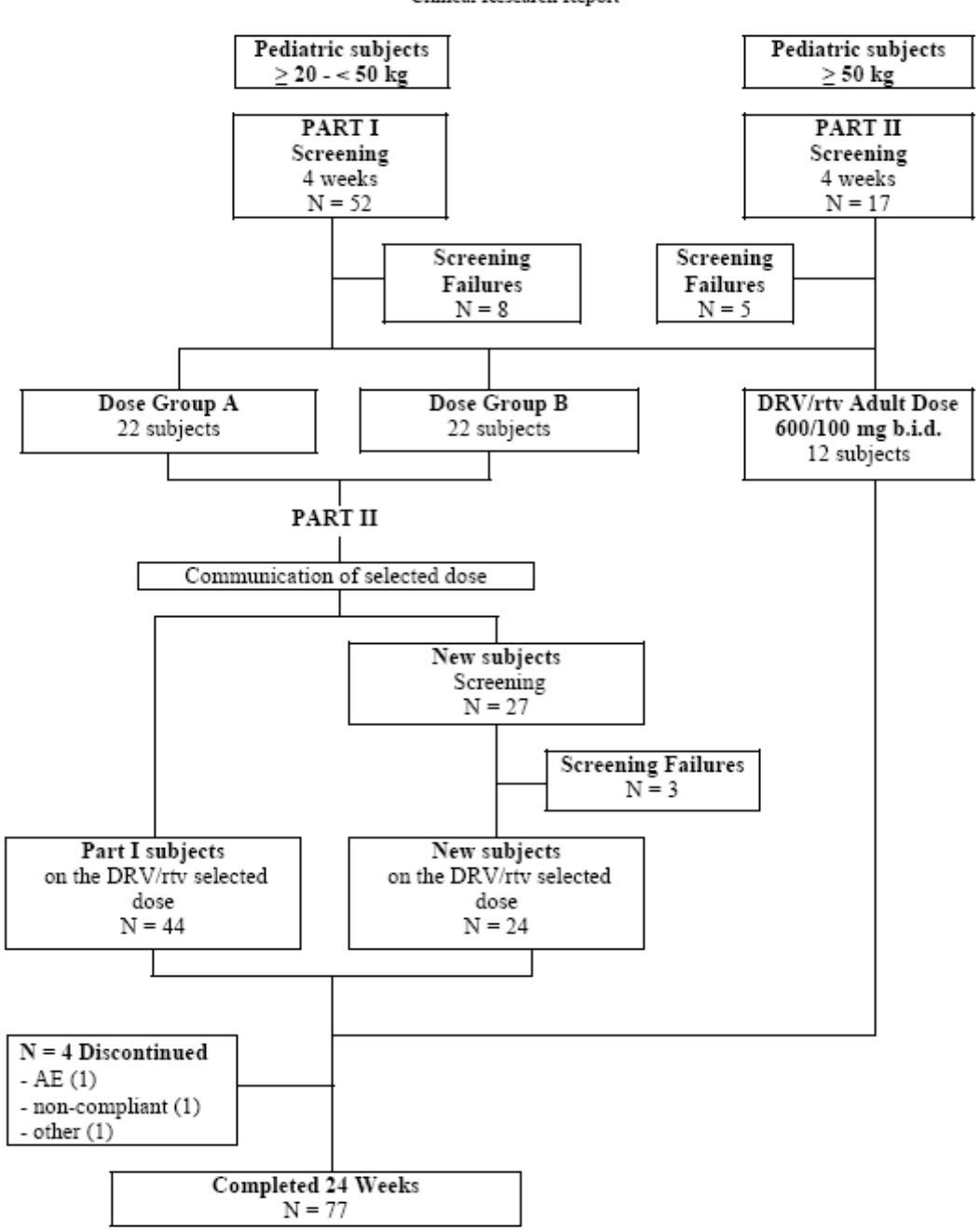
Table 2: Studies conducted in support of this submission

Study Name	Type of Study	Number of Subjects Enrolled	Number of subjects 24 week dat
C112	A phase 1/2a randomized open-label pediatric study	80	77

Table 3: Subjects enrolled in study 1182.14

Country	Number of Sites Enrolling	Number of Subjects Enrolled	Number Prematurely Discontinued
United States	6	18	1
Argentina	4	17	
Romania	3	15	1
Brazil	4	10	
Spain	2	5	
South Africa	2	5	
France	1	4	1
Canada	2	3	
Italy	2	3	

Figure 1: Subject Disposition



Source: TMC114-C112 Clinical Study Report

5.2 Review Strategy

Study C112 was reviewed for safety, tolerability, pharmacokinetics and efficacy. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. This clinical reviewer evaluated study design, patient demographics,

adverse events and laboratory safety monitoring data and reviewed the efficacy and safety results using the JMP Statistical software. Study results (i.e. virologic outcome) described in the label was also confirmed an FDA statistician.

Please note that for all tables and figures that were not created by this reviewer, a foot note has been included to describe the source of the data. If the table or figure is created by this reviewer, no foot note is included.

5.3 Discussion of Study TMC114-C112

A single study was submitted in support of use of darunavir in the pediatric population. Study TMC114-C112 is the pivotal study conducted in pediatric subjects and supports the approval of darunavir co-administered with ritonavir in combination with other antiretroviral drugs in HIV-1 infected treatment-experienced pediatric subjects. The 24 week data was submitted as an interim study report. In addition, a safety update was submitted for subjects who have continued beyond Week 24. A full study report with dataset is expected for submission after the last patient completes treatment for 48 weeks.

Study TMC114-C112: "A Phase I/IIA study of safety, tolerability, and pharmacokinetics of darunavir in combination with ritonavir in HIV-1 infected treatment experienced children". The study was an international, multi-center, open-label, randomized study, conducted in two parts. Part 1 was a dose finding study where 2 doses of darunavir were compared in 44 subjects randomized in 1:1 ratio. The selected dose was then used for Part 2 of the study- a 48 week safety, tolerability and antiviral activity study.

Part 1: The objectives were:

- To evaluate the pharmacokinetic profile of two different doses of DRV in combination with low-dose ritonavir administered b.i.d. in the pediatric population at steady-state: AUC_{12h}, C_{max} and C_{min};
- To identify an appropriate dose of DRV/rtv per body weight in pediatric subjects of ≥ 20 kg to < 50 kg;
- To evaluate short-term safety, tolerability and antiviral activity of two different doses of DRV/rtv administered b.i.d. in treatment-experienced pediatric subjects.

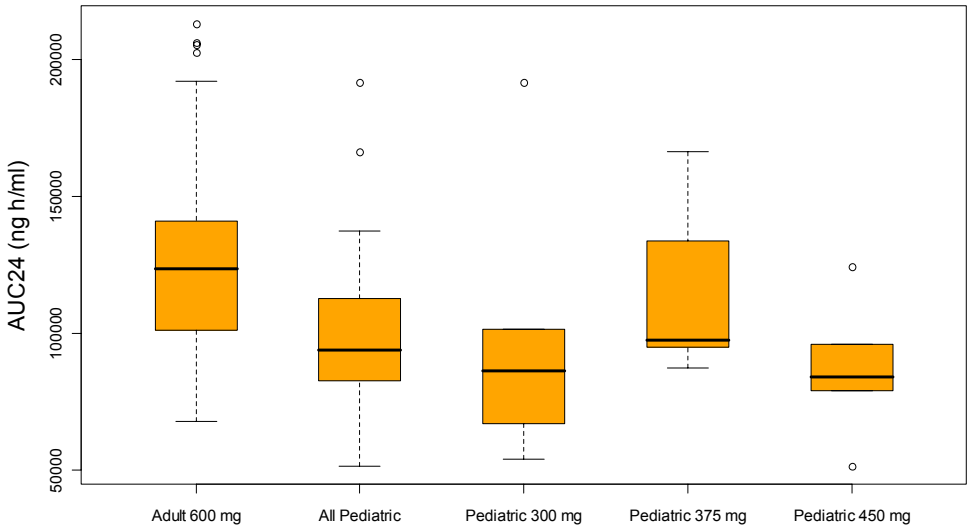
The dosing regimens studied were as follows:

Group A:
1) ≥ 20 – < 30 kg: 300 mg DRV/50 mg ritonavir b.i.d. [(4 tablets of 75 mg **or** 1 tablet of 300 mg DRV) + (0.625 mL ritonavir)]
2) ≥ 30 – < 40 kg: 375 mg DRV/60 mg ritonavir b.i.d. [(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.75 mL ritonavir)]
3) ≥ 40 – < 50 kg: 450 mg DRV/100 mg ritonavir b.i.d. [(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV + (one 100 mg capsule ritonavir)]

Group B:
1) ≥ 20 – < 30 kg: 375 mg DRV/50 mg ritonavir b.i.d. [(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.625 mL ritonavir]
2) ≥ 30 – < 40 kg: 450 mg DRV/60 mg ritonavir b.i.d. [(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV) + (0.75 mL ritonavir)]
3) ≥ 40 – < 50 kg: 600 mg DRV/100 mg ritonavir b.i.d. [(8 tablets of 75 mg **or** 2 tablets of 300 mg DRV) + (one 100 mg capsule ritonavir)]

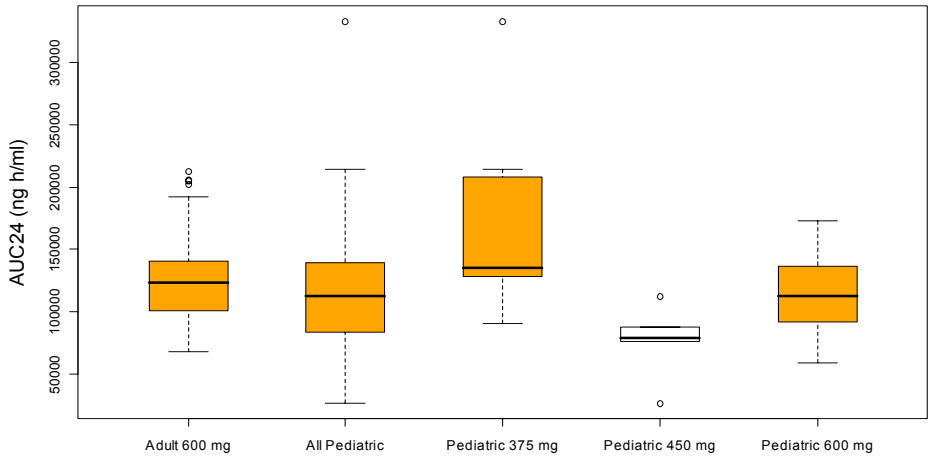
Assessment of pharmacokinetics, safety and efficacy were performed at Week 2. Overall, the mean DRV exposure in Group A was lower than the exposure in adults whereas in Group B, exposure was higher than the exposure in adults. Mean values of DRV AUC_{24h}, C_{0h} and C_{max} in Group A were found to be 81%, 91% and 88%, respectively, of the corresponding mean adult pharmacokinetic parameter whereas in Group B, mean values of DRV AUC_{24h}, C_{0h} and C_{max} were 102%, 114% and 112%, respectively, of the corresponding mean adult pharmacokinetic parameters.

Figure 2: Comparison of pediatric exposure to adult exposure (Part 1, Group A- Intensive PK analysis)



Source: Dr. Kevin Krudys's pharmacometrics review

Figure 3: Comparison of pediatric exposure to adult exposure (Part 1, Group B- Intensive PK analysis)



Source: Dr. Kevin Krudys's pharmacometrics review

During the 2-week treatment period there was no substantial difference between the dose groups with respect to the incidence of adverse events. The percentage of subjects with a plasma viral load < 400 copies/mL at Week 2 was 27.3% in Group A and 40.0% in Group B.

Based on the favorable individual pharmacokinetics data and the overall safety and efficacy profile for Group B, the higher dose was selected for study during Part 2.

Part 2: The objective of Part 2 of the study was to evaluate long-term safety, tolerability and efficacy of DRV in combination with low-dose ritonavir administered b.i.d. and other ARV agents over a 24-week treatment period at the selected pediatric (≥ 20 kg to < 50 kg) and adult (≥ 50 kg) doses.

The secondary objectives were to evaluate long-term safety, tolerability and efficacy of DRV in combination with low-dose ritonavir administered b.i.d. and other ARV agents over a 48-week treatment period at the selected pediatric (≥ 20 kg to < 50 kg) and adult (≥ 50 kg) doses; and to evaluate immunology, resistance characteristics, pharmacokinetic parameters and pharmacokinetic/pharmacodynamic (PD) relationships of DRV/rtv over 48 weeks of treatment.

All 44 subjects who were dosed during Part 1 of the study were scheduled to continue into Part 2 of the study. Those who received the lower dose were switched to the higher dose at the next following visit. An additional 36 subjects were enrolled into Part 2 of the study. Subjects were stratified according to their weights into 3 cohorts (≥20 to <30 kg, ≥30 to <40 kg, 40 to <50 kg). Note that a forth cohort ≥ 50 was also used during safety and efficacy analysis. However, this forth cohort received the same dose as cohort 3 (i.e. 600 mg DRV/100 mg ritonavir b.i.d.). Subjects must have been able to swallow tablet formulation in order to qualify for study entry. Subjects were permitted to switch from ritonavir oral solution to capsules.

6 REVIEW OF EFFICACY

Efficacy Summary

Please refer to Section 5.2 for additional details. Study C112 was an open-label, randomized study. Subjects were stratified according to weight (≥20 to <30 kg, ≥30 to <40 kg, 40 to <50 kg) and received DRV/rtv doses based on the 3 weight bands with background ARV therapy chosen by their local investigator. Analysis of intensive PK sampling, safety and efficacy performed on a subset of subjects at Week 2 to determine the optimal darunavir dose led to the selection of the higher dose. The dose selected is approximately 30% higher when compared to the adult dose. The dose selection was also recommended by an outside study monitoring board (DSMB).

Darunavir (75 mg or 300 mg tablets) co-administered with ritonavir exhibited good antiretroviral activity when used in combination with at least 2 antiretroviral drugs over the 24 weeks of the study period. Overall, 66% of study subjects achieved and sustained an HIV RNA level < 400 copies/mL and 51% reached an HIV RNA level < 50 copies/mL over the 24 weeks study period. The overall treatment response was higher in the younger age group when compared to the older

age group: 92% vs. 55%, respectively for viral load <400 copies/mL and 79% vs. 41%, respectively for viral load <50 copies/mL. The difference was also apparent when comparing the lower weight band group to the highest weight bands: 75% vs. 58%, respectively for viral load <400 copies/mL. Table 4 summarizes treatment responses by age groups at Week 24. Table 5 summarizes treatment responses by weight band groups.

Significant increases in CD4 cell counts and declines in mean log change in HIV RNA levels were also noted in all patient groups analyzed.

Table 4: Proportion of subjects with HIV RNA < 400 copies/mL and <50 copies/mL, by age group

	6-<12 N=24	12-18 N=56	Total N=80
Virologic responders <400 c/mL <50 c/mL	**21 (92%)** 21 (92%) 18 (79%)	**32 (55%)** 32 (55%) 23 (41%)	**53 (66%)** 53 (66%) 41 (51%)
Treatment failures rebound Never suppressed Other (AE; D/C)*	**3 (8%)** 1(4%) 1 (4%) 1(4%)	**24 (46%)** 9(16%) 11(20%) 4 (7%)	**27 (34%)** 10(13%) 12(15%) 5(6%)

*Other includes those who discontinued for any reason prior to week 24 and those without recorded Week 24 viral load.

Table 5: Proportion of subjects with HIV RNA < 400 copies/mL and <50 copies/mL, by weight band

	20 kg N= 20	30kg N=24	40 kg N=24	50kg N=12	Total N=80
Virologic responders <400 c/mL <50 c/mL	**15 (75%)** 15 (75%) 10 (50%)	**18 (75%)** 18 (75%) 16 (67%)	**13 (54%)** 13 (54%) 9 (38%)	**7 (58%)** 7 (58%) 6 (50%)	**53 (66%)** 53 (66%) 41 (51%)
Treatment failures rebound Never suppressed Other (AE; D/C)*	**5 (25%)** 1 (5%) 3 (15%) 1 (5%)	**6 (25%)** 4(17%) 1 (5%) 1(5%)	**11 (46%)** 2 (8%) 8 (33%) 1 (5%)	**5 (42%)** 3 (25%) 0 (0%) 2(17%)	**27 (34%)** 10 (13%) 12(15%) 5 (6%)

*Other includes those who discontinued for any reason prior to week 24 and those without recorded Week 24 viral load.

6.1 Indication

PREZISTA, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected subjects who are treatment-experienced. This indication is based on analyses of plasma HIV-1 RNA levels from study C112.

6.1.1 Methods

No formal statistical review was conducted by a statistician from the FDA as the study was uncontrolled and all patients received weight based DRV dosing.

For assessment of virologic response, the following endpoints were used by this reviewer:

- Proportion of subjects with a viral load <400 copies/mL at Week 24 (primary efficacy endpoint)

- Proportion of subjects with a viral load <50 copies/mL at Week 24 (secondary efficacy endpoint)
- Subjects were considered failures if treatment was discontinued prior to week 24 (for any reason)
- Subjects were considered failures if no laboratory (virologic) assessment was performed at the Week 24 visit.

The efficacy analysis compared treatment response between the two age groups as well as among the 4 weight bands. This reviewer included all subjects who were randomized and received at least one dose of the study drug in the efficacy analysis.

In addition to virologic parameters, resistance parameters, immunologic parameters (CD4+ cell count and percentage), and exposure-response were also assessed as part of the efficacy evaluation.

Note that this reviewer used a snapshot analysis approach for assessing virologic response since 24 week data was being analyzed. According to FDA's guidance, a snapshot approach should be used to assess outcome at Week 24. Briefly, a snapshot approach only evaluates the Week 24 virologic number and classifies it as above or below the selected virologic parameters (i.e. <400copies/mL or <50 copies/mL). In addition, 24 week efficacy data displayed in the Prescribing Information are based on a snapshot analysis. The guidance recommends a time to virologic failure analysis using the TLOVR algorithm for a 48 week data analysis.

The sponsor used the TLOVR algorithm for assessment of Week 24 virologic response. Therefore, minor differences have occurred between the Sponsor's and this reviewer's efficacy results. The efficacy analysis using TLOVR resulted in a less favorable outcome (by few percentage points) when compared to the snapshot analysis.

6.1.2 Demographics

Demographics are summarized in Table 6. The number of subjects in each weight band group was balanced. However, there was a disparity between the two genders – 71% male vs. 29% female. This is unusual in pediatric HIV-1 infection clinical trials where no difference exists in prevalence or incidence of HIV infection among children. The difference in number of subjects enrolled for the two age groups and for the race categories is not unusual. Most pediatric studies tend to enroll older children and Caucasians. The randomized pediatric subjects had a median age of 14 years (range 6 -17) and were 54% Caucasian, 30% black, 9% Hispanic, and 8% other.

Table 6: Demographics

Baseline Characteristics	**DRV/rtv**
Population	**N = 80**
Demographic Data	
Gender, n (%)	
Female	23 (28.8)
Male	57 (71.3)
Age (years), median (range)	14.0 (6 – 17)

Age category (years), n (%)	
6 - < 12	24 (30.0)
12 - < 18	56 (70.0)
Weight band as stratified (kg)	
20 - 29	19 (23.8)
30 - 39	21 (26.3)
40 - 49	28 (35.0)
≥ 50	12 (15.0)
Race, n (%)	
Caucasian	43 (53.8)
Black	24 (30.0)
Hispanic	7 (8.8)
Other	6 (7.5)

6.1.3 Baseline HIV Characteristics

Baseline disease characteristics are summarized in Table 7. The median baseline plasma HIV-1 RNA was 4.8 (range 2.7 to 6.6) log10 copies/mL and median baseline CD4+ cell count was 330 (range 6 to 1505) cells/mm3. Overall, 38% of subjects had a baseline HIV-1 RNA of >100,000 copies/mL. Half of the subjects were CDC classification clinical category C at the time of enrollment into the study.

Vertical transmission was the most common cause for acquisition of HIV infection (78%). Other risk factors identified for acquiring HIV include blood transfusion and sexual contacts.

Table 7: Baseline characteristics

Baseline Disease Characteristics	DRV/rtv N=80
Log10 viral load: median (range), copies/mL	4.82 (2.72; 6.57)
Viral load at baseline, n (%)	
<20,000 copies/mL	28 (35)
20,000- <50,000 copies/mL	8(10)
50,000-<100,000 copies/mL	14 (18)
>100,000 copies/mL	30 (38)
CD4+ cell count: median (range), x 106 cells/L	330 (6; 1505)
CD4%, median (range)	16.8 (0.7; 47.4)
Duration of known HIV infection: median (range), years	11.0 (2.7; 17.3)
Mode of transmission, n (%)	
Mother to child	62(78)
Nosocomial	6(8)
Blood transfusion	4(5)
Other*	8(10)
Clinical Stage of HIV infection, n (%)	
N	5(6)
A	10(13)
B	25(31)
C	40(50)

*other includes: homosexual contact, parenteral, sexual abuse, vaccination, breast milk, and unknown

Previous Antiretroviral Treatment History

All subjects had previous ART use, a minimum of 3 and maximum of 19. All subjects had previous use of at least 2 NRTI. Most subjects (79%) had previous use of an NNRTI and 96% had previously used a PI.

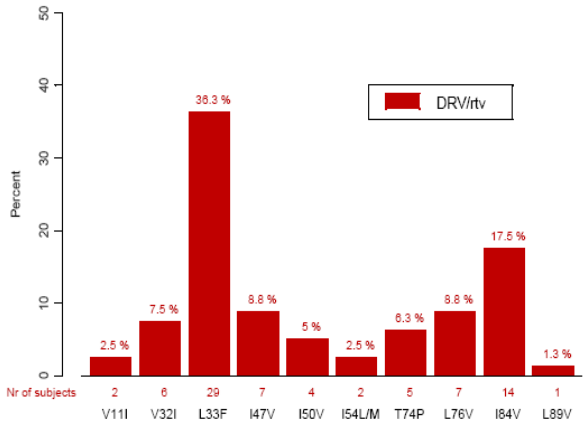
Baseline HIV Resistance

In summary, as described by the applicant, as subjects were treatment experienced, most subjects had evidence of resistance at baseline (80.0% had 1 or more primary PI mutation(s) and 51.3% had 1 or more DRV RAMs).

Overall, the median number of primary PI mutations was 3 (range: 0 - 6); the median number of PI RAMs was 11 (range: 0 - 19); the median number of DRV RAMs was 1 (range: 0 - 4).
A graphical presentation of the prevalence of DRV RAMs at baseline is provided in Figure 4.

Phenotype was assessed by means of the Antivirogram® assay in order to determine the number of susceptible drugs at baseline. Overall, 83.6% of subjects were still susceptible to at least 1 PI at baseline, 38.4% were susceptible to at least one NNRTI and 87.7% were susceptible to at least one NRTI. Ninety two percent of subjects had a DRV FC at baseline of ≤10 and one subject (1.4%) had a DRV FC of > 40.

Figure 4: Prevalence of DRV RAMs at baseline



Source: TMC114-C112 Clinical Research Report

Dr. Lisa Naeger, the Division's microbiology reviewer evaluated the baseline resistance by age and weight groups. The older age group had more baseline resistance compared to the younger age group (Table 5), likely reflecting the longer history of treatment with ART in the older age group and leading to increased resistance. No significant differences were noted when baseline analysis was evaluated according to the weight bands (Table 6).

Table 5: Baseline Resistance by Age

Age	IAS-Defined Primary PI mutations (median)	DRV-Associated PI Mutations (median)	Proportion with ≥ 2 DRV Mutations	Proportion DRV Resist at Baseline (>7 FC)
6-<12y	2	0	6/23 (26%)	11/8(12%)
12-<18y	3	1	18/56 (32%)	7/8(88%)

Source: Dr. Lisa Naeger's Analysis

Table 6: Baseline Resistance by Weight

Weight(Kg)	IAS-Defined Primary PI mutations (median)	DRV-Associated PI Mutations (median)	Proportion with ≥ 2 DRV Mutations	Proportion DRV Re at Baseline (>7 I
20-29kg	3	1	6/20(30%)	2/19(11%)
≥30-39	3	0	7/23(30%)	2/21(10%)
≥40-49	3	0.5	7/24(29%)	3/22(14%)
≥ 50	3	1	4/12(33%)	1/10(10%)

Source: Dr. Lisa Naeger's Analysis

6.1.4 Patient Disposition

Seventy-seven (96%) subjects completed the 24 week period and 3 (4%) discontinued prematurely. Of the subjects who discontinued prematurely, 1 (1%) discontinued due to adverse events, and 2 (2%) discontinued due to other reasons (non-compliance, moved away). Table 9 summarizes subjects' enrollment and disposition.

Table 9: Patient Disposition

	Total
	N (%)
Total screened	96
Screening failures	16
Total randomized	80
Total treated	80
Total completed at Week 24	77 (96)
Total prematurely discontinued	3 (4)
Reason for premature discontinuation	
Adverse event	1(1)
Non-adherence	1(1)
Other (moved away)	1(1)

6.1.5 Analysis of Primary Endpoint(s)

The primary endpoint parameter used by the applicant was virologic response defined as the percentage of subjects with a confirmed decrease of at least 1 $\log_{10}$ from baseline in plasma viral load at Week 24 (TLOVR) (Table 10, Figure 5). According to the applicant, 79% of the subjects

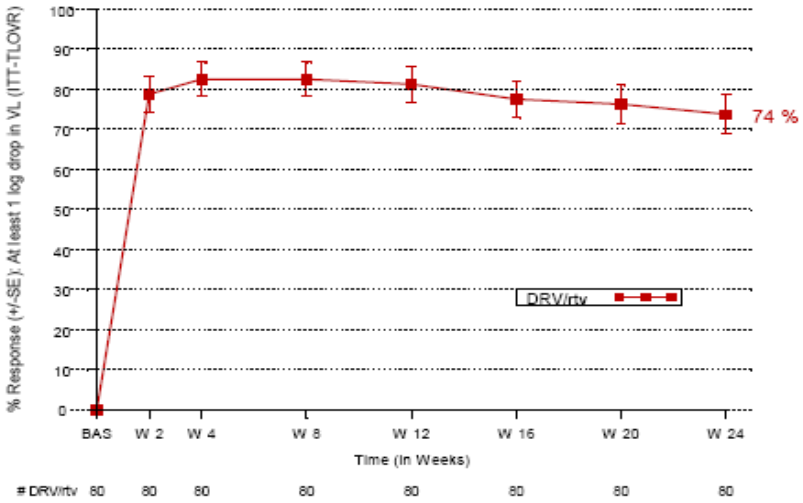
met the primary endpoint parameter at week 24. The primary endpoint parameter used by this reviewer is virologic response defined as percentage of subjects with viral load <400 copies/mL at Week 24 (Table 11). Overall, 66% of the subjects had viral load <400c/mL at week 24. Based on TLOVR analysis by the sponsor, 64% of the subjects had viral load <400c/mL. Additional parameters used by both the applicant and this reviewer include percentage of subjects with viral load <50 copies/mL at Week 24.

Table 10: Confirmed Virologic Response (at least 1 log 10 decrease in viral load, ITT, TLOVR)

	DRV/rtv N=80
Number of responders	n(%)
≥ 1 log10 Decrease from Baseline	
Week 2	63(79)
Week 4	66(83)
Week 8	66(83)
Week 12	65(81)
Week 16	62(78)
Week 20	61(76)
Week 24	59(73)

Source: TMC114-c112 Clinical Research Report

Figure 4: Confirmed Virologic Response (at least 1 log 10 decrease in viral load, ITT, TLOVR)



Source: TMC114-c112 Clinical Research Report

Table 11: Proportion of subjects with HIV RNA < 400 copies/mL

	Total N=80
Proportion of subjects with virologic response (< 400 copies/mL) (FDA snapshot analysis)	53 (66%)
Proportion of subjects with virologic response (< 400 copies/mL) (Sponsor's TLOVR analysis)	51 (64%)

6.1.6 Analysis of Secondary Endpoint(s)

Overall, the proportion of subjects with viral load <50 copies/mL at Week 24 was 41(51%). Based on the applicant's TLOVR analysis, the proportion of subjects with viral load <50copies/mL at Week 24 was 40(50%)

Reasons for Treatment Failure
The most common reason for treatment failure was never achieving virologic suppression. Table 12 summarizes the results.

Table 12: Reasons for Treatment Failure (24 weeks)

	Total N=80
Proportion of subjects with virologic response	53 (66%)
<400 c/mL	53 (66%)
<50 c/mL	41 (51%)
Proportion of subjects who were treatment failures	27 (35%)
Virologic failure	22(28%)
rebound	10 (13%)
Never suppressed	12 (15%)
Other* (AE; D/C)	5 (6%)

*Other includes those who discontinued for any reason prior to week 24 and those without recorded Week 24 viral load.

6.1.7 Other Endpoints

Key secondary analysis endpoints also included determination of DRV and ritonavir pharmacokinetic parameters at steady-state.

M.O. Comment: Please refer to Clinical Pharmacology Review by Dr. Au for detailed discussion.

6.1.8 Subanalysis

Analysis by Age
Efficacy of darunavir was analyzed by the two age groups: 6-<12 and 12 to <18 years of age. When analyzed by age group, the younger age group had a higher proportion of subjects with virologic response (92% vs. 55% for viral load <400 copies/mL, and 79% vs. 41% for viral load <50 copies/mL). This difference is likely due to the extent of prior ART history and the likelihood of harboring resistant HIV-1. Older children and adolescents are likely to have been exposed to longer years of treatment with ART as most pediatric patients acquire HIV from vertical transmission. As noted in Section 6.1.3, for most of the subjects (78%) maternal child transmission was the route of HIV acquisition. Table 12 summarizes treatment response based on age. The applicant's analysis is slightly different from this reviewer as TLOVR was applied to assess virologic response. For example, based on the applicant's TLOVR analysis, the proportion of subjects with viral load <50c/mL is 75% in the 6 to <12 years old group and 39% in the 12 to <18 years old group.

Table 13: Proportion of subjects with HIV RNA < 400 copies/mL and <50 copies/mL, by age

	6-<12 N=24	12-18 N=56	Total N=80
Proportion of subjects with virologic response	**21 (92%)**	**32 (55%)**	**53 (66%)**
<400 c/mL	21 (92%)	32 (55%)	53 (66%)
<50 c/mL	18 (79%)	23 (41%)	41 (51%)
Proportion of subjects with virologic failure	**3 (8%)**	**24 (46%)**	**27 (34%)**
Rebound	1(4%)	9(16%)	10(13%)
Never suppressed	1 (4%)	11(20%)	12(15%)
Other (AE; D/C)	1(4%)	4 (7%)	5(6%)

Analysis by Baseline Viral Load

Regardless of the age group, the proportion of subjects who responded to treatment was higher if the baseline viral load was lower (i.e. <20,000). In addition, for all viral load cohorts, the proportion of subjects who responded to treatment was higher in the lower age group when compared to the older age group, reflecting the degree of treatment experience (and hence resistance) in the older age group. Table 14 summarizes the findings.

Table 14: Proportion of subjects with HIV RNA < 400 copies/mL by age and baseline viral load

	6-<12 N=24			12-18 N=56			Total N=80		
Baseline viral load	<20,000 N=12	20-<100,000 N=6	>100,000 N=6	<20,000 N=12	20-<100,000 N=6	>100,000 N=6	<20,000 N=12	20-<100,000 N=6	>100,000 N=6
Virologic responders (<400 c/mL)	12 (100)	5(83)	4 (66)	12 (100)	5(83)	4 (66)	12 (100)	5(83)	4 (66)

Analysis by Weight Bands

Efficacy of darunavir was analyzed based on the 4 stratified weight bands (≥20-<30 kg, ≥30 - <40kg, ≥40 - <50kg, and ≥50kg), as summarized in Table 15. More subjects in the lower weight bands responded to treatment compared to the higher weight group. In general younger subjects tend to weigh less than older subjects, thus there were more younger subjects in the lower weight bands. Again, the younger subjects likely harbor less resistant virus since they have shorter history of treatment with ART.

Table 15: Proportion of subjects with HIV RNA < 400 copies/mL and <50 copies/mL by weight bands

	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
Proportion of subjects with virologic response	**15 (75%)**	**18 (75%)**	**13 (54%)**	**7 (58%)**	**53 (66%)**
<400 c/mL	15 (75%)	18 (75%)	13 (54%)	7 (58%)	53 (66%)
<50 c/mL	10 (50%)	16 (67%)	9 (38%)	6 (50%)	41 (51%)
Proportion of subjects with treatment failure	**5 (25%)**	**6 (25%)**	**11 (46%)**	**5 (42%)**	**27 (34%)**
rebound	1 (5%)	4(17%)	2 (8%)	3 (25%)	10 (13%)
Never suppressed	3 (15%)	1 (5%)	8 (33%)	0 (0%)	12(15%)
Other (AE; discont.)	1 (5%)	1(5%)	1 (5%)	2(17%)	5 (6%)

Analysis by Baseline Mutations

Based on the sponsor's analysis, subjects with higher baseline DRV fold change or mutations were least likely to respond to treatment (Table 16).

Table 16: Treatment Response based on baseline DRV Fold Change and Mutations

	N	Number of responders n(%)
Baseline DRV Fold Change, n(%)		
≤ 10	67	37 (55)
>10	6	0
Number of Baseline DRV Mutations, n(%)		
0	39	23(59)
1	17	10(59)
2	15	7(47)
≥ 3	9	0

Source: TMC114-C212 Clinical Research Report

Dr. Lisa Naeger analyzed the 22 subjects with virologic failure to establish correlation between the microbiologic findings and reasons for failure. Table 17 summarizes the findings. For both age groups, approximately one third of the subjects who were virologic failures had baseline DRV resistance (33% for the 6-<12 years old group and 28% for the 12-<18 years old group). For these subjects (n=6), the likely reason for failure can thus be attributed to their baseline status. The remaining subjects with virologic failure (n=16) appear to have had no baseline resistance or DRV Fold Change (>7FC). It is plausible that these subjects (most of whom were in the older age group, n=14) may have developed resistance while on treatment, i.e. rebound. (See section below – Analysis by Adherence). As discussed in the adherence section, most of the subjects who reported difficulties with adherence were in the adolescent age group (i.e. >12 years of age). This finding is not unique to the current application. Compliance has been previously described as a challenge for adolescents.

An exposure-response analysis was also performed for the 22 subjects with virologic failure (see section below). No relationship between exposure (i.e. low exposure) and virologic failure was found for the 22 subjects with virologic failure.

Table 17 Virologic Failures

Age	Virologic Failures	Proportion with ≥?? DRV Mutations	Median DRV Mutations	Median DRV FC	Proportion FRV Resistant at Baseline (>7FC)
6-<12 y	3(13%)	2/3(66%)	2	5.8	1/3(33%)
12-<18 y	19(34%)	9/19(47%)	1	2.5	5/18(28%)

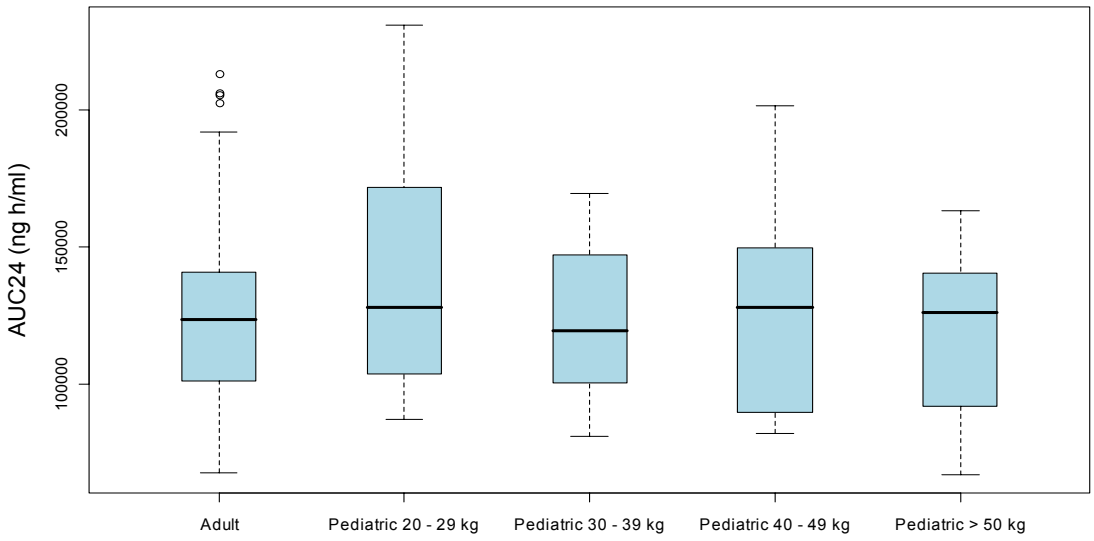
Source: Dr. Lisa Naeger's analysis

Analysis by Exposure

Please refer to Dr. Krudys's pharmacometrics review for full details. In summary, response in the pediatric population was driven by the inhibitory quotient (IQ) as it was shown in adults.

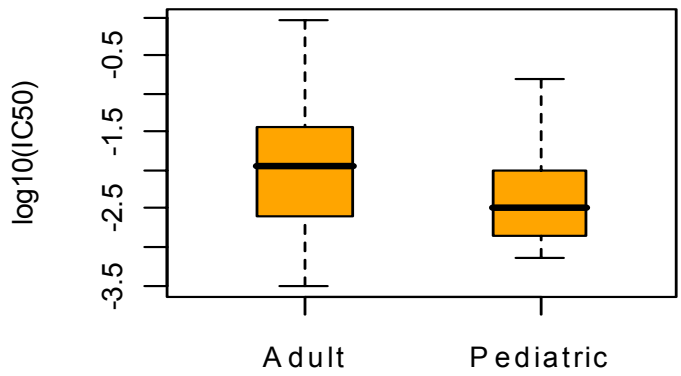
Figure 5 shows that the AUC derived from population PK during Part 2 of the pediatric study was similar to that of the adults. Figures 6a, and 6b show the IC_{50} and IQ in adult and pediatric populations were comparable. Figure 7 shows the proportion of responders (viral load <50c/mL) increased with increasing IQ. Further increase in darunavir concentrations did not lead to an increase in proportion of responders. As shown in Figure 8, the 22 subjects with virologic failure, as indicated in the box plots, no trend toward lower exposures (C0h) was noted to explain the virologic failures; however, there were higher IC_{50} values observed, with resulting lower IQs, indicating viral resistance as the driving factor.

Figure 5: Population PK (AUC_{24}) of pediatric subjects compared to adults



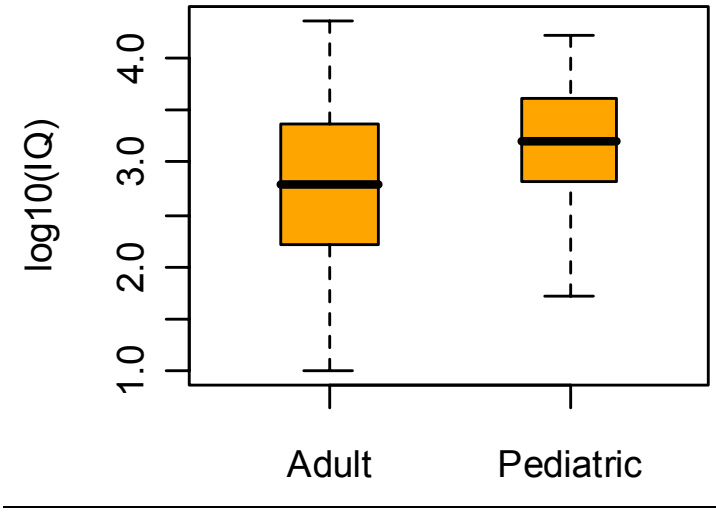
Source: Dr. Krudy's review

Figure 6a: IC_{50} (log_{10}) adult vs. pediatric



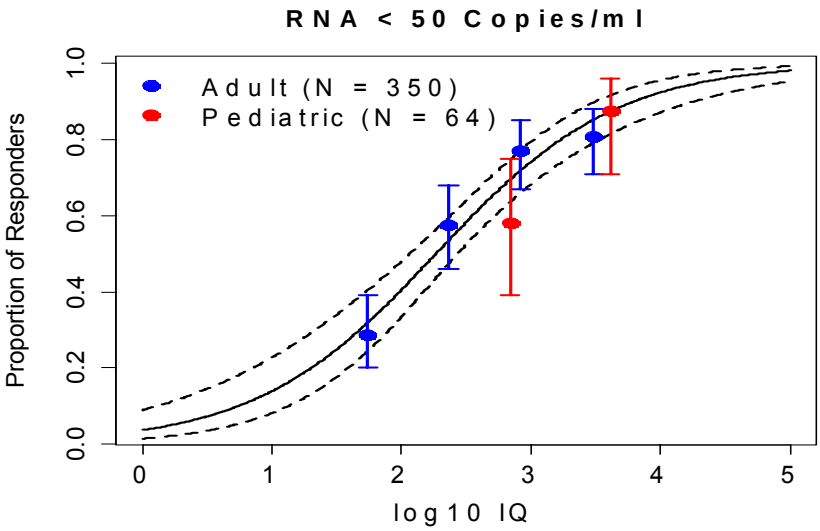
Source: Dr. Krudy's review

Figure 6b: IQ in adults and pediatric subjects



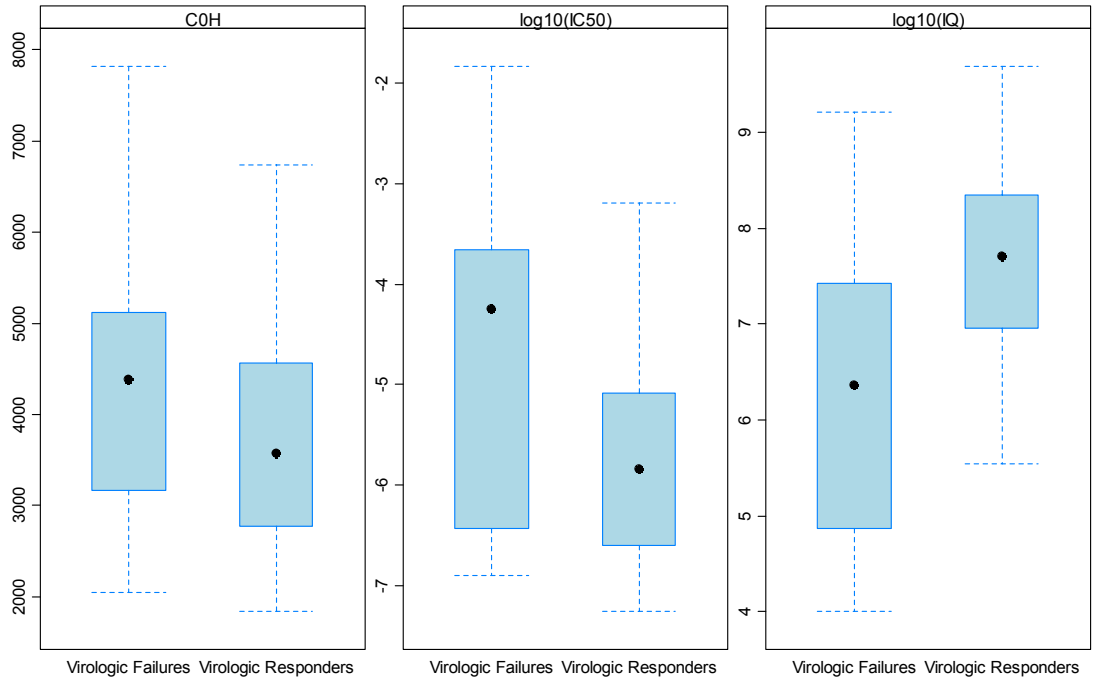
Source: Dr. Krudy's review

Figure 7: Proportion of responders (vL < 50 c/mL) increases with increasing IQ



Source: Dr. Krudys's review

Figure 8: Exposure-Response relationship for the 22 subjects with virologic failure



Source: Dr. Krudys's review

Analysis by Adherence

Treatment compliance was assessed by a self-reporting adherence questionnaire and by pill-counts. Overall compliance was high. According to the applicant, the proportion of subjects with DRV plasma concentration below the level of detection limit was ≤ 3%.

Among the questions asked for assessment of adherence includes: "Over the last 3 days, how many doses did you miss?" and "Doses missed during the last 2 weeks." Based on the two questions, it appears the younger age group had better adherence to medication. For example, out of the 17 subjects who missed medication dose "over the last 3 days" 15(88%) were ≥ 12 years of age. In addition, of the 21 subjects who had missed doses during the "last two weeks", 19 (90%) were ≥ 12 years of age. A more frequent reporting of lack of adherence in the adolescent age group is not surprising; such a finding is consistent with what is observed in clinical practice.

Immunologic response

Overall, there was immunologic benefit after 24 weeks of treatment. The absolute CD4+ cell count was chosen as the primary analysis for immunologic response since all of the subjects are older than 5 years of age. At baseline, 25 (31%) subjects had a CD4+ of < 200 cells/L and 19 (24%) subjects had a CD4+ of ≥ 500 cells/L. By Week 24, 10 (12%) subjects were severely immunosuppressed (CD4+ <200 cells/L) and 32 (40%) subjects had CD4+ ≥ 500 cells/L (Table 18).

Table 18: Change from baseline in CD4%

CD4+ cell count (Week 24)	CD4+ at Baseline ($x10^6$ cells/L), n (%)			Total (Week 24)
	<200	≥ 200 to < 499	≥ 500	
<200	10 (40)	0(0)	0	10(12)
≥ 200 to < 499	15(60)	22(61)	1(5)	38(46)
≥ 500	0(0)	14(39)	18(95)	32(40)
Total (baseline)	25(100)	36(100)	19(100)	80

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose selection and recommendations for the three weight bands were based on the following results:

1) The selected twice daily regimens provided darunavir plasma concentrations similar to or slightly higher than those obtained in adults receiving 600/100 mg twice-daily.

2) The HIV viral load at week 24 was comparable to the adult HIV-viral load at week 24. Below is a comparison of the 24 week efficacy results between the pediatric study TMC114-C112 and adult studies (C213 and C202):

- Virologic responders (decrease of at least 1 log10 from baseline) :
  - 73% (pediatric) vs. 74% (adults)
- Virologic responders (VL< 400 c/mL):
  - 66% (pediatric) vs. 65% (adults)
- Virologic responders (VL< 50 c/mL):
  - 51% (pediatrics) vs. 52% (adults)

In summary, the recommended dose for all age groups is:

- Pediatric Patients 6 to < 18 years of age

Recommended Dose for Antiretroviral Treatment-Experienced Pediatric Patients (6 to < 18 years of age) for PREZISTA® Tablets with ritonavir		
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

*≥ 20 – < 30 kg: 375 mg DRV/50 mg ritonavir b.i.d.
[(5 tablets of 75 mg **or** 1 tablet of 300 mg + 1 tablet of 75 mg DRV) + (0.625 mL ritonavir]

≥ 30 – < 40 kg: 450 mg DRV/60 mg ritonavir b.i.d.
[(6 tablets of 75 mg **or** 1 tablet of 300 mg + 2 tablets of 75 mg DRV) + (0.75 mL ritonavir)]

≥ 40 – < 50 kg: 600 mg DRV/100 mg ritonavir b.i.d.
[(8 tablets of 75 mg **or** 2 tablets of 300 mg DRV) + (one 100 mg capsule ritonavir)]

Pediatric Patients < 6 years of age:

- The safety and efficacy of PREZISTA®/rtv in pediatric patients 3 to < 6 years of age has not been established
- Do not administer PREZISTA®/rtv in pediatric patients below 3 years of age

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

The study submitted is a 24 week interim study report. A full 48 week study report will be submitted as a separate supplement as soon as the report (and data) is available. Of note, a study summary submitted as part of periodic safety update report demonstrated that among the subjects who had reached week 48, the antiviral activity of DRV/rtv co-administered with optimized background therapy continued to persist.

6.1.11 Additional Efficacy Issues/Analyses

The efficacy of darunavir demonstrated in this pediatric trial was comparable to the adult trials (week 24 data).

The extrapolation of efficacy for antiretroviral drugs is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c).[3] DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

7 REVIEW OF SAFETY

Safety Summary

Overall, darunavir co-administered with ritonavir in combination with other antiretroviral drugs was safe and tolerable when administered to pediatric subjects 6 to 18 years of age. The types of adverse events reported were similar to adults. An exposure-safety relationship was not shown

either for the hepatic adverse events or for rash adverse events. Note the study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in adverse event incidences. Descriptive statistics were applied to describe the observed findings. Interpretation of these results should be with caution.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety profile of darunavir has already been established in adults with adequate number of subjects.

Study C112, which is currently ongoing, was the pivotal pediatric study conducted to assess safety and efficacy of darunavir in pediatric subjects. The population studied includes HIV-1 infected pediatric subjects who were 6 to 18 years of age at the time of randomization. All were treatment experienced. Part of the primary objectives of this study was to assess the safety and tolerability of darunavir co-administered with ritonavir in combination with other ARV drugs.

7.1.2 Adequacy of Data

The data submitted support safety and tolerability of darunavir co-administered with ritonavir in combination with other ARVs. The PWR required a minimum of 100 patients followed for safety at the to-be-marketed dose or higher for 24 weeks. As this submission is an interim study report as well as a partial response to the PWR, more data (i.e. data on 48 week duration treatment as well as data on additional subjects between 3 to <6 years of age, and data on treatment of treatment naïve subjects aged 3 to <18 years of age) are expected in the future. The submitted data are adequate with regards to number of subjects exposed to darunavir and duration of exposure. The data was submitted by SAS transport file for analysis using JMP software. Adverse events were depicted using System Organ Class/MedDRA preferred terms. All adverse events were graded using DAIDS standardized Toxicity Table for Grading Severity of Pediatric (>3 months of age) Adverse Events.

Additional studies will be conducted on pediatric subjects 3 to 6 years of age and in pediatric subjects who are treatment-naïve. No studies will be conducted on pediatric subjects less than 3 years of age. Please refer to Section 2.5 for expected timelines for submission of various pediatric studies and to Section 2.6 for discussion of the rationale to exclude subjects <3 years of age.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant has submitted safety data on 80 pediatric subjects with at least 24 week safety data. Further, although not a full 48 study report, preliminary summary report for subjects receiving DRV for at least 48 weeks was also submitted.

7.2.2 Explorations for Dose Response

During the pediatric development plan (i.e. Part 1), 2 doses were selected for study. The first darunavir/ritonavir dose (Group A) was allometrically scaled by body weight to the 600/100 mg adult dose. A higher dose (Group B), projected to be a 30% increase in the adult dose was selected to account for potential increase in metabolism and clearance of the drug in pediatric subjects. A dose response relationship has been explored both for safety and efficacy. Greater reductions in HIV RNA were seen at Week 2 with the higher dose. However, no immediate tolerability issues were noted with the higher dose or exposure when compared to the lower dose.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the original and the traditional review of darunavir for detail. No new animal and/or in vitro testing was submitted with this sNDA.

7.2.4 Routine Clinical Testing

Protocol defined routine clinical and laboratory testing were conducted during the trial. These tests were adequate. Subjects were evaluated for adverse events and laboratory tests were performed at appropriate frequencies (weeks 2, 4, 6, and 8). After study Week 8, routine assessments were conducted every 4 weeks. Pre-specified adequate monitoring plans were also in place for hepatic adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

During the study period, cholesterol, triglycerides, and glucose were followed to monitor for protease inhibitor class adverse effects. In addition, darunavir specific adverse events noted in adults (namely hepatic adverse events and rash) were also monitored.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the 24 week study period. No deaths were reported in the study summary submitted for weeks 24 through 48.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Serious adverse events (SAE) were reported by 8 (10%) subjects during the 24 week study period. The number of subjects with SAE did not change significantly by the safety update cut-off date (i.e. week 48). Fourteen percent (11/60) subjects reported SAE at week 48. The number of SAEs was slightly higher in the lower weight bands compared to the higher weight bands. The majority of SAE reports were considered not related to study drug.

Table 19: Serious Adverse Events

System Organ Class n(%)					
Any AE					8 (10)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
Infection & Infestations					6(8)
Cellulitis	0	1	0	0	1(1)
Hepatitis A	1	0	0	0	1(1)
Mastoiditis	0	1	0	0	1(1)
Chronic osteomyelitis	0	0	0	1	1(1)
Pneumonia	1	0	0	0	1(1)
Pyothorax	1	0	0	0	1(1)
Gastrointestinal Disorders					2(3)
Enteropathy	1	0	0	0	1(1)
GI fistula	0	0	0	1	1(1)
Investigations					1(1)
ALT increase	0	1	0	0	1(1)
Alk Phos increase	0	1	0	0	1(1)
Amylase increase	0	1	0	0	1(1)

During the adult clinical trials, the system organ class in which most subjects reported SAEs were Investigations (17%), Infections and infestations (9%), Gastrointestinal disorders (7%).

7.3.3 Dropouts and/or Discontinuations

During the 24 week treatment period, 1 subject discontinued the trial due to AE. This was a 17 year old subject (in the 20- <30 kg weight band), who discontinued due to "acute anxiety" which was Grade 3, non-serious, and considered not related to drug. Subject had no previous history or psychiatric disorders.

The number of pediatric subjects who discontinued study drug remained at 1% when subjects were followed beyond the 24 week period (i.e. 48 weeks).

7.3.4 Significant (Grade 3 and/or 4) Adverse Events

Overall, 18(23%) reported adverse events ≥ Grade 3. No significant differences were noted among the weight bands.

Table 20: Severity of AEs

System Organ Class n(%)					DRV/rtv
Any AE					18(23%)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
Blood and Lymphatic Disorders					5(6)
Neutropenia	4	1	0	0	5(6)
leukopenia	1	0	0	0	1(1)
Investigations					4(5)
Amylase increase	0	1	0	0	1(1)
ALT increase	0	1	0	0	1(1)
Alk phos increase	0	1	0	0	1(1)
Bicarbonate decreased	1	0	0	0	1(1)
INR	0	1	0	0	1(1)
Platelet decreased	0	0	1	0	1(1)
General Disorders and Administration Site Disorders					4(5)
Pain	0	0	1	2	3(4)
Infection & Infestations					4(5)
Hepatitis A	1	0	0	0	1(1)
Mastoiditis	0	1	0	0	1(1)
Chronic osteomyelitis	0	0	0	1	1(1)
Pneumonia	1	0	0	0	1(1)
Gastrointestinal Disorders					1(1)
GI fistula	0	0	0	1	1(1)
Metabolism and Nutrition Disorder					1(1)
hypercholesterolemia	0	1	0	0	1(1)
Musculoskeletal and Connective Tissue Disorders					1(1)
Osteochondrosis	0	1	0	0	1(1)
Psychiatric Disorders					1(1)
Anxiety	1	0	0	0	1(1)

7.3.5 Submission Specific Primary Safety Concerns

GI and Hepatic AEs (selected)

Within the MedDRA System Organ Classes, group of adverse events were selected for analysis. These included: Nausea, vomiting, diarrhea, abdominal pain, hepato-, investigation, LFT, ALT, AST, alk. phos., GGT, and bilirubin. Tables 21 and 22 summarize AEs by weight band groups. Overall, 12(15%) reported GI associated adverse events; no significant differences were noted among the weight bands. Five subjects (6%) reported hepatic related adverse events. No subject in the >50Kg weight band had hepatic adverse events. Hepatic adverse events appear to be slightly more common in the lower 2 weight bands. This is unlikely to be due to higher exposure. As shown previously, the overall exposure among the weight bands appears to be similar, although subjects in the lowest weight band group may have had individuals with higher exposures compared to the higher weight band groups. Despite higher exposure in some individuals, adverse events are unlikely to be related to exposure as formal exposure-safety analysis did not find any relationship between the two variables (see section below).

Table 21: GI associated adverse events

					DRV/rtv
Any GI related AEs					12(15)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
Vomiting	2	2	3	2	9(11)
Diarrhea	2	2	3	2	9(11)
Abdominal pain	2	2	1	3	8(10)
Nausea	2	0	1	0	3(4)
Parotid gland enlargement	1	0	0	0	1(1)
GI disorder (enteropathy)	1	0	0	0	1(1)
GI fistula	0	0	0	1	1(1)
Enterocutaneous fistula	0	0	0	1	1(1)

Table 22: Hepatic related adverse events

					DRV/rtv
Any Liver related AEs					5(6)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
ALT	0	2	0	0	2 (3)
Alk Phos	0	1	0	0	1(1)
INR	0	1	1	0	2(3)
PT	0	1	0	0	1(1)
Hepatomegaly	1	0	0	0	1(1)
Hepatitis A	1	0	0	0	1(1)

Rash

Within the MedDRA System Organ Classes for Skin and Soft Tissue, selected adverse events have been included to describe proportions of subjects with rash in each weight band group. Specifically, terminologies such as rash, papular, macular, maculo-papular, urticaria, drug rash, hypersensitivity, pruritic rash and pruritis were selected. Overall the number of subjects with rash (regardless of causality) was 12(15%). "Rash" and "maculopapular rash" are the two categories which can be associated with drug exposure. Such adverse events were observed in five subjects (6%). Table 23 summarizes the findings.

Table 23: Number (%) of Subjects Developing Rash

					DRV/rtv
Any Rash					12(15)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
rash	0	3	1	0	4(5)
Macular rash (localized)	1	0	0	0	1(1)
Maculopapular rash	0	0	1	0	1(1)
Papular rash (localized)	0	1	0	0	1(1)
pruritis	1	0	0	0	1(1)
Allergic rash	0	0	1	0	1(1)
Skin lesion	0	1	0	0	1(1)
blister	1	0	0	0	1(1)
ecchymosis	0	0	1	0	1(1)
acne	0	0	1	0	1(1)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The number of subjects with common AEs was similar between the weight groups.

Table 24: AE reported in >2% of subjects

System Organ Class n(%)					DRV/rtv
Any AE					71 (89%)
	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
Infection & Infestations					48 (60)
URI	1	5	3	3	12(15)
PNA	4	2	1	1	8(10)
sinusitis	3	3	2	0	8(10)
Herpes simplex	2	3	1	1	7(9)
Nasopharyngitis	2	1	2	1	6(8)
Tonsillitis	1	1	0	3	5(6)
Ear infection	1	1	1	1	4(5)
Pharyngitis	0	1	3	0	4(5)
Rhinitis	1	0	3	0	4(5)
Oral candidiasis	1	2	1	0	4(5)
Cellulitis	1	2	0	0	3(4)
Tacheobronchitis	0	1	1	1	3(4)
Dental caries	2	0	0	0	2(3)
Impetigo	2	0	0	0	2(3)
Pyoderma	0	2	0	0	2(3
General Disorders and Administration Site Disorders					22(28)
Pyrexia	1	3	1	2	9(11)
Injection site nodule	0	0	3	2	5(6)
Pain	1	0	1	2	3(4)
Chest pain	1	1	0	0	2(3)
Fatigue	0	0	1	1	2(3)
Respiratory, Thoracic and Mediastinal Disorders					23(29)
Cough	5	4	4	1	14 (18)
Bronchospasm	3		2	0	4(6)
Asthma	0	2	2	0	4(4)
Epistaxis	0	2	2	0	4(4)
Nasal congestion	0	1	2	0	3(4)
Rhinorrhea	0	1	1	1	3(4)
Wheezing	0	1	1	1	3(4)
Pharyngolaryngeal pain	1	0	0	1	2(3)
Rhinitis allergic	0	2	0	0	2(3)
Gastrointestinal Disorders					22(28)
Vomiting	2	2	3	2	9(11)
Diarrhea	2	2	3	2	9(11)
Abdominal pain	2	2	1	3	8(10)
nausea	2	0	1	0	3(4)
Blood and Lymphatic Disorders					13(16)
lymphadenopathy	4	3	2	0	9(11)
Neutropenia	4	1	0	0	5(6)
Skin and Subcutaneous Tissue Disorders					12(15)
Rash	0	3	1	0	4(5)
Eye Disorders					5(6)
Conjunctivitis	1	2	1	0	4(5)

Investigations					6(8)
ALT	0	2	0	0	2(3)
INR	0	1	1	0	2(3)
LDL	0	1	1	0	2(3)
Amylase	0	1	0	0	1(1)
Nervous System Disorders					7(9)
Headache	1	2	3	1	7(9)
Musculoskeletal and Connective Tissue Disorders	0	2	2	1	5(6)
Ear and Labyrinth Disorders					3(4)
Ear pain	0	1	0	1	2(3)
Injury, Poisoning And Procedural Complication					3(4)
Metabolism and Nutrition Disorder					3(4)
Hypoalbuminemia	2	0	0	0	2(3)
Psychiatric Disorders	1	0	0	1	2(3)
Reproductive System	1	1	0	0	2(3)

The most frequently reported System Organ Class (SOC) adverse events (>2%) were Respiratory Disorders, Gastrointestinal Disorders and Infection and Infestations. The most frequent AEs (all causes) were URI (15%), vomiting (11%), diarrhea (11%), pyrexia (11%) and lymphadenopathy (11%).

At the Week 24 study analysis in the adult trials (TMC114-C213 and TMC114-C202), the most common treatment-emergent adverse events (>5%) reported, regardless of causality were injection site reaction (25%), nausea (22%), diarrhea (19%), fatigue (19%), URI (16%) and headache (16%).

7.4.2 Laboratory Findings

Chemistry

DAIDS Grades 1-4 laboratory adverse events are summarized in Table 25. The majority of the liver-related laboratory abnormalities were grade 1 or 2. Grade 2-4 ALT increases were observed in 4 (5%) subjects. Two subjects (3%) experienced Grade 3-4 ALT increases. A 7 year old female, in the 20-29kg weight band, had a Grade 4 increase in ALT and Grade 3 increase in AST at Week 16. Subsequent follow-up after 1 week showed the toxicity to have improved to Grade 2 ALT and Grade 1 AST. The subject continued treatment and all ALT/AST laboratory values after the Week 16 visits were Grade 0. No subject had a Grade 4 AST increase. Hyperbilirubinemia was observed in only one subject. The subject had Grade 1 total hyperbilirubinemia with normal direct bilirubin levels. This subject also had a Grade 1 increase in ALT at the time of the reported hyperbilirubinemia but had normal AST.

Table 25: Liver related laboratory abnormalities

ALT	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
ALL Grades					15 (19)
Grade 1	4	6	3	1	14(18)
Grade 2	1	1	0	0	2(3)
Grade 3	0	1	0	0	1(1)
Grade 4	1	0	0	0	1(1)
AST	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					18(23)
Grade 1	9	4	2	2	17(22)
Grade 2	0	1	1	0	2(3)
Grade 3	1	0	0	0	1(1)
Grade 4	0	0	0	0	0
Alk Phos	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					20(25)
Grade 1	2	6	7	3	18(23)
Grade 2	0	1	1	0	2(3)
Grade 3	1	1	0	0	2(3)
Total Bili	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades	0	0	1	0	1(1)
Grade 1	0	0	1	0	1(1)
GGT	20kg	30kg	40kg	50kg	total
ALL Grades	0	0	0	0	0
PT	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades	0	0	0	0	2(3)
Grade 1	1	0	0	0	1(1)
Grade 2	0	1	0	0	1(1)
INR	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades	0	0	0	0	9(11)
Grade 1	2	2	2	1	7(9)
Grade 2	1	1	0	0	2(3)

Grade 2-4 increases in amylase was observed in 8(10%) subjects while 2(3%) subjects experienced Grade 2-4 increases in lipase. One subject was reported to have a Grade 4 increase in amylase with Grade 2/3 increases in lipase. This subject discontinued treatment due to "acute anxiety" in less than a month after starting treatment. All subjects were asymptomatic and no cases of pancreatitis were reported.

Table 26: Pancreas related laboratory abnormalities

Amylase	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
ALL Grades					22(28)
Grade 1	3	6	9	2	20(25)
Grade 2	1	2	3	1	7(9)
Grade 3	0	1	1	0	2(3)
Grade 4	1	0	0	0	1(1)
Lipase	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					3(4)
Grade 1	0	0	0	0	0
Grade 2	1	0	1	0	2(3)
Grade 3	1	0	0	0	1(1)

The most frequent lipid related laboratory abnormality was an increase in total cholesterol. Majority of the abnormalities were Grade 1 or 2.

Table 27: Lipid related laboratory abnormalities

Total cholesterol	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
ALL Grades					32(40)
Grade 1	3	3	8	2	16(20)
Grade 2	6	4	3	3	16(20)
Grade 3	0	1	0	0	1(1)
Lipids (LDL)	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					22(28)
Grade 1	3	1	3	2	9(11)
Grade 2	3	4	3	2	12(15)
Grade 3	0	2	0	0	2(3)

Hematology

The most frequently reported hematological abnormality was low count in neutrophils (26%). Most were Grade 1 in severity. Of the 48 subjects with Infection and Infestation reported as an adverse events, 9 (19%) had low counts of Neutrophils. In addition, there were no differences in the types and severity of infections reported between the subjects with low neutrophis counts and those with normal neutrophil count. No Grade 4 laboratory abnormality was reported for low platelets or leukopenia.

Table 28: Hematological laboratory abnormalities

Leukopenia	≥20 - <30kg N= 20	≥30- <40kg N=24	≥40 - <50kg N=24	≥50kg N=12	Total N=80
ALL Grades					4(5)
Grade 1	2	2	0	0	4(5)
Grade 2	1	1	0	0	2(3)
Grade 3	2	0	0	0	2(3)
Low Neutrophils	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					21(26)
Grade 1	5	5	1	2	13(16)
Grade 2	1	2	3	1	7(9)
Grade 3	2	1	1	1	5(6)
Grade 4	3	0	0	0	3(4)
Low Platelets	20-<30kg	30-<40kg	40-<50kg	>50kg	Total
ALL Grades					2(3)
Grade 1	0	0	1	0	1(1)
Grade 2	0	0	1	1	2(3)
Grade 3	0	0	0	1	1(1)

7.4.3 Vital Signs

Vital signs (HR, BP) were collected for all randomized subjects. No significant differences were noted when comparing baseline to on-treatment values.

7.4.4 Electrocardiograms (ECGs)

No ECG analysis was done during Part 2 of Study C212. During Part 1 of the study, ECG assessment (descriptive statistics) was performed. Small mean changes from baseline were reported in ECG parameters. These changes were not considered clinically relevant. In addition, the sample size was small (n=44) and paired samples were not used for this analysis.

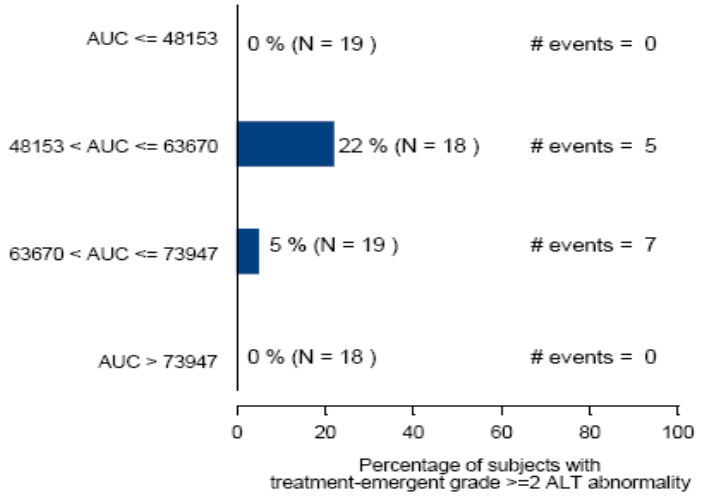
7.4.5 Immunogenicity

Please refer to the original NDA for further detail. Darunavir is a protease inhibitor and is not expected to have an immunogenic effect.

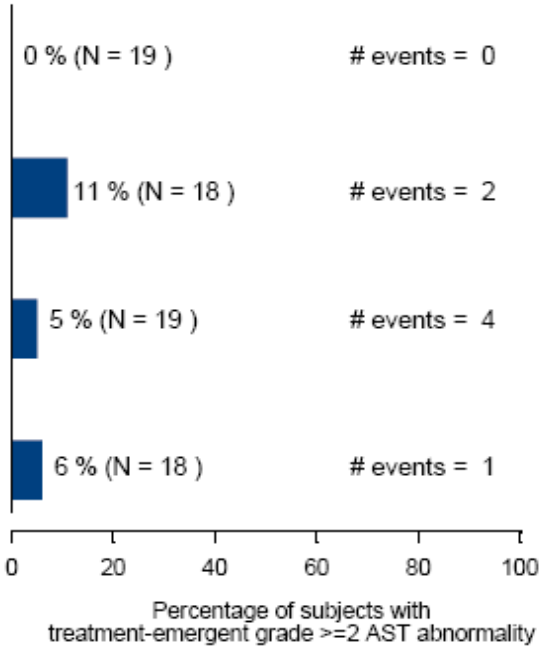
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

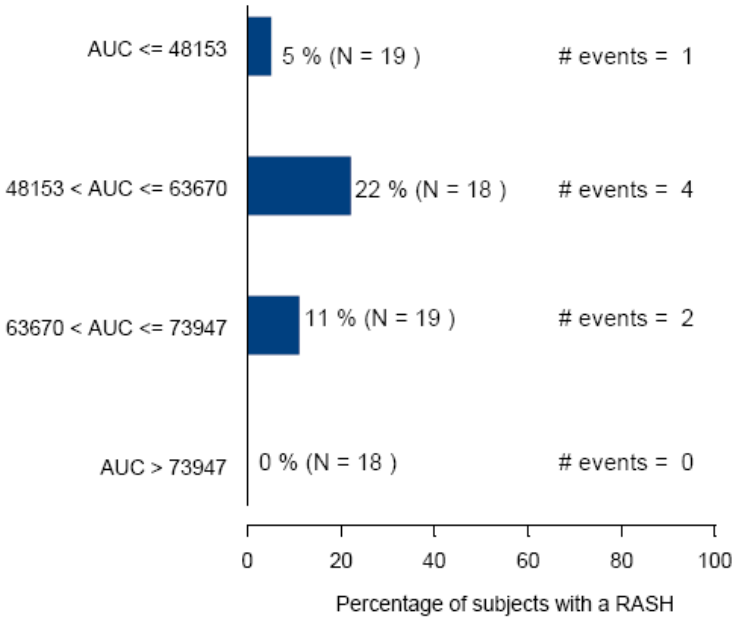
As discussed previously, the pharmacometrics team has done a formal analysis on exposure-safety relationship for darunavir. The analysis of safety and exposure focused on rash and liver enzyme tests (ALT, AST). No apparent relationship was shown between exposure and rash or liver enzymes. Figures 9, 10 and 11 summarize the exposure-safety analysis



Source: Dr. Krudys's review



Source: Dr. Krudys's review



Source: Dr. Krudys's review

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

This sNDA evaluated use of darunavir in the pediatric population. The study results were also analyzed by age (6 to <12, 12 to 18 years). Clearance (per body weight) of darunavir appears to decrease toward adult values as age increases. Despite some pharmacokinetic profile differences between the youngest and older age groups, the overall safety profile was similar among the two age groups.

7.5.4 Drug-Disease Interactions

Darunavir was not administered as a monotherapy. However, similar to adults, administration of darunavir in combination with low dose ritonavir and other ART appears to have decreased the HIV-1 viral load in the host. In addition, CD4+ cell counts and percentages have improved across all age groups after initiation of treatment with darunavir co-administered with ritonavir in combination with other ART.

7.5.5 Drug-Drug Interactions

It is expected that the same types of drug interactions will be observed in pediatric subjects as those that have been observed in adult subjects taking darunavir/ritonavir. Drug-Drug interactions are included in the label.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Please refer to the original NDA reviews.

7.6.2 Human Reproduction and Pregnancy Data

Darunavir was previously categorized as Class B for use in pregnancy. Data submitted during the accelerated approval in 2006 includes nonclinical fertility studies, where DRV was shown to have no effect on fertility and early embryonic development. However, inadequate exposures were seen in the species tested when compared with humans; the poor exposures limited the interpretability. Recent findings in the juvenile toxicology studies raised concern of darunavir use in pregnant women and neonates. As mentioned previously, pediatric studies in subjects below the age of 3 years have been waived due to mortality observed in the juvenile toxicity studies. When considering the nonclinical juvenile data in addition to the nonclinical fertility data which was difficult to interpret, the risks posed to a developing human fetus are not well known or characterized. Consequently, an additional warning regarding the lack of evidence for safe use in pregnancy became necessary. After consultation with the Maternal Health Team, the pregnancy category was changed from B to C.

7.6.3 Pediatrics and Effect on Growth

BMI, height and weight were expressed by means of absolute values and z-scores to adjust for gender and age. Z-scores were calculated for assessment of growth. The applicant states that at baseline, the age adjusted z-score values showed that subjects were below the normal population median value for BMI (mean -0.7), height (-1.4) and weight (-1.4). The finding is consistent with what is seen in children with chronic diseases. After starting treatment, significant responses were noted for all 3 growth parameters (BMI, height and weight). At Week 24, within-group comparison for the changes from baseline revealed statistically significant differences with respect to all anthropometric parameters (see Table 28).

Table 28: Effect of darunavir on growth

Parameter	DRV/rtv				
	N	Baseline (mean)	N	Mean change from Baseline (SE)	p-value
BMI	80	18.1	77	0.6 (0.12)	<0.001
Age-adjusted BMI z-score	80	-0.7	77	0.2 (0.06)	0.008
Height (cm)	80	146.6	77	2.3 (0.20)	< 0.001
Age-adjusted Height z-score	80	-1.4	77	0.1 (0.03)	0.010
Weight (kg)	80	40.0	77	2.8 (0.30)	< 0.001
Age-adjusted Weight z-score	80	-1.4	77	0.2 (0.05)	<0.001

N, number of subjects
[a] Exploratory p-values based on 2-sided Wilcoxon signed rank-test for comparison vs baseline
Source: TMC114-C112 Clinical Research Report

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no withdrawal or abuse potential with darunavir. There is no information on overdoses in pediatric subjects.

7.7 Additional Submissions

Not Applicable

8 POSTMARKETING EXPERIENCE

Darunavir has not been previously approved for use in the pediatric population. The applicant will continue to provide periodic safety updates in addition to providing full 48 week study report for Study TMC114-C112.

9 APPENDICES

9.1 References

1. NDA (Traditional)
sNDA 21-976
Reviewer: Wendy Carter, DO
Approved: October, 2008

2. NDA (Accelerated)
NDA 21-976
Reviewer: Neville Gibbs, MD
Approved: June 2006

3. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

4. Pediatric Written Request (PWR)
See Attachment 1

5. Postmarketing Commitment (PMC) Pediatric Research Equity Act (PREA)
See Attachment 2

9.2 Labeling Recommendations

Indications and Usage

Pediatric Patients

PREZISTA, co-administered with ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of HIV infection in pediatric patients 6 years of age and older [*see Use in Specific Populations (8.4)*].

This indication is based on 24-week analyses of plasma HIV RNA levels and CD4+ cell counts from an open-label Phase 2 trial in antiretroviral treatment-experienced pediatric patients 6 to < 18 years of age.

In treatment-experienced adult and pediatric patients, the following points should be considered when initiating therapy with PREZISTA/rtv:

- Treatment history and, when available, genotypic or phenotypic testing should guide the use of PREZISTA/rtv [*see Clinical Pharmacology (12.4)*].
- The use of other active agents with PREZISTA/rtv is associated with a greater likelihood of treatment response [*see Clinical Pharmacology (12.4) and Clinical Studies (14.3)*].

Dosage and Administration

Pediatric Patients (age 6 to < 18 years)

Do not use once daily dosing in pediatric patients.

Healthcare professionals should pay special attention to accurate dose selection of PREZISTA, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and underdose.

Prescribers should select the appropriate dose of PREZISTA/rtv for each individual child based on body weight (kg) and should not exceed the recommended dose for treatment-experienced adults.

Before prescribing PREZISTA, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of PREZISTA tablets may not be appropriate.

The recommended dose of PREZISTA/rtv for pediatric patients (6 to < 18 years of age and weighing at least 44 lbs (20 kg)) is based on body weight (see Table 1) and should not exceed the recommended treatment-experienced adult dose (PREZISTA/rtv 600/100 mg b.i.d.). PREZISTA tablets should be taken with ritonavir twice daily and with food.

Table 1: Recommended Dose for Pediatric Patients (6 to < 18 years of age) for PREZISTA Tablets with ritonavir

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

The safety and efficacy of PREZISTA/rtv in pediatric patients 3 to < 6 years of age have not been established.

Do not administer PREZISTA/rtv in pediatric patients below 3 years of age [*see Warnings and Precautions (5.11) and Nonclinical Toxicology (13.2)*].

9.3 Advisory Committee Meeting

Not Applicable

Attachment 1:

PEDIATRIC WRITTEN REQUEST

WRITTEN REQUEST – AMENDMENT 1

IND 62,477/NDA 21-976

Tibotec, Inc.
Attention: Jenny Z. Lin, Pharm.D.
Sr. Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your correspondence dated May 10, 2007, requesting changes to FDA's November 17, 2006 Written Request for pediatric studies for PREZISTA™ (darunavir).

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated November 17, 2006.

To obtain needed pediatric information on darunavir (PREZISTA™), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Types of studies:

A multiple-dose pharmacokinetic, safety, and activity study of darunavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

The objective of these studies will be to determine the pharmacokinetic and safety profile of darunavir across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

Indication to be studied:

Treatment of HIV infection in pediatric patients.

Age group in which studies will be performed:

HIV-infected pediatric patients from 3 years to adolescence.

Drug Information

- Dosage form: age appropriate-formulation
- Route of administration: oral
- Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide safety data including assessment of rash, gastrointestinal-related adverse events, liver enzyme elevations, lipid profiles, amylase and lipase elevations and any other parameters pertinent to use in the pediatric population.

Safety of darunavir must be studied in an adequate number of pediatric patients to characterize adverse events across the age range. A minimum of 100 patients with at least 24 weeks safety data is required.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients.

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

3 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients must be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max}, C_{min}, T_{max}, AUC and apparent oral clearance at steady-state.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. In addition, please also submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received darunavir.

Activity

Assessment of changes in plasma HIV RNA levels and CD4 cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving darunavir, particularly from those who experience loss of virologic response.

Labeling that may result from the studies:

Information regarding dosing, safety, and activity in HIV-infected pediatric population.

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analyses, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or
other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or not Hispanic/Latino.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before December 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency of your intent to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of

supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Elizabeth Thompson, M.S., Project Manager, at 301-796-0824.

Sincerely,
{See appended electronic signature page}
Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment 2:

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to below 3 years of age because of evidence strongly suggesting the drug would be unsafe in this pediatric age group. This decision is based on the results of juvenile rat toxicology studies that provide evidence of a potential safety risk as a result of overt toxicity in this age group and evidence of potential drug-brain accumulation.

Your deferred pediatric studies required by section 505B(a) of the Federal Food and Drug and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. We remind you of the deferred pediatric studies as listed in the October 21, 2008, approval letters for NDA 21-976/006 and NDA 21-976/007, respectively.

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects 3 to 6 years of age. Please evaluate dose requirements and safety in treatment-experienced pediatric patients 3 to 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

Protocol Submission:	December 31, 2008
Final Report Submission:	June 30, 2011

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Submission of final protocol:	June, 2009
Submission of final study report:	July, 2012

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 3 to <12 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety over 48 weeks.

Submission of final protocol:	March, 2011
Submission of final study report:	March, 2015

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)".**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yodit Belew
12/17/2008 04:02:05 PM
MEDICAL OFFICER

Kimberly Struble
12/17/2008 04:07:51 PM
MEDICAL OFFICER