CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202895Orig1s000

MEDICAL REVIEW(S)

Clarification to Amendment 2 to MOR of NDA 202-895
Dec. 13, 2011

As per FAX to Applicant from the Agency regarding storage temperature reports in the EMA inspections:

• Please clarify whether any (b) (4) darunavir and ritonavir long term stability data has been generated at either (b) (4)

• In regards to darunavir/ritonavir samples from the TMC114-C228 trial that were stored at (b) (4), please provide information on the following: a) the number of trial sites and the number of subjects at each site that had darunavir/ritonavir samples stored at (b) (4), b) the total number of darunavir/ritonavir samples at each trial site that had samples stored at -(b) (4), and c) the maximum length of time

In Amendment 2 the following statement was made:
"The Applicant's response to the Division's RFI for the first question is the subject of this amendment. The Chemistry Reviewer, Dr. M Paciga, will provide an in depth review of stability and temperature issues, however his assessment indicated that based on stability data and reported temperature deviations significant changes in product quality or performance are not expected."

Clarification as per Chemistry Reviewer:

There were 2 stability/storage temperature issues identified during the clinical site inspections:

1) storage and stability of drug product (darunavir oral suspension, and possibly ritonavir) at temperatures in the range of 10-30degC; and

2) storage of blood/plasma PK samples at (b) (4) degC rather than -20degC.

It is unlikely that storage of the drug product over the range of temperatures noted (all above refrigeration or freezing) before administration to patients would adversely affect product quality or performance.

Storage of drug product at (b) (4) degC would likely impact product performance. On the other hand, storage of plasma at (b) (4) degC would not likely adversely impact chemical stability of the analytes (darunavir, metabolites).

Note: MOR #2 refers erroneously to storage at [redacted] deg and product quality/performance. As noted above plasma storage at [redacted] would not affect plasma quality not drug quality. Drug product stored at specified range of temperatures was also not affected.

Regina Alivisatos, MD

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/s/

M R ALIVISATOS
12/13/2011

Medical Officer Review
Amendment to Review of NDA 202-895

Date	November 20, 2011
From	Regina Alivisatos, M.D.
Subject	Medical Officer Review Amendment
NDA # and Supplement #	NDA 202895/000 and SNDA 21976/S-20
Applicant	Tibotec Inc.
Date of Original Submission	March 29, 2011
Original PDUFA Goal Date	September 30, 2011
Date of Major Amendment	September 28, 2011
Revised PDUFA Date	December 30, 2011
Proprietary Name / Established (USAN) names	Prezista (darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 300 mg tablets, 150 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

This is the second amendment to the NDA package. The first, authored by the Cross Discipline Team Leader, Dr. Yodit Belew, dated September 26, 2011, had as its subject the revised dosing recommendation made by the Division for subjects weighing 10 to less than 15 kg. This recommendation was subsequently accepted by the Applicant. Specifically, the Division recommended that for subjects 3 years of age and older and weighing 10 to less than 15 kg, the dose should be calculated based on darunavir 20 mg/kg co-administered with ritonavir 3mg/kg.

Several reasons led to this change in dosing recommendation to 20/3 mg/kg instead of the Applicant's proposed (b) (4) in subjects weighing 10- <15 kg. The primary reason was the Division's assessment of a revision to the population PK analysis submitted by the Applicant to correct for an error, primarily in subjects weighing 10 - <15 kg. In this revised analysis, these subjects would have mean AUC exposure that is 53% higher that the targeted mean adults exposure value. As the lower dose did not present similar pharmacokinetic concerns and had similar efficacy and safety it was determined that this dose was the appropriate one to be included in labeling.

In addition because of concerns that the initial dosing device supplied by the Applicant could lead to dosing errors, the device was changed to an (b) (4) syringe device. Details of this device were provided in the major amendment under review including instructions for use. Both the device and the instructions are acceptable to the Division as well as to DRISK and DMEPA.

The current amendment to the MOR has been included because of the, unsolicited by the Division, submission on September 27, 2011 (SNDA 202-895/SN 41) by the Applicant of clinical sites inspection reports from the EMA for the ARIEL study (TMC114-C228). The ARIEL study was the primary pharmacokinetic and clinical study submitted in both

the US and Europe in support of dosing recommendations for subjects weighing between 10 and 20 kg. The site reports generated concerns regarding the quality of the data submitted in support of the NDA submission from 3 of the sites including the Kenya site (N = 6), and two South African sites (Drs. Violari and Moultrie (N = 9). As the PDUFA due date of September 30, 2011 did not allow adequate time for review of the data as well as for the submission of additional explanatory data from the Applicant, the site inspection submission was deemed a major amendment and the review time was extended (FAX communication to Tibotec 9/29/11). In a FAX dated October 6, 2011 the Agency requested that the Applicant supply the following:

- Provide a copy of your assessment to the inspection reports issued by the EMA (CHMP). In addition, submit your rationale for using/accepting the data from the three sites inspected in support of pediatric labeling for children 3 to <6 years of age.

- Please clarify whether any (b) (4) darunavir and ritonavir long term stability data has been generated at either (b) (4) .

- In regards to darunavir/ritonavir samples from the TMC114-C228 trial that were stored at (b) (4), please provide information on the following: a) the number of trial sites and the number of subjects at each site that had darunavir/ritonavir samples stored at (b) (4), b) the total number of darunavir/ritonavir samples at each trial site that had samples stored at (b) (4) and c) the maximum length of time

The Applicant's response to the Division's RFI for the first question is the subject of this amendment. The Chemistry Reviewer, Dr. M Paciga, will provide an in depth review of stability and temperature issues, however his assessment indicated that based on stability data and reported temperature deviations significant changes in product quality or performance are not expected.

Review of Response to RFI Question 1:

A single study TMC114-C228 was submitted in support of use of darunavir in the pediatric population ages 3 - < 6 years (NDA 202-895). Study TMC114-C228 is the only study conducted in this age group and the patients were treated with a new oral solution formulation.

Study TMC114-C228 is an ongoing, open-label, Phase 2 trial to evaluate the pharmacokinetics, safety, and antiviral activity to support dose recommendations by body weight of darunavir in combination with low-dose ritonavir (DRV/r) and other antiretroviral (ARV) agents, in treatment-experienced HIV-1 infected children ages from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/r are being evaluated in combination with other ARVs over a 48-week treatment period. The study was conducted in two parts. The first two weeks of the

TMC114-C228 trial were designed to support dose recommendations of DRV/r in the studied population. The pharmacokinetic profile of DRV/r dosed twice daily at the initially selected dose at steady-state in the studied population was evaluated at Week 2. Safety, tolerability and antiviral activity were also assessed at the Week 2 timepoint. Based on the PK analyses and simulations, dosing was adjusted primarily at or around week 12 of treatment. It should be noted that although these adjustments were made, they were made based on inaccurate information due to the omission of certain data. Follow-up analyses revealed that these adjustments ultimately led to unacceptably high Cmax and AUC in the lower weight band but were acceptable in the upper band. Two weeks after the dose adjustment, an additional pharmacokinetic assessment was performed, followed by another planned pharmacokinetic assessment at Week 24. Safety and tolerability, as well as antiviral activity, were also evaluated at these time points. The mean duration of DRV/r treatment from trial start up to the cut-off date of the Week-24 analysis was 30.5 weeks.

Subjects received DRV/r according to their body weight. The initial dose of DRV was 20 mg/kg in combination with ritonavir 3 mg/kg. According to their body weight, subjects received a DRV dose between 200 and 380 mg twice daily and a ritonavir dose between 32 and 48 mg twice daily. DRV/r was taken together with an optimized background regimen (OBR).

Twenty-seven treatment-experienced subjects (15 male and 12 female) were enrolled in the study and were stratified by weight and received DRV/r according to their respective weight band- 14 subjects (51.9%) in the 10 to < 15 kg weight group, and 13 subjects (48.1%) in the 15 to < 20 kg weight group. At the time of the Week-24 analysis, 1 subject had prematurely discontinued (due to an AE [vomiting], grade 2, not related to DRV).

The primary efficacy endpoint in this trial was plasma viral load < 50 copies/mL at Week 24. In the initial analysis, the virologic response defined as the percentage of subjects with a confirmed virologic response (plasma viral load < 50 copies/mL) was 59% (16/27) based on the FDA snapshot analysis. Nine subjects were classified as virologic failures and there was one each with missing data and no data because of early discontinuation.

In Table 1 below is the distribution of patients by country. As noted above concerns regarding the integrity of the submitted data were raised by the EMA inspectors for the Kenyan and the South African sites. In dispute are 16 patients, 6 from Kenya and 10 from S Africa. An initial review of the inspection reports raised serious concerns about the Kenyan site whereas there were fewer issues noted from the S African sites.

Subjects enrolled in Trial 228

Country	Number of Sites Enrolling	Number of Subjects Enrolled	Number Prematurely Discontinued
Argentina	3	4	0
Brazil	3 (2 enrolled)	6	1
Kenya	2	6	0
South Africa	3	10	0
India	1	1	0

The Applicant also submitted a Marketing Authorization Application (MAA) to EMA on May 4, 2011. The application consisted of trial TMC114-C228 which was also submitted to the US FDA. As a part of the MAA review process, between August 24 and September 2, 2011, the EMA Inspectorate conducted clinical site inspections at three sites in Kenya and S. Africa (Dr. Kimutai, Dr. Moultrie, and Dr. Violari) that were part of the TMC114-C228 study. The inspection reports were provided to the Applicant on Sept 26, 2011 and subsequently provided to NDA 202-895 (sequence 0041) on Sept 29, 2011. The initial inspection reports consisted of multiple minor and few major and critical issues as defined by the EMA for each site. A finding that was common to each of the three inspection reports, involved inconsistencies in data in the Week 24 dataset when compared to the Week 48 dataset. Other issues included:

- Lack of calibration of storage area thermometers *(minor)*
- Storage temperature went below the recommendations of the sponsor (minor).
- Lack of documentation of lower temperatures in the monitoring reports
- No timely notification of temperature excursion(major)
- No timely evaluation of the usage of IMP was performed by investigator site and sponsor (major).

A number of issues were specific to the Kenya site and included:

- No PPB approval for the conduct of the trial from 1st September 2010 to 24th November 2010 due to delay in renewal (major)
- Investigator TMF was not adequately maintained
- Monitoring not adequate
- The site was closed on the 21st June 2011, despite the fact that all necessary documents were not in the appropriate files
- Ethics correspondence, including letters from the ERC (dated 24th August 2011 and June 24th 2011) and a notification to the ERC regarding trial closure (dated 21st June 2011) were misfiled in the Temperature and Humidity Log Section.
- Correspondence was not filed in chronological order.
- Correspondence was filed in duplicate within the same section of the file, for example, letters to the ERC dated 28th September 2009, regarding submission of KEMRI protocol Version 2.0, and, dated 29th September, regarding clarification of approved protocols and PILs.

- Correspondence was filed in duplicate across different sections for no logical reason. For example the Continuing Review Reports were filed in the section entitled "interim, annual and final reports" and section entitled "cover letter, application forms section".
- Letters were on file in duplicate, but with different handwritten dates on the letters. For example the letter to the PPB regarding resubmission of IB, Safety Updates and Insurance for the trial.
- A document entitled "KEMRI SSC Protocol \ 1570 Reviewer comments (Site responses embedded in bold), signed and dated by Kimutai 11th March 2009, was on file with the PPB correspondence.
- Issues with consent form review committee make-up as well as with the consent form itself and the procedures followed in obtaining informed consent. Issues included translation, omission of dosing instructions, the performance of genetic testing etc. (Critical)
- Inaccurate documentation in the eCRF of the physical exam findings at screening, at baseline, similar issues for previous treatments and medical history,

The inspection reports were reviewed by the Applicant and responses were provided to the EMA on Oct 31, 2011 and to the Division on November 9. 2011.

For the Kenya site, a review of the Applicant's responses revealed that most of the issues were acknowledged as indicative of "sloppy work". Corrective actions taken for future projects included a commitment by the Applicant to ensure adequate training of all personnel involved in a trial as well as the hiring of a specific onsite clinical monitor who will ensure timely and adequate documentation of all parts of the trial. Issues such as inadequate representation of pediatricians of the informed consent committee were also acknowledged and will be avoided in future trials.

Comment: The Division acknowledged that the Applicant will in the future correct the issues that were found by the EMA inspectors however the informed consent issues are deemed too significant to allow for the inclusion of the data from the Kenya site into the data used to make a final decision regarding the approvability of the application.

With regards to the inconsistencies found between the 24 and 48 week datasets across the sites, Tibotec performed a detailed assessment of both datasets. Overall, there were 228 inconsistencies in the Week-24 dataset for the entire trial that were already corrected prior to inspection, by the time of the Week-48 analysis. When excluding the inconsistencies for laboratory data (a local laboratory was used for the site of Dr. Kimutai in Kenya, and the (b) (4) laboratory for the other sites), 130 corrected inconsistencies were shown to be related to the inspected sites (3 sites, 15 subjects) and 47 corrected inconsistencies were related to the non-inspected sites (8 sites, 12 subjects). The inconsistencies identified are either additions or corrections of the Week-24 dataset, generally pertaining to screening and baseline data.

There were no consequences of the inspection findings on the handling on the safety of the subjects in the trial (the trial subjects were monitored according to local medical standards). There were no negative consequences for the pharmacokinetic/efficacy/safety conclusions of the primary Week-24 and Week-48 analyses and the local Kenyan lab results did not affect the main objective of the trial.

Comment: From a clinical standpoint the inclusion of all patients who received any dose of study drug in the safety analysis is standard procedure and the exclusion of any of the 27 treated subjects would be unreasonable. From an efficacy standpoint however, the Kenya site patients were excluded for the reasons stated above. It should also be noted however that as per the Clinical Pharmacology Reviewer, Dr. Stanley Au, all Kenyan patients' data was previously excluded from the PK analyses and therefore no changes in the PK conclusions were expected.

The revised efficacy analysis excluding the three Kenyan patients originally included in the analysis (one virologic failure and two successes) is as follows:

Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL (FDA snapshot analysis/Original Dataset)
Week 24

n (%)	**DRV/r N = 27**
Virologic Success	16 (59.3)
Virologic Failure	9 (33.3)
No virologic data week 24-discontinued due to AE/death	1 (3.7)
Missing data week 24	1 (3.7)

N = # of responders, n = # of patients

Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL (FDA snapshot analysis/Revised Dataset)
Week 24

n (%)	**DRV/r N = 24**
Virologic Success	14 (58.3)
Virologic Failure	8 (33.3)
No virologic data week 24-discontinued due to AE/death	1 (3.7)
Missing data week 24	1 (3.7)

N = # of responders, n = # of patients

Therefore the exclusion of the Kenya patients did not substantively alter the efficacy analysis.

Conclusion and Recommendations: The Applicant submitted a response to the EMA inspection reports and deficiencies found at three of the sites where trial TMC114-C228 took place. The inspection reports and the response constituted a major amendment to the

NDA package. After review of both the inspection reports and the responses the Reviewer concluded that the Applicant performed inadequate monitoring at the respective sites, however generally the deficiencies did not affect the PK, efficacy and safety conclusions drawn from trial 228 regarding dosing in pediatric patients ages 3 – 6 and weighing between 10 and < 20 kgs. It was necessary to exclude the patients from the Kenya site because of significant deficiencies in the informed consent process. The exclusion of these patients did not affect the efficacy, safety or pharmacokinetic conclusions of trial TMC114-C228.

The Reviewer recommends an approval of NDA 202-895 with labeling as agreed upon including dosing for patients weighing between 10 - < 15 kg at the 20/3 mg/kg dose level and the exclusion of the Kenya patienys' data from the efficacy analyses presented in labeling.

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/s/

M R ALIVISATOS
12/13/2011

CLINICAL REVIEW

Application Type	NDAs 202-895 and 21-976
Submission Number	000 and S-20
Submission Code	Type 3 and SE5
Letter Date	March 29, 2011/June 28, 2011
Stamp Date	March 30, 2011
PDUFA Goal Date	September 30, 2011
Reviewer Name	Regina Alivisatos, M.D.
Review Completion Date	July 30, 2011
Established Name	Darunavir
(Proposed) Trade Name	PREZISTA
Therapeutic Class	Protease Inhibitor
Applicant	Tibotec
Priority Designation	P
Formulation	Oral Suspension 100 mg/ml Tablets 400 mg
Dosing Regimen	Twice daily (BID)
Indication	Treatment of HIV-1 Infection

Intended Population Pediatric Population 3 - < 6 years of Age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This original New Drug Application (NDA 202-895) provides pharmacokinetic, safety, tolerability and virologic response data that support weight-based dosing recommendations of Prezista (Darunavir, DRV) in combination with ritonavir and other antiretroviral drugs for the treatment of HIV-1 infected pediatric patients ages 3 to < 6 years and weighing between 10 and 20 kilograms. This application also provides for a new oral suspension formulation (100 mg/mL) that is suitable for achieving weight based dose adjustments. An approval is recommended for this NDA application. Darunavir co-administered with ritonavir, in combination with other drugs, resulted in reduction in HIV-1 viral load and increases in CD4 cell counts over the 24 week study period in pediatric patients ages 3 - < 6 years who weigh between 10 and 20 kilograms.

No deficiencies were identified in this NDA that would preclude the approval.

Darunavir/ritonavir (DRV/r) was studied in one phase 2, open-label, randomized study. Subjects were stratified according to weight (≥10 - < 15kg, ≥ 15- < 20 kg) and received DRV/r according to their body weight. The initial dose of DRV was 20 mg/kg in combination with ritonavir 3 mg/kg. Both DRV and ritonavir were administered as oral suspensions. According to their body weight, subjects received a DRV dose between 200 and 380 mg and a ritonavir dose between 32 and 48 mg twice daily. DRV/r was taken together with an optimized background regimen (OBR) consisting of ≥ 2 active ARVs with available pediatric dose recommendations.

To support dose recommendations of DRV/r in the patient population under study, pharmacokinetic assessments were performed at Week 2 when DRV/r at the initially selected dose had reached steady-state. Following the Week-2 analysis, pharmacokinetic simulations were performed to predict DRV exposures as a function of body weight and dose. Based on a comparison of these simulations with the target DRV exposure (between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL achieved with DRV/r 600/100 mg twice daily), as well as on the safety and efficacy evaluations at Week 2, the initial dose of DRV/r 20/3 mg/kg twice daily was adjusted to DRV/r 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg. The adjusted DRV/rtv dose for the lower body weight group resulted in a mean DRV exposure that was higher than the adult target exposure (140%) thus reducing the risk of underexposure in this weight band. The adjusted DRV/rtv dose for the higher body weight group resulted in a DRV mean exposure that was within the adult target exposure range (122%).

Twenty-seven treatment-experienced subjects (15 male and 12 female) were enrolled in the study and were stratified by weight and received DRV/r according to their respective weight band- 14 subjects (51.9%) in the 10 to < 15 kg weight group, and 13 subjects (48.1%) in the 15 to < 20 kg weight group. At the time of the Week-24 analysis, 1 subject had prematurely discontinued (due to an AE [vomiting], grade 2, not related to DRV).

The primary efficacy endpoint in this trial was plasma viral load < 50 copies/mL at Week 24. Overall, the virologic response defined as the percentage of subjects with a confirmed virologic response (plasma viral load < 50 copies/mL) was 59% (16/27) based on the FDA snapshot analysis. Nine subjects were classified as virologic failures and there was one each with missing data and no data because of early discontinuation. When the endpoint of viral load less than 400 copies/ml at 24 weeks was assessed, 24/27 patients or 89% had evidence of virologic effectiveness. Similar response rates were observed for virologic response defined as viral load < 400 copies/mL and ≥ 1.0 log10 decrease in plasma viral load from baseline, and the mean change in log10 viral load from baseline are similar with those of trial TMC114-C212 (Phase 2 trial to establish weight based dosing with DRV/r in pediatric patients ages 6 – 18) where the proportion of patients with virologic response was approximately 88% in the younger 6 – 12 year old age group at 24 weeks compared to 54% in the older 12 – 18 years group. However, virologic response defined as a confirmed plasma viral load < 50 copies/mL at Week 24 was lower in the TMC114-C228 trial under review compared with that obtained in the lower age group (6 to 12 years) of the TMC114-C212 trial with a virologic response rate of 75% in the 6- 12 year old group and 39% in the 12 – 18 year old group in trial 212 at 24 weeks as compared to approximately 56% in the trial 228 under review. Similarly virologic responses in trial 212 were higher in the in the smaller weight groups: 75% in the 20-39 kg group vs. 50% in the 40- 49 kg group, vs. 58% in the >50kg group.

This difference in response rates between age and weight groups is consistent with those found by "The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Response to combination antiretroviral therapy: variation by age. AIDS 2008, 22: 1463-73"and it is expected that the virologic response rates will increase in the ensuing 24 weeks of ARV treatment.

The Applicant demonstrated an acceptable safety profile for darunavir co-administered with ritonavir in combination with other antiretroviral drugs. While adverse events were common, 23 (85.2%) subjects experienced ≥ 1 AE, significantly fewer were serious in nature Five (18.5%) subjects experienced a grade 3 or 4 AE; 4 (14.8%) subjects had a grade 3 AE and 1 (3.7%) subject had a grade 4 AE. Only one patient discontinued treatment prior to week 24 due to an adverse event (vomiting). Three patients sustained a SAE during the treatment period, however, none were considered related to DRV. Clinically significant laboratory abnormalities were also relatively uncommon and did not lead to treatment discontinuation.

The most frequent (> 3 subjects) AEs, by preferred term, were upper respiratory tract infection (9 subjects, 33.3%), diarrhea (8 subjects, 29.6%), hypokalemia (5 subjects, 18.5%), alkalosis, cough, and nasopharyngitis (each in 4 subjects, 14.8%).

The most frequent (> 3 subjects) AEs of special interest were gastrointestinal (GI) AEs (11 subjects, 40.7%) and rash (4 subjects, 14.8%).

No exposure-safety relationship was able to be demonstrated for either hepatic adverse events or for rash adverse events due to the small number of patients in this trial.

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 was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe the findings.

1.2 Risk Benefit Assessment

Darunavir/ritonavir in combination with other antiretroviral drugs has previously been shown to be effective in treating HIV-1 infected treatment experienced adults as well as in pediatric patients ages 6 – 18 years of age. Similar results were obtained at 24 weeks in trial 228 submitted to support DRV/r dosing in patients ages 3 - < 6 years of age. Virologic activity and immunologic benefit was demonstrated in both the lower and higher weight groups.

The observed risks for darunavir are well known and the type and rate of adverse events were similar to those seen in the older pediatric patients and in adults with few exceptions. The rate of diarrhea was greater in the younger patients enrolled in trial 228 (30%, N = 8) as compared to that seen in trial 212 in the older pediatric patients (11%). Interestingly the rate was similar to that seen in adult patients (32%). In the trial under review (228) all reported episodes of diarrhea were rated as mild and did not lead to treatment discontinuation. Further almost all reports of diarrhea ceased after DRV/r dose adjustment occurred after the first 2 weeks of treatment.

Risks identified with the use of darunavir/ritonavir include hepatotoxicity (including drug-induced hepatotoxicity), which are displayed under the Warning and Precaution section in the current label.

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 in the 212 trial (ages 6- 18), there were 2 (3%) pediatric subjects with ≥ Grade 2 elevation in AST, ALT and/or alkaline phosphatase. Only one subject had Grade 4 increase in ALT and no subjects had Grade 4 increase in AST or alkaline phosphatase. In trial 228, three patients (3/27) had one liver-related AE (AST increased, blood ALP increased, hepatosplenomegaly). AST increased and hepatosplenomegaly were grade 2 in severity and no severity grading was coded for blood ALP increased. AST increased was considered possibly related to DRV, while the other liver-related AEs were considered not related to DRV. There were no reported serious liver events.

Of the other events of interest considered related to DRV treatment, there were four reported rash events all grade 1 severity. These events were reported by three patients and included erythema

(1 subject), rash (1 subject), and rash papular and rash pruritic (both in the same subject). One rash-related AE was considered at least possibly drug related (rash papular).

Cardiac AEs (all grade 1) were reported in four patients. Tachycardia was reported in two patients, and ECG QT prolonged and QRS axis abnormal occurred in 1 one patient each. One cardiac AE was considered at least possibly related to DRV (ECG QT prolonged). This patient experienced a transient prolongation of the uncorrected QT interval, while QTcF was with normal limits; the patient showed no clinical symptoms and the event resolved with continued dosing and without concomitant medication.

There are currently limited protease inhibitors available for use in pediatric patients under 6 years of age. Darunavir would provide an alternative treatment option for HIV-1 infected pediatric patients ages 3 and greater. Given no apparent increase in clinically significant adverse events, including hepatotoxicity, rash, and cardiac events, the virologic and immunologic benefit demonstrated in the 3 - < 6 year old age group outweighs the observed and potential risks.

This Reviewer concurs with the CMC and Clinical Pharmacology reviews and supports approval for the oral suspension formulation (100 mg/mL). The Applicant has provided sufficient data to demonstrate the relative bioavailability at steady state for the oral suspension (trial 169). In addition, the exposure-response data in young children further support approval of the oral suspension.

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 the 3 month safety update there were no additional serious adverse events reported. The Applicant will continue to submit periodic safety reports for review.

No additional pediatric postmarketing risk management activities are planned.

1.4 Recommendations for other Post Marketing Study Commitments

A PMC will be issued for a study to establish dosing recommendations in children ages 6 – 12 with the oral suspension. A new study is needed as the initial bioequivalence study provided in the NDA did not meet the DSI standards for approval. Please refer to Clinical Pharmacology Review by Dr. Stanley Au for additional details.

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 patients 3 to < 6 years of age

Proposed Dose and regimen:

(b) (4)

Dosage forms: 75mg, 150mg, 400 mg, and 600 mg tablets
100 mg/ml oral suspension

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 the treatment of HIV-1 infection in treatment experienced adults. In 2008 it received an approval for use in pediatric patients ages 6 – 18 years.

2.2 Tables of Currently Available Treatments for Proposed Indications

Protease inhibitors (PIs) have become the mainstay of highly active antiretroviral therapy (HAART) when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combination antiretroviral (ARVs) drugs are now the standard of care for the treatment of HIV-1. 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. In addition, the needs of the pediatric population of patients are still largely unmet especially with newer ARVs. ARV drugs that are currently approved for use in pediatric patients are listed in the following table:

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 (TDF)	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®
	Darunavir	Prezista®
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 names Prezista. The formulation used in this NDA submission is a new oral suspension (100 mg/mL) which has been shown to be bioequivalent to the existing tablet formulations. In addition, a dose proportional 75 mg tablet has been developed for use in pediatric subjects.

2.4 Important Safety Issues with Consideration to Related Drugs

General safety issues associated with the protease inhibitor class of ARVs include side effects such as liver toxicity, 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 19th, 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/r 600/100 mg twice daily. The clinical section of the NDA was submitted in September 2005 and accelerated approval was granted in June 2006. The traditional approval of darunavir took place 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.

In October 2008, an approval was granted for treatment of HIV-1 infection in treatment naïve adults. In accordance, a new PMC was issued at the time of that 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 PWR was also amended to reflect inclusion of both treatment experienced and treatment naïve pediatric subjects.

A full pediatric waiver was granted for patients < 3 years old (NDA 21-976/S-006 Approved 21 Oct 2008) because of potential toxicity issues (see section 2.6).

The currently submitted New Drug Application 202-895 is submitted as a complete response (CR) to the Pediatric Written Request for PREZISTA® (Darunavir) tablets originally issued on 17 November 2006 and amended on 16 August 2007 (Amendment 1). All studies have been completed and the study reports have been submitted within the time frame stipulated in the Written Request – Amendment 1. In accordance with the exclusivity provisions of Section 505A of the Federal Food, Drug, and Cosmetic Act, Tibotec, Inc. is requesting six months of pediatric exclusivity for PREZISTA® (Darunavir) tablets and oral suspension. This request was granted by the Agency Pediatric Exclusivity Board (June, 2011).

The submitted study provides an interim study report to one of the 4 PMC as well as a new dosage form as required under PREA. The Applicant plans to submit a 48 week safety and efficacy final study report at a later date. In addition with this application for the oral suspension formulation the Applicant requested [redacted] (b) (4)

2.6 Other Relevant Background Information

In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5-11 days) or multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. In some animals, the 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 three 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 days 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.

As noted in section 2.5, a full pediatric waiver has been granted for patients < 3 years old (NDA 21-976/S-006 Approved 21 Oct 2008).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA 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 Harmonization 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 sites were chosen for DSI investigation by the Biopharmaceutics Review group given that both studies submitted in support of the dosing regimen were designed as PK studies. Of note the site that performed the PK assessments for study 228 has been closed and DSI is requesting the records of that site. These sites were chosen because the plasma concentration data for the TMC114-TiDP29-C228 trial that administered darunavir (Prezista) oral suspension in

combination with ritonavir solution is pivotal in evaluating whether the proposed weight based darunavir dosing recommendations for HIV-1 infected pediatric patients 3 to < 6 years old are appropriate. All TMC114-C228 plasma samples were analyzed at the (b) (4) bioanalytical laboratory in (b) (4).

The plasma concentration data in adults for the TMC114-TiDP29-C169 trial is pivotal in evaluating whether darunavir tablets and oral suspension can be used interchangeably without requiring adjustments in the darunavir dosage regimens. All TMC114-C169 plasma samples were analyzed at the (b) (4) laboratory in (b) (4)

The Clinical Pharmacology Review Team requested an Inspection (DSI) of the analytical sites for both studies 169 and 228.
1. The inspectors concluded that data from the analytical portion of study TMC114 - TiDP29-C169 can be used for review. However, in absence of reserve samples at the clinical site (see DBGC evaluation for inspectional finding at the clinical site and information provided in Attachment 1) the authenticity of the test and reference products used in study TMC114-TiDP29-C169 cannot be assured. Overall, DBGC recommends that the study TMC114-TiDP29-C169 not be accepted for Agency review.
2. The analytical portion for study TMC114-TiDP29-C228 can be accepted for agency review.

Due to the inability of the agency to accept the bioequivalence data for study 169, dosing recommendation for children older the 6 years of age or weighing greater than 20 kg with the oral suspension cannot be made. A PMC will be issued for a second study in order to address this dosing issue.

3.3 Financial Disclosures

The Applicant submitted financial disclosure information. None of the principal or secondary investigators who participated in this trial held financial interests in the Applicant, Tibotec, or Johnson and Johnson, the Applicant's parent company.

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 see. Clinical Microbiology Review for detail.

4.3 Preclinical Pharmacology/Toxicology

The Applicant submitted the results of pharmacology/toxicology study in order to fulfill a 2008 post-marketing requirement (PMR) issued at the time of approval of NDA 21,976. This PMR requested that the Applicant "perform a nonclinical reproductive study in a relevant species which achieves an adequate AUC exposure margin (compared to human serum exposure) in order to establish the safety profile of Darunavir in utero. "

The Applicant conducted a range finding study and a developmental study in rats and was able to establish a NOAEL in the former that allowed them to proceed with the DART study. This study indicated incomplete ossification of a number of bones as well as delayed thymus development and confirmed the in utero toxicity of DRV. The Agency Pharmacology Toxicology Review

Team determined that the Applicant fulfilled the PMR requirement and that they should be released from the PMR and the label updated with the new reproductive toxicology study information.

For further details, Please see the Pharmacology/Toxicology review by Dr. Peyton Myers.

4.4 Clinical Pharmacology

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.

Pharmacodynamics

Please refer to Dr. Au's and Liu' Pharmacometrics review of this NDA. Briefly, the pharmacometrics review focused on the following questions:

1. Is the DRV exposure at the proposed dose in pediatric subjects (10 -20 kg) similar to those in heavier pediatric subjects (> 20 kg) and adults?

The pediatric exposures in pediatric patients 10 - < 20 kg are slightly higher than those in heavier pediatric patients and in adults.

2. Is there an exposure-response for efficacy in pediatric patients ages 3 – 6 years consistent to that in older pediatric patients (ages > 6 to 17) and adults?

The exposure response relationship in pediatric patients ages 3 - < 6 years was consistent with that seen in older pediatric patients and adults.

3. Is there exposure-safety relationship for DRV?

The analysis of safety and exposure conducted, focused on rash and diarrhea. There was no apparent relationship shown between the events as exposure increases. This can easily be seen by the fact that the rate of adverse events decreased subsequent to the dose increases and therefore the increase in exposure. It should also be noted that the ability to determine a relationship between exposure and safety is limited because of the very small number of patients studied and the small number of AEs that occurred.

Pharmacokinetics

Please refer to Dr. Stanely Au's Clinical Pharmacology review of this sNDA.

5 Sources of Clinical Data

This submission contains data from a single randomized pediatric study, Study TMC114-C228. The study was conducted by the Applicant and utilized 11 investigators, 11 clinical sites, in 6 countries.

This submission contains electronic materials documenting the study results and the Applicant's conclusions regarding Study C228, 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 for review. Datasets (as SAS transport files) of demographic, safety and efficacy data were also submitted.

The submission also includes a study report, safety and pharmacokinetic datasets from study 169, a bioequivalence study submitted in support of the oral suspension formulation that was used in study 228.

5.1 Tables of Clinical Studies

The following tables summarize the studies (228 and 169) submitted in support of this application. Table 4 summarizes the subjects enrolled in Study C228 by country and site.

Table 2
Studies conducted in support of this submission

Trial Number	Design	Subjects	Treatment regimen	Status
TMC114-C228	OL, Phase 2	27 15 M/12 F	First 2 weeks DRV/r 20/3 mg/kg bid Dose adjustment after interim analysis: 10 - < 15 kg DRV/r 25/3 mg/kg bid 15 - < 20 kg DRV/r 375/50 mg bid	Ongoing

Table 3
Clinical BioPharmaceutic Trial by Dosage Form

Clinical Trial	Darunavir Dosage Form	Co-administered Drug
TMC114-C169	300 mg oral tablet 100 mg/mL oral suspension	RTV: 100 mg capsule

Table 4
Subjects enrolled in Trial 228

Country	Number of Sites Enrolling	Number of Subjects Enrolled	Number Prematurely Discontinued
Argentina	3	4	0
Brazil	3 (2 enrolled)	6	1
Kenya	2	6	0
South Africa	3	10	0
India	1	1	0

5.2 Review Strategy

Trial C228 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. No formal statistical analysis confirming the endpoints were performed by an FDA statistician as the study was a single arm study. 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 v10 Statistical software.

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.

5.2 Discussion of Study TMC114-C228

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

A single study was submitted in support of use of darunavir in the pediatric population ages 3 - < 6 years. Study 228 is the only study conducted in this age group and the patients were treated with a new oral suspension formulation. This study supports the approval of darunavir co-administered with ritonavir in combination with other antiretroviral drugs in HIV-1 infected pediatric patients ages 3 - < 6 years. The 24 week data was submitted as an interim study report. In addition, a summary study report has been submitted for subjects who have reached Week 48. A full study report with datasets is expected for submission when available.

Study TMC114-C228 is an ongoing, open-label, Phase 2 trial to evaluate the pharmacokinetics, safety, and antiviral activity to support dose recommendations by body weight of darunavir in combination with low-dose ritonavir (DRV/r) and other antiretroviral (ARV) agents, in treatment-experienced HIV-1 infected children ages from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/r are being evaluated in combination with other ARVs over a 48-week treatment period. The study was conducted in two parts. The first 2 weeks of the TMC114-C228 trial were designed to support dose

recommendations of DRV/r in the studied population. The pharmacokinetic profile of DRV/r dosed twice daily at the initially selected dose at steady-state in the studied population was evaluated at Week 2. Safety, tolerability and antiviral activity were also assessed at the Week 2 timepoint. Based on the PK analyses and simulations, dosing was adjusted. It should be noted that although these adjustments were made, they were made based on inaccurate information due to the omission of certain data. Follow-up analyses revealed that these adjustments ultimately led to acceptable Cmax and AUC in both weight bands and therefore the doses were not changed a second time. Two weeks after the dose adjustment, an additional pharmacokinetic assessment was performed, followed by another planned pharmacokinetic assessment at Week 24. Safety and tolerability, as well as antiviral activity, were also evaluated at these time points. The mean duration of DRV/r treatment from trial start up to the cut-off date of the Week-24 analysis was 30.5 weeks.

Subjects received DRV/r according to their body weight. The initial dose of DRV was 20 mg/kg in combination with ritonavir 3 mg/kg. According to their body weight, subjects received a DRV dose between 200 and 380 mg twice daily and a ritonavir dose between 32 and 48 mg twice daily.

DRV/r was taken together with an optimized background regimen (OBR) consisting of ≥ 2 active ARVs with available pediatric dose recommendations. The ARVs in the OBR had to be selected by the investigator based on the results of resistance testing performed at screening and the child's ARV history. Single substitutions of ARVs in the OBR were allowed for tolerability and/or toxicity reasons.

The primary objectives were:

- To evaluate the pharmacokinetic profile of DRV in combination with low-dose rtv administered twice daily at steady-state in children aged from 3 to < 6 years and weighing between 10 and < 20 kg.
- To support dose recommendation of DRV/rtv to be used in this population by comparing the DRV exposure achieved in these treatment-experienced HIV-1 infected children to that in HIV-1 infected adults and older children weighing > 20 kg.
- To evaluate short-term safety, tolerability, and antiviral activity of DRV/rtv twice daily in treatment-experienced children aged from 3 to < 6 years over a 2-week treatment period.
- To evaluate safety, tolerability and antiviral activity of DRV/rtv twice daily and other ARVs over a 24-week treatment period at the selected dose for HIV-1 infected children aged from 3 to < 6 years.

The secondary objectives were:

- To evaluate long-term safety, tolerability and efficacy of DRV/rtv b.i.d. and other ARVs over a 48-week treatment period at the selected dose for HIV-1 infected children aged from 3 to < 6 years.
- To evaluate immunology, resistance characteristics, pharmacokinetics, and pharmacokinetic/pharmacodynamic relationships over a 48-week treatment period.

The steady state (Week 2) pharmacokinetic assessments and simulations, their comparison with the target DRV exposure (between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL achieved with DRV/r 600/100 mg twice daily), as well as the safety and efficacy evaluations at Week 2, led to the adjustment of the initial dose of DRV/r 20/3 mg/kg twice daily to DRV/r 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg. The adjusted DRV/r dose for the lower body weight group resulted in a mean DRV exposure that was higher than the adult target exposure (140%) thus reducing the risk of underdosing. The adjusted DRV/r dose for the higher body weight group resulted in a DRV mean exposure that was within the adult target exposure range (122%)

6 Review of Efficacy

Efficacy Summary

Please refer to Section 5.2 for additional details. Study 228 is an ongoing, open-label, study. Subjects were stratified according to weight (≥ 10 to <15 kg or ≥ 15 to < 20 kg) and received DRV/r doses based on the two weight bands with background ARV therapy chosen by their local investigator. Analysis of intensive PK sampling, safety and efficacy was performed on all patients after Week 2 to determine the optimal darunavir dose in both bands. The dose selection was also recommended by an outside study monitoring board (DSMB).

Darunavir oral suspension (100 mg/mL) 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. The primary efficacy parameter was virologic response defined as percentage of subjects with confirmed plasma viral load < 50 HIV-1 RNA copies/mL at Week 24 calculated according to the FDA TLOVR algorithm. Based on this a priori defined TLOVR analysis, at Week 24, 15 subjects (55.6%) had a confirmed virologic response at week 24. Numerous sensitivity analyses (observed case analysis, NC = F analysis, and TLOVR non-VF-censored) were performed including the FDA snapshot analysis which is currently the standard Agency analysis on which outcome determinations are based. Accordingly with the snapshot analysis, at week 24, 16 patients (59%) of patients achieved and sustained an HIV RNA level < 50 copies/mL. Secondary efficacy parameters were virologic response defined as the percentage of subjects with 1) a confirmed plasma viral load < 400 HIV-1 RNA copies/mL, and 2) a confirmed ≥ 1 log10 decrease in plasma viral load from baseline, calculated according to the FDA TLOVR algorithm.

At Week 24, 24 subjects (89%) had a confirmed plasma viral load < 400 copies/mL, and 23 subjects (85%) had a confirmed ≥ 1 log10 decrease in plasma viral load from baseline. For both the primary and secondary endpoints, the number of patients with an appropriate decrease in plasma viral load increased over time. Only one patient had attained the primary endpoint of HIVRNA < 50 copies/mL at week 2 as compared to 16 at week 24. Nine patients had attained the secondary endpoint of < 400 copies/mL at week 2 as compared to 24 at week 24.

The mean change in viral load can be seen in the following figure:

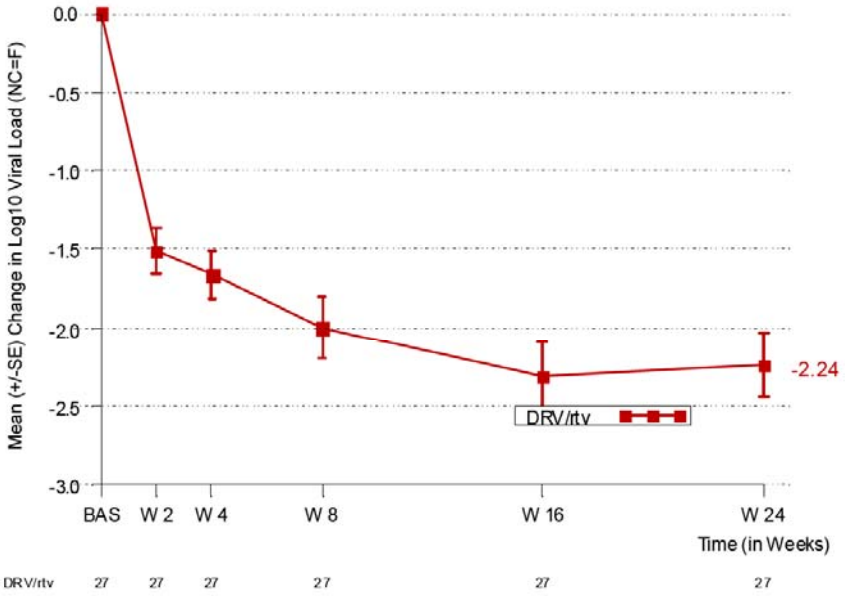


Figure 10: Mean Change in log_{10} Viral Load From Baseline Over Time (ITT – NC = F)
Source: Display EFF.1, Display EFF.3

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

6.1 Indication

PREZISTA, co-administered with ritonavir, is indicated, in combination with other antiretroviral drugs, for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels from study C112.

Methods

No formal statistical review was conducted by a statistician from the FDA as the study was single armed.

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

- Proportion of subjects with a viral load < 50 copies/mL at Week 24 (primary efficacy endpoint)
- Proportion of subjects with a viral load < 400 copies/mL at Week 24 (secondary efficacy endpoint)

Efficacy analysis compared treatment response between the two weight bands as well as with results of previous pediatric study 112 performed in older pediatric patients. All patients who were randomized and received at least one dose of the study drug were included in the Agency efficacy analysis. If a patient had a missing efficacy parameter value (i.e. viral load < 400 copies/mL or <50copies/mL), the patient was considered a failure.

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.

Demographics

Demographics are summarized below. The number of subjects in each weight band group was balanced. The study population was also balanced for gender with a small difference in favor of male patients (15/27 (56%). The randomized pediatric subjects had a median age of 4.5 years (range 3 - < 6) and were 22% Caucasian, 67% black, 11% other. This is not unexpected as two of the primary sites were in Africa.

Table 5
Demographics

Baseline Characteristics	**DRV/r**
Population	**N = 27**
Demographic Data	
Gender, n (%)	
Female	12 (44.4)
Male	15 (55.6)
Age (years), median (range)	4.5 (3.1; 5.8)
Weight band as stratified (kg)	
10 - < 15	14 (51.9)
15 - < 20	13 (48.1)
Race, n (%)*	
Caucasian	6 (22.2)
Black	18 (66.7)
Other	3 (11.1)

- Note 37% of patients were classified as Hispanic or Latino and the remaining 17 as non-Hispanic or Latino.

Baseline HIV Characteristics

Baseline disease characteristics are summarized in the table below. The median baseline viral load for all patients was 4.51 (2.85; 5.74) log10 copies/mL and the median baseline CD4+ count (N = 21) was 927 (range 209 - 2429) cells/mm^3. Eleven subjects (40.7%) had a baseline viral load < 20,000 copies/mL while seven subjects (25.9%) had a baseline viral load ≥ 100,000

copies/mL. Sixteen patients (59%) had advanced or severe disease based on WHO classification at the time of enrollment into the study.

Vertical transmission was the only cause for acquisition of HIV infection in the patients enrolled in this study.

Table 6
Baseline characteristics

Baseline Disease Characteristics	DRV/r N = 27
Log10 viral load: median (range), copies/mL	4.51 (2.85; 5.74)
Viral load at baseline, n (%)	
<20,000 copies/mL	11 (41)
20,000- <50,000 copies/mL	5 (19)
50,000-<100,000 copies/mL	4 (15)
>100,000 copies/mL	7 (26)
CD4+ cell count: median (range), x 106 cells/L	927 (209 - 2429)
CD4%, median (range)	27.7 (15.6; 51.1)
Duration of known HIV infection: median (range), years	3.8 (0.1; 5.4)
Mode of transmission, n (%)	
Mother to child	27 (100)
WHO Clinical Stage of HIV Infection	
Clinical Stage 1 (asymptomatic)	6 (22.2)
Clinical Stage 2 (mild symptoms)	5 (18.5)
Clinical Stage 3 (advanced symptoms)	12 (44.4)
Clinical Stage 4 (severe symptoms)	4 (14.8)

Previous Antiretroviral Treatment History

All subjects had previous ART use, a minimum of three and maximum of eight. All subjects had previous use of at least two NRTIs. Nineteen subjects (70%) had previous use of ≥ 1NNRTI and 16 (59.6%) had previously used a PI (lopinavir in all).

Baseline HIV Resistance

In summary, as described by the Applicant, the majority of subjects had no primary PI mutations (23 subjects, 85.2%) and no DRV RAMs (25 subjects, 92.6%) at baseline, and 21 subjects (77.8%) had ≥ 3 PI RAMs (non-primary resistance-associated mutations).

Overall, the median number of primary PI mutations was 0 (range: 0 - 3); the median number of PI RAMs was four (range: 1 - 13); the median number of DRV RAMs was 0 (range: 0 - 2).
A graphical presentation of the prevalence of DRV RAMs at baseline is provided in Figure 2.

Phenotype was assessed by means of the Antivirogram® assay in order to determine the number of susceptible drugs at baseline. Overall, 100% of patients were susceptible to at least one PI at baseline, 20 (95%) were susceptible to ≥ 3 NRTIs and 16 (73%) were susceptible to ≥ 1 NNRTI.

All patients were infected with virus susceptible to DRV at baseline. The median DRV FC was 0.5; range: 0.2 - 2.

Please refer to Dr Naeger's DAVP Microbiology Review for further detail.

Table 7
Applicant Table 13 Number of Susceptible Drugs at Baseline

Table 13: Number of Susceptible Drugs per Class at Baseline, Based on Antivirogram®

Number of Subjects With Susceptible Drugs per Class, n (%)	DRV/rtv
Total	
Total susceptible drugs, N	**22**
≥ 5 susceptible	22 (100)
Total susceptible in the initial OBR, N	**21**
0 susceptible	1 (4.8)
1 susceptible	6 (28.6)
≥ 2 susceptible	14 (66.7)
PI	
Total susceptible drugs, N	**22**
≥ 1 susceptible	22 (100)
NRTI	
Total susceptible drugs, N	**21**
1 susceptible	1 (4.8)
≥ 3 susceptible	20 (95.2)
Total susceptible in the initial OBR, N	**21**
0 susceptible	1 (4.8)
1 susceptible	6 (28.6)
≥ 2 susceptible	14 (66.7)
NNRTI	
Total susceptible drugs, N	**22**
≥ 1 susceptible	16 (72.7)

N = number of subjects; n = number of observations
[a] All currently available PIs = (fos)amprenavir, atazanavir, indinavir, LPV, nelfinavir, saquinavir, tipranavir, DRV.
Source: Display ADD.1

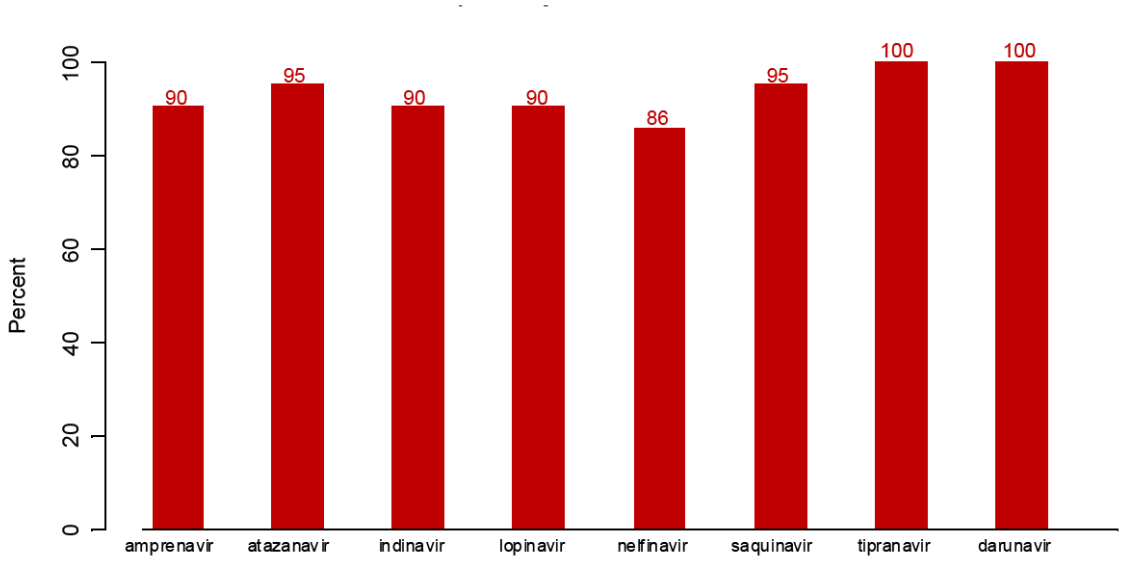


Figure 1: Susceptibility to Individual PIs Based on Antivirogram® at Baseline
Source: Display ADD.2

Patient Disposition

Twenty-six patients (96%) completed the 24 week period and 1 (4%) discontinued prematurely. This patient discontinued because of an adverse event (vomiting).

Table 8
Subject Disposition and Trial Termination

N (%)	DRV/r
ITT Population	
N screened	42
N treated	27
N not treated	25
Discontinuations-Reason, n (%)	**1 (3.7)**
AE	1 (3.7)
Ongoing	**26 (96.3)**

N - # of patients, n = number of observations

Analysis of Primary Endpoint(s)

The primary efficacy parameter as defined a priori by the Applicant was virologic response defined as percentage of subjects with confirmed plasma viral load < 50 HIV-1 RNA copies/mL at Week 24 calculated according to the FDA TLOVR algorithm. Based on this analysis, at Week 24, 15 subjects (55.6%) had a confirmed virologic response. Numerous sensitivity analyses (observed case analysis, NC = F analysis, and TLOVR non-VF-censored) were performed including the FDA snapshot analysis which is currently the standard analysis on which outcome determinations are based. Accordingly, at week 24, 16 patients (59%) of patients achieved and sustained an HIV RNA level < 50 copies/mL.

Table 9
Outcome Table
Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL
(FDA snapshot analysis)
Week 24

n (%)	DRV/r N = 27
Virologic Success	16 (59.3)
Virologic Failure	9 (33.3)
No virologic data week 24-discontinued due to AE/death	1 (3.7)
Missing data week 24	1 (3.7)

N = # of responders, n = # of patients

The Medical Reviewer was able to recreate the snapshot analysis using the Viral Load Snapshot Analysis Dataset provided in section 5 of the electronic submission. In addition both the Applicant and the Agency performed numerous sensitivity analyses which confirmed the Applicant's conclusions.

Table 10
Virologic Response Defined as % of Patients with Viral Load less than 50 copies/mL
(ITT-TLOVR) per Time Point

Time Point	DRV/r	
	n	N (%)
Week 2	27	1 (3.7)
Week 4	27	3 (11.1)
Week 8	27	8 (29.6)
Week 16	27	14 (51.9)
Week 24	27	15 (55.6)

N = # of responders, n = # of patients

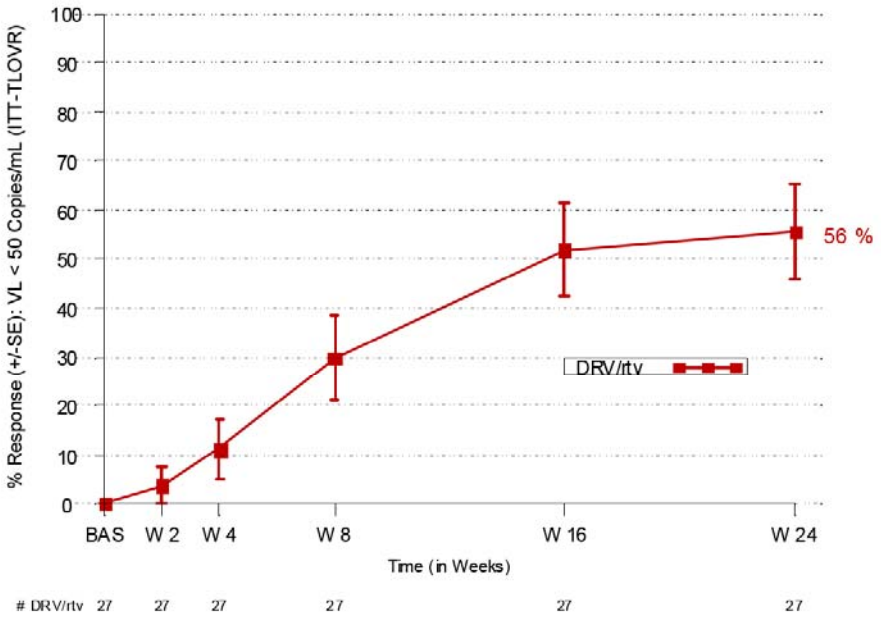


Figure 8: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL (ITT – TLOVR) Over Time

Source: Display EFF.7

Analysis of Secondary Endpoint(s)

Secondary efficacy parameters were virologic response defined as the percentage of subjects with 1) a confirmed plasma viral load < 400 HIV-1 RNA copies/mL, and 2) a confirmed ≥ 1 log10 decrease in plasma viral load versus baseline, calculated according to the FDA TLOVR algorithm.

At Week 24, 24 subjects (88.9%) had a confirmed plasma viral load < 400 copies/mL, and 23 subjects (85.2%) had a confirmed ≥ 1 log10 decrease in plasma viral load versus baseline. This analysis was confirmed by the medical reviewer using the Viral Load Analysis Dataset.

Reasons for Treatment Failure

According to the Agency analysis, 26 patients completed treatment through the 24 week time period. One patient discontinued treatment early because of an AE (vomiting attributed to ritonavir). Of the 26 patients that continued treatment and were included in the 24 week analysis, 16 attained virologic success as defined by the protocol (HIV RNA < 50 copies/mL) nine met the definition of virologic failure and one subject each had either discontinued or had missing data. All patients with virologic failure had an HIV RNA < 400 copies/mL at week 24 but > 50 copies/mL thus meeting the protocol definition for failure but appeared to be responding to the ARV treatment.

Table 11
Reasons for Treatment Failure (24 weeks)

	Total N=27
Proportion of subjects with virologic response	
<400 c/mL	24 (69%)
< 50 c/mL	15 (56%)
Proportion of subjects with Virologic failure	9 (33%)
Rebound	0
Never suppressed	0
Other (AE; D/C)	2 (7%)

Other Endpoints

Key secondary analysis endpoints also included determination of DRV and ritonavir pharmacokinetic parameters at steady-state (Cmax, Cp0, Cp10h, Cp12h, AUC0-10h, AUC0-12h, tmax, CL, V, t1/2).

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

Reviewer Analyses:

Analysis by Weight Bands

Efficacy of darunavir was analyzed based on the two stratified weight bands (≥ 10- < 15kg, ≥15- < 20kg), as summarized in the following table. As compared to study 112 where more subjects in the lower weight bands responded to treatment compared to the higher weight group, in study 228 more patients in the higher weight group met the primary endpoint of HIV RNA< 50 copies/mL at week 24. However the number of patients in this study is too small to draw any valid conclusions about response by weight band.

Table 12
Proportion of subjects with HIV RNA <50 copies/mL) by weight bands

	≥ 10 - < 15 kg	≥15 - < 20 kg	Total
	N= 14	N=13	N= 27
Proportion of subjects with virologic response < 50 c/mL	7 (50%)	9 (69%)	16 (59%)
Proportion of subjects with virologic failure	6 (43%)	3 (23%)	9 (33)
Other (AE; discontinuations, missing data.)	1 (7%)	1 (8%)	2 (8%)*

*includes one patient with missing data and on discontinuation due to an AE.

Analysis by Baseline Mutations

At baseline, 2 patients harbored DRV RAMs (PID 228-0009 had L33F and L76V, and PID 228-0015 had L76V). Both subjects responded virologically (HIV-1 RNA <50 copies/mL) at Week 24. Patient 009 was in the lower weight band and patient 0015 was in the higher weight band.

Analysis by Exposure

To support dose recommendations of DRV/r in the pediatric population ages 3 - < 6 years weighing between 10 to < 20 kg, pharmacokinetic assessments were performed at Week 2 when DRV/r at the initially selected dose had reached steady-state. Following the Week-2 analysis, pharmacokinetic simulations were performed to predict DRV exposures as a function of body weight and dose. Based on a ultimately erroneous (see below) comparison of these simulations with the target DRV exposure (between 80% to 130% of the mean adult exposure of 62.3 µg.h/mL achieved with DRV/r 600/100 mg twice daily), as well as on the safety and efficacy evaluations at Week 2, the initial dose of DRV/r 20/3 mg/kg twice daily was adjusted to DRV/r 25/3 mg/kg twice daily for children weighing between 10 and < 15 kg, and to a fixed dose of DRV/r 375/50 mg twice daily for children between 15 and < 20 kg. The adjusted DRV/rtv dose for the lower body weight group resulted in a mean DRV exposure that was higher than the adult target exposure (140%). However it was determined that this exposure was within the acceptable limits and that it would reduce the risk of underexposure in this weight band. The adjusted DRV/rtv dose for the higher body weight group resulted in a DRV mean exposure that was within the adult target exposure range (122%). Please refer to Dr. Liu's' pharmacometrics for full details.

Pharmacokinetic Results at Week 2 Relative to Dosing change:
(Applicant analysis)

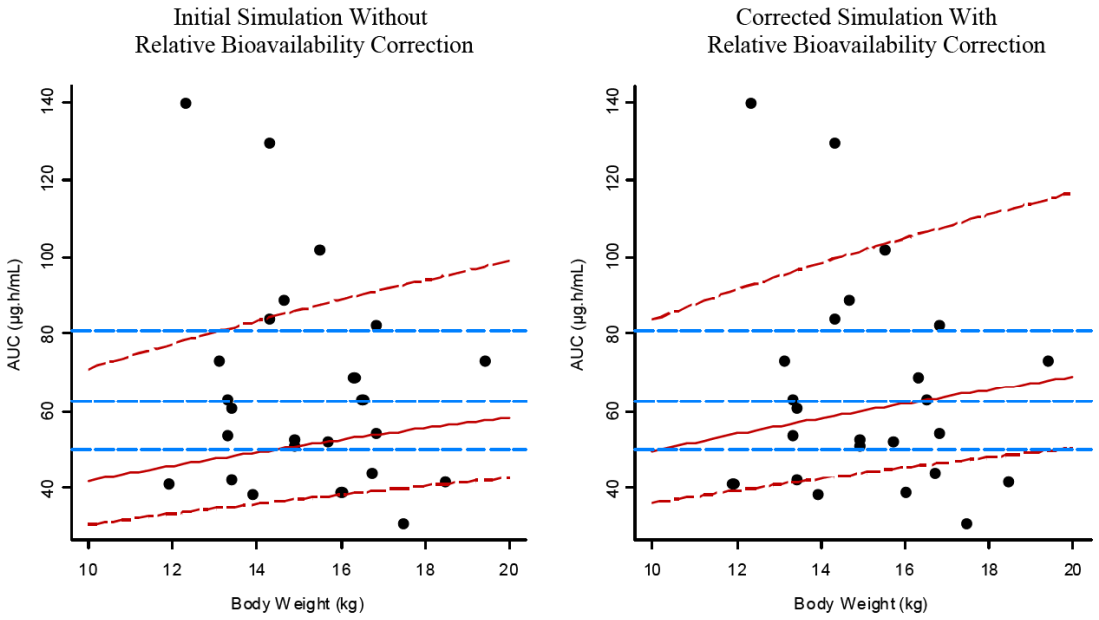
After 2 weeks of dosing with the 20/3 mg/kg twice daily DRV/r regimen, pharmacometric assessments were performed. In order to avoid underexposure (NOTE: it is unclear to the clinical reviewer if the initial doses actually were associated with true underexposure given that the Applicant inadvertently omitted relevant data as described below) these analyses led the Applicant to modify the dosing for each weight band as follows:

- ≥ 10 - < 15 kg to 25/3 mg/kg DRV/r twice daily
- ≥15 - < 20 kg to 375/50 mg DRV/r twice daily

After the database lock for the Week-24 analyses (i.e., after the dose adjustment had been implemented), it was discovered that a relative bioavailability parameter was erroneously not taken into account in this prediction of exposure, yielding a 15% underprediction of the expected exposure. The simulations were repeated (this time taking into account relative bioavailability), and the impact of the error on the dose adjustment decision was assessed.

The updated simulations for the 20/3 mg/kg twice daily dosing, including the relative bioavailability correction, showed higher than expected DRV exposures overall, but for children with a lower body weight, the expected DRV exposure continued to be on the low side. Therefore, as the risk of underexposing persisted the dose adjustment to a dose of DRV/rtv 25/3 mg/kg twice daily for children weighing between 10 to < 15 kg remains valid. The DSMB concurred on the dose adjustment, before as well as after the correction of the simulations.

Clinical Study Report



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

Figure 2: Predicted DRV AUC_{12h} in 3 to < 6 Years-Old Children Weighing Between 10 and < 20 kg After Administration of DRV/rtv 20/3 mg/kg b.i.d.
Source: Module 5.3.3.5/TMC114-C228-CPOP/Figure 4

Comment: As can be appreciated from the Applicant's Figure 2, dosing at the initial 20/3 mg/kg DRV/r dose appeared to achieve the appropriate exposures in patients of both weight bands. However as there did not appear to be a safety issue with the greater exposures achieved with the higher doses, they appear acceptable from a clinical standpoint.

The actual doses after dose adjustment (b) (4) by body weight can be seen in the Applicant's table 20 copied from the edr submission:

Table 20: Actual Doses in After Dose Adjustment Targeting the Dose of DRV/rtv 25/3 mg b.i.d. in Subjects Weighing Between 10 to < 15 kg, and DRV/rtv 375/50 mg in Subjects Weighing Between 15 to > 20 kg

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

[a] The DRV oral suspension was administered with a pipette with a 0.2-mL accuracy gradation; the rtv oral solution was administered with a pipette with a 0.1-mL accuracy gradation. Due to the accuracy limitations of the pipettes, a rounding was performed when calculating the doses to be administered per weight band.

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

Note: For comparison with the initial dose, see Table 1.

Immunologic response

CD4% was available for only 21 of 27 patients at baseline (77%). Of these 21, eight had CD4% less than 25% (range 15.6 – 24.9) and 13 had CD4 % greater than 25% (range 26.4 – 51.1%). As expected in pediatric patients less than 5 years of age, CD4 percentages were relatively high because of the young age of the patients and the lesser time for development of greater degrees of immunosuppression in them. Of the eight patients with CD4% less than 25%, four (50%) were categorized as virologic failures at the week 24 visit as compared to four of the 13 patients (31%) of those with CD4% greater than 25%. Three of the four patients with CD4% < 25% and virologic failure were in the less than 15 kg group. Of the 4 virologic failures with CD4%'s > 25%, two were in each weight band.

At Week 24, the mean (and median) change in CD4+ percentage from baseline was 4%. The mean (SE) change in CD4+ absolute cell count at Week 24 from baseline was 109 (87.1) x 106/L, and the median (range) change was 41 (498 - 757) x 106/L).

Three of the eight patients with CD4% at baseline less than 25% increased the percentage to greater than 25%. Therefore at week 24, five patients had a CD4% less than 25% and 16 greater than 25%.

Analysis of Clinical Information Relevant to Dosing Recommendations

The dose selection and recommendations for the two weight bands, was based on the following results:

1) The selected twice daily regimens provided darunavir plasma concentrations similar to those obtained in adults receiving 600/100 mg twice-daily or similar to the concentrations achieved in children ages 6 – 18 receiving weight based dosing twice daily.

2) The HIV viral load at week 24 was comparable to the adult and pediatric patients (ages 6 – 18) HIV-viral load at week 24. Below is a comparison of the 24 week efficacy results between the pediatric studies TMC114-C112 and TMC-114-C228 and adult studies (C213 and C202):

- Virologic responders (decrease of at least 1 log10 from baseline) :
  - 85.2% (pediatric 228) vs. 69% (pediatric112) vs. 74% (adults)
- Virologic responders (VL< 400 c/mL):
  - 69% (pediatric 228 vs. 63% (pediatric 112) vs. 65% (adults)
- Virologic responders (VL< 50 c/mL):
  - 59% (pediatric 228)vs. 45% (pediatrics 112) vs. 52% (adults)

In summary, the recommended dose for pediatric patients including the 3 - < 6 age group copied from proposed draft labeling dated August 16, 2011 is:

(b) (4)

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 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/r co-administered with optimized background therapy continued to persist. A formal 48 week analysis will be conducted by the DAVP.

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 like darunavir 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)[4] 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), non-nucleoside 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 patients 3 to < 6 years of age. The types of adverse events reported were similar to those reported in adults and in pediatric patients ages 6 – 18 years. Exposure-safety relationships were not shown for hepatic, cardiac or 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

Clinical Studies Used to Evaluate Safety

The safety profile of darunavir has already been established in adults and pediatric patients-with adequate number of patients.

Study C228, which is currently ongoing, was the pediatric study conducted to assess pharmacokinetics, safety and efficacy of darunavir in pediatric patients ages 3 - < 6. The population studied includes HIV-1 infected pediatric patients who were 3 to < 6 years of age at the time of randomizations. All were treatment experienced. Among 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 in this age group.

Adequacy of Data

The data submitted support safety and tolerability of darunavir co-administered with ritonavir in combination with other ARVs. This submission is the final component of the required studies outlined in the PWR. With this submission the Applicant has fulfilled the requirement of the PWR (a minimum of 100* patients followed for safety at the to-be-marketed dose or higher for 24 weeks). 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 patients 12 to 18 years of age 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.
*80 patients from C112 and 27 from C228

7.2 Adequacy of Safety Assessments

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

The Applicant has submitted safety data on 27 pediatric patients with at least 24 week safety data. Further, although not a full 48 week study report, a preliminary summary has been submitted for review. This review presents safety both before and after dose adjustment (approx week 12) which was based on pharmacometric simulations performed on samples obtained at the end of week 2 of dosing.

Explorations for Dose Response

In study C228 patients initially received a 20/3 mg/kg DRV/r twice daily dose independent of weight band. After 2 weeks of dosing with the 20/3 mg/kg twice daily DRV/r regimen, pharmacometric assessments were performed. In order to avoid underexposure theses analyses led the Applicant to modify the dosing for each weight band as follows:

- ≥ 10 - < 15 kg to 25/3 mg/kg DRV/r twice daily
- ≥15 - < 20 kg to 375/50 mg DRV/r twice daily

A dose response relationship was not established for either the initial dose or the doses used after the pharmacometric analyses. There was no significant increase in adverse events noted with the higher doses or exposure when compared to the initial 20/3 mg dose.

Special Animal and/or In Vitro Testing

Please refer to section 4.3 of this review for a description of the pharmacology/toxicology submitted with this NDA.

Routine Clinical Testing

Protocol defined routine clinical and laboratory testing were conducted during the trial. These tests were adequate. Patients 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.

Metabolic, Clearance, and Interaction Workup

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

Deaths

No deaths occurred during the 24 week study period.

Safety Pre -dose Adjustment:

Up to Week 2, 12 patients (44%) experienced ≥ 1 AE. The reported AEs were primarily grade 1 or 2 in severity and considered not related to the trial medication. There were no SAEs. One patient (3.8%) permanently discontinued the trial due to an AE on Day 1 (vomiting, grade 2, not related to DRV, very likely related to rtv as per the PI). There were no grade 4 AEs, and three patients (11%) had ≥ 1 grade 3 AE: 1 patient (CRF ID 228-0005) experienced acidosis, 1 patient (CRF ID 228-0014) experienced alkalosis, and 1 patient (CFR ID 228-0018) experienced acidosis, hyponatremia and neutropenia. All grade 3 AEs were considered not related to the trial medication.

For 2 of the patients with Grade 3 AEs, pharmacokinetic analyses showed no apparent relationship between their events (acidosis and alkalosis) and Cmax and AUC12h for either DRV or ritonavir. Both were in the expected range. No further information was provided for patient 228-0014 other than that the alkalosis was reported on the first day of treatment and lasted for 16 days. The patient had abdominal pain but nausea, vomiting, dehydration or other symptoms were not described. In addition further labs were not provided. This patient developed pneumonia approximately 1 month later and had no evidence of alkalosis at that time.

For patient 228-005 (acidosis, Grade 2) a narrative was not provided as this event was not considered serious or severe.

DRV Cmax and AUC12h were higher compared to other patients for patient 228-0018 because this patient received a higher dose in error (175% of the DRV dose); however, it was concluded that there was no relationship between the grade 3 AEs for this patient (of which acidosis and neutropenia already occurred on Day 1) and DRV dose. For patient 228-0018, the instigators of both his acidosis (bicarbonate as low as 12.5) and his alkalosis (bicarbonate reported as high as 20.2) are unclear given that both occurred on the same day (Day 1). They were concurrent with the patient's neutropenia which also pre-existed the start of treatment. For reasons unclear, the patients' labs were not performed centrally but at a local facility which may have led to errors. Nevertheless the patient did receive the wrong dose from which he recovered as described above. In addition the reported bicarbonate value did not appear to be consistent with a true alkalosis.

Nonfatal Serious Adverse Events (SAEs)

Three patients (11.1%) experienced an SAE during the treatment period: one patient each: pneumonia, trigger finger (stenosing tenosynovitis), and asthmatic crisis. All were grade 3 or 4 in severity, and none were considered related to DRV. None of the SAEs led to treatment discontinuation and 2 occurred before the dose switch. The asthmatic crisis occurred 40 days after the dose switch.

Serious Adverse Events

Table 13
Serious Adverse Events during Treatment
(Independent of Causality or Severity)

System Organ class Dictionary derived term n (%)	DRV/r		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
Mean exposure (weeks)	30.5	12.8	18.4
Any SAE	3 (11)	2 (7)	1 (4)
Infections and Infestations	1 (4)	1 (4)	0
Pneumonia	1 (4)	1 (4)	0
Musculoskeletal and Connective Tissue Disorders	1 (4)	1 (4)	0
Trigger finger	1 (4)	1 (4)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (4)	0	1 (4)
Asthmatic crisis	1 (4)	0	1 (4)

N = total # of subjects, n = # with disorder

The frequency of SAEs in study 228 (11%) was consistent with that of study 112 and that of the adult clinical trials. In study 112 which assessed DRV/r in pediatric patients ages 6 – 18, 10% of eight of 80 patients had an SAE. Most commonly SAEs were reported in the Infections and Infestations SOC (8% or 6) followed by SAEs from the GI SOC (3% or 2) and the Investigations SOC (1% or 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%).

Dropouts and/or Discontinuations

During the 24 week treatment period, 1(4%) patient discontinued the trial due to AE. This AE, vomiting, in a 5 year old female patient (CRF ID 228-0030) started on Day 1 of the treatment period, was grade 2 in severity and continued through study day 14. As per the narrative, the PI considered the vomiting not related to DRV, but very likely related to ritonavir. The vomiting resolved immediately after treatment discontinuation. The patient's surrogate markers for HIV-disease during the trial were: CD4+ cell count at Screening was 706 cells x 106/L and 24.0%, at Baseline was 738 cells x 106/L and 27.3%, and at early withdrawal (was 832 cells x 106/L and 22.4%. The viral load at Screening (was 70100 copies/mL, at Baseline (7 January 2010) was 214000 copies/mL, and at early withdrawal was 8540 copies/mL.

Significant (Grade 3 and/or 4) Adverse Events

Overall, five patients (19%) reported adverse events ≥ Grade 3. No significant differences were noted among the weight bands. Of note however all grade 3 or 4 AEs occurred before the dose switch except for one event (asthmatic crisis) which occurred afterwards. The reported events were most frequently from the Metabolism and Nutrition Disorders SOC (three patients 11%). All grade 3 AEs, except 2, occurred in only one patient. The two grade 3 AEs reported in > 1

patient were acidosis and alkalosis (each in 2 subjects, 7.4%). There was only one grade 4 AE (trigger finger). None of the grade 3 or 4 AEs in this trial were considered drug related.

Comment: Most of the significant AEs occurred before dose adjustment most likely due to tolerability issues that slowly resolved over the first few weeks of treatment. It is likely that most of the GI events were related to the ritonavir component and that as expected they resolved over time. Generally though there were few to no significant AEs in this trial and DRV/r was well tolerated by the age group under study. All analyses were independently confirmed by the Medical Officer using jmp statistical software and the "AEAD" dataset provided by the Applicant. In addition, all narratives were reviewed and briefly summarized below.

Table 14
Grade 3 and 4 Adverse events occurring during Treatment
(Independent of Causality)

System Organ class Dictionary derived term n (%)	DRV/r		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
Mean exposure (weeks)	30.5	12.8	18.4
Any Grade 3 or 4 AE	5 (19)	4 (15)	1 (4)
Blood and Lymphatic System Disorders	1 (4)	1 (4)	0
Neutropenia	1 (4)	1 (4)	0
Infections and Infestations	1 (4)	1 (4)	0
Pneumonia	1 (4)	1 (4)	0
Metabolism and Nutrition Disorders	3 (11)	3 (11)	0
Acidosis	2 (7)	2 (7)	0
Alkalosis	2 (7)	2 (7)	0
Hypokalemia	1 (4)	1 (4)	0
Hyponatremia	1 (4)	1 (4)	0
Musculoskeletal and Connective Tissue Disorders	1 (4)	1 (4)	0
Trigger finger	1 (4)	1 (4)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (4)	0	1 (4)
Asthmatic crisis	1 (4)	0	1 (4)
Skin and Subcutaneous Tissue Disorders	1 (4)	1 (4)	0
Neurodermatitis	1 (4)	1 (4)	0

N = total # of subjects, n = # with disorder

Individual Subject Narratives for Deaths, Other SAEs, Premature Discontinuations, Grade 3 or 4 AEs of Special Interest, and Herpes Cases:

SAEs:

- **228-0006:** 3 year old girl started treatment with DRV/r 20/3 mg/kg twice daily on (b) (6) with 2 NRTIs (stavudine and abacavir). Subsequently revised to 25/3 mg/kg bid 12

weeks later. She was also receiving primary prophylaxis for *Pneumocystis jiroveci* pneumonia with sulfamethoxazole/trimethoprim. Fifty-six days after treatment start, physical examination showed a flexion deformity of the right interphalangeal joint, reported as finger deformity, a grade 1 AE. 105 days after treatment start, trigger finger was reported as a grade 4 SAE. The subject was unable to fully extend the thumb, especially the interphalangeal joint, and was hospitalized for a right trigger thumb. Patient underwent surgery for release of congenital trigger thumb. Patient recovered and events considered to be not related to the study medication by the investigator. At Week 16, patient had HIV RNA < 50 copies/mL.

- **228-0014:** 5-year-old boy with stage 2 HIV infection and baseline CD4+ cell count of 487 cells x 106/L,.started treatment with DRV/r 20/3 mg/kg twice daily in (b) (6) with 2 NRTIs (zidovudine and abacavir). Dose was changed in 4/10 to 375 mg DRV/50 mg ritonavir twice daily/. The patient had cough, abdominal pain, and occasional fever prior to study start that were resolving. He was receiving prophylaxis for opportunistic infections with sulfamethoxazole/trimethoprim. The patient began treatment with cloxacillin 3 times daily on (b) (6) for pustular skin lesions (grade 1 AE, onset (b) (6), resolved (b) (6) Fifty-nine days after treatment start, early pneumonia was reported as a grade 3 SAE. The subject had a cough and runny nose. Fine days later he presented with fever, headaches, tachycardia and abdominal pain.. He was hospitalized for pneumonia and treated with IV benzylpenicillin potassium and paracetamol. Patient recovered from the pneumonia 5 days later). The SAE was considered to be not related to the study medication by the investigator. At Week 16, the HIV RNA was < 50 copies/mL.

- **228-0019:** 4-year-old girl started treatment with DRV/r 20/3 mg/kg twice daily (1/10) and with 2 NRTIs (lamivudine and zidovudine). Following dose revision in (b) (6) the DRV dose was changed to 25 mg/kg twice daily. The concurrent conditions included asthma and rhinitis. She was receiving no concomitant medications at study entry. Sixty-six days after treatment start, asthmatic crisis was reported as a grade 2 AE. The asthmatic crisis resolved 10 days later with appropriate treatment. One hundred ten days after start an asthmatic crisis was reported as a grade 3 SAE. She was admitted and treated for this event and recovered 11 days later. Another asthmatic event occurred (Grade 2) at126 days after treatment start with resolution 9 days later. Another event of asthmatic crisis (grade 2 AE) occurred 163 days after treatment start with no reported date of resolution or outcome of the asthmatic crisis. All events of asthmatic crisis were considered to be not related to the study medication by the investigator. The HIV RNA at week 24 was 168 copies/mL.

AEs leading to Discontinuation:

- **228-0030:** 5-year-old girl started treatment with DRV/r 20/3 mg/kg twice daily with 2 NRTIs (lamivudine and zidovudine). No change was made to this initial dose. She was receiving no concomitant medication at study entry. On the first day of study treatment, vomiting was reported as a grade 2 AE. Vomiting continued throughout the 14 days of treatment. No treatment was reported and no change made to study medication at that

time. Thirteen days later, study medication was discontinued and the event resolved the same day. The investigator considered the event of vomiting to be not related to DRV, but very likely related to ritonavir.

AEs of Special Interest:
Note this category includes rash-related, cardiac, GI, pancreatic, liver related, lipid-related, glucose-related, and hematologic AEs

- **228-0018**: 5-year-old boy started treatment with DRV/r 20/3 mg/kg twice daily with 2 NRTIs (lamivudine and abacavir). The starting dose should have been DRV/r 480 mg/76 mg daily but the patient erroneously received a daily dose of DRV/r 840 mg/80 mg for 14 days. Following a revision of the dose recommendation, the DRV dose was changed to 25 mg/kg twice daily 12 weeks later. At screening, neutrophil count was within range at 32.8%, bicarbonate was 19.0 mmol/L (grade 1), chloride was 103 mmol/L (within normal limits), potassium was 3.68 mmol/L (grade 0), and glucose was 4.2 mmol/L (grade 0). He was receiving no other concomitant medications at study entry. On the first day of study treatment (prior to dosing), the patient's WBC was 5.1 with 17.2% neutrophils. neutropenia (17.2%, below) was reported as a grade 3 AE in the CSR, however in the datasets it was reported as a Grade 0 AE.. The neutropenia resolved over the ensuing 2 weeks (WBC 9.1, 39.3% neutrophils) and was probably attributable to previous zidovudine treatment. The neutrophil count remained within normal range thereafter. Also at study start the patient had tachycardia (grade 1 AE, 128 beats per minute, sitting) on physical examination, which resolved 55 days later. In addition AEs of grade 3 acidosis and grade 2 alkalosis were reported. No arterial blood gas tests were performed. No corrective treatment was reported. The events resolved within 3 – 4 weeks. The patient's HIV RNA was less than 50 copies/mL at the study conclusion. These AEs were considered not treatment related as they pre-existed at study start.

- **228-0025:** 4-year-old boy started treatment with DRV/r 20/3 mg/kg twice daily with 2 NRTIs (lamivudine and zidovudine). Following a revision of the dose recommendation, the DRV dose was changed to 25 mg/kg twice daily 12 week later. At study entry, he was taking oral cefalexin and gentamicin for impetigo (grade 1 AE) with onset 5 days before the first dose of study medication. One hundred nine days after treatment start, herpes viral infection (varicella) was reported as a grade 2 AE. No treatment was reported and no change made to study medication. On 4 May 2010, the subject had polymorphic lesions all over his body, consistent with chickenpox, cough, runny nose, subcrepitant rales and generalized small lymphadenopathy probably related to the skin lesions. The herpes viral infection resolved 11 days later and was considered to be not related to the study medication by the investigator. At week 16 the patient's HIV RNA was <50 copies/mL.

- **228-0041:** 4-year-old girl started treatment with DRV/r 20/3 mg/kg twice daily with 2 NRTIs (lamivudine and zidovudine). Following a revision of the dose recommendation, the DRV dose was changed to 25 mg/kg twice daily. Two hundred days after treatment

start, oral herpes viral infection was reported as a grade 1 AE. No treatment was reported and no change was made to study medication. The oral herpes viral infection was resolved 6 days later. The investigator considered the event to be not related to the study medication. At Week 24 the HIV RNA was <50 copies/mL.

Adverse Events and Relatedness:

Eight AEs considered at least possibly related to DRV were reported in 5 patients (18.5%). Three events were reported under the category of SOC Investigations (3 patients, 11.1%) and included blood cholesterol increased, prolonged QT and AST increased in one patient each. Two patients reported related episodes of diarrhea (3 reports) from the SOC of GI Disorders. One event of rash was reported from the SOC of Infections and Infestations (varicella rash) and one event of rash was reported from the SOC of Skin and Subcutaneous disorders.

Table 15
Adverse Events Considered Related to Treatment
(Investigator Assessment)

System Organ class Dictionary derived term n (%)	DRV/r		
	Overall N = 27	Before Dose Adjustment N = 27	After Dose Adjustment N = 26
Mean exposure (weeks)	30.5	12.8	18.4
Any AE at least possibly related to DRV	5 (19)	3(11)	2 (8)
Gastrointestinal Disorders	2 (8)	2 (8)	0
Diarrhea	2 (8)	2 (8)	0
Infections and Infestations	1 (4)	1 (4)	0
Rash Pustular	1 (4)	1 (4)	0
Investigations	3 (11)	1 (4)	2(8)
AST Increased	1 (4)	1 (4)	0
Blood cholesterol Increased	1 (4)	0	1 (4)
ECG QT Prolonged	1 (4)	0	1 (4)
Skin and Subcutaneous Tissue Disorders	1 (4)	0	1 (4)
Rash Papular	1 (4)	0	1 (4)

N = total # of subjects with data, n = # of observations

AEs at least possibly related occurred in three subjects before the dose switch, and in two subjects after the dose switch. Blood cholesterol increased and rash papular (both in 1 patient) occurred 17 and 15 days, respectively, after the dose switch. ECG QT prolonged (with normal QTcF) in another subject occurred 85 days after the dose switch in another patient. In addition, 2 cases of vomiting (including the subject who discontinued treatment) were considered related to ritonavir but not to DRV.

Of the related events, two reported from one patient each were Grade 2 or greater severity (AST increased (before dose adjustment) and blood cholesterol increased (after dose adjustment). All events resolved without intervention.

Medical Officer's Comment: *After review of the reported related adverse events the Medical Officer agreed with the Investigators' determinations of relatedness for all events except for the varicella rash (pustular) and the episode of QTc prolongation. The former was clearly not related to treatment and in the latter case of prolongation, further review revealed that there was no actual prolongation documented.*

Submission Specific Primary Safety Concerns

GI, Pancreatic, 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, hepatomegaly, LFT, ALT, AST, alk. phosphatase, GGT, and bilirubin.

Overall, GI AEs were reported in 11 patients (40.7%) during the treatment period (16 events). Diarrhea occurred in eight patients (29.6%, 11 events), and vomiting occurred in 3 patients (11.1%, 5 events). One case of vomiting was rated as grade 2 in severity and led to treatment discontinuation; all other GI AEs were grade 1 in severity. Diarrhea was considered at least possibly related to DRV in two patients; all other GI AEs were considered not or doubtfully related to DRV. In addition, two cases of vomiting (including the subject who discontinued treatment) were considered related to rtv (but not to DRV).

No GI AEs were reported as an SAE and all GI AEs occurred before the dose adjustment. A possible explanation for this is that most gastrointestinal adverse events were most likely related to ritonavir and the symptoms resolved as the patients became more tolerant thus leading to a decrease in adverse event reporting.

There were no pancreatic AEs reported in trial 228.

Three patients (11%) had 1 liver-related AE during the treatment period (AST increased, blood ALP increased, hepatosplenomegaly). AST increased and hepatosplenomegaly were grade 2 in severity and no severity grading was coded for blood ALP increased (Subject 228-0010, Kenyan local laboratory data: found to be a grade 2 abnormality). AST increased was considered possibly related to DRV, while the other liver-related AEs were considered not related.
No liver-related AEs were reported as an SAE, or led to permanent treatment discontinuation.
All liver-related AEs occurred in patients without hepatitis B or C co-infection.

Rash

Within the MedDRA System Organ Classes for Skin and Soft Tissue terminologies such as rash, papular, macular, maculo-papular, urticaria, drug rash, hypersensitivity, pruritic rash and pruritis were selected. Overall the number of patients with rash was 3 (11%). These patients reported

four events including erythema (1 patient), rash (1 patients), and rash papular and rash pruritic (both in the same patient). However if rash events considered unlikely to be related to drug are excluded, the proportion of patients with rash drops to 1 (4%). All rash-related AEs were grade 1 in severity, and 1 rash-related AE was considered at least possibly related to DRV (rash papular, possibly related).

No rash-related AEs were reported as an SAE, or led to permanent treatment discontinuation.

One additional rash (pustular) was reported under Infections and Infestations. This patient developed varicella during the trial. The PI determined that this rash was possibly related to treatment. However, after review of this case it was determined that the rash was indeed a varicella rash and unlikely related to treatment.

Lipid related adverse events

Only one patient had a lipid-related AE (blood cholesterol increased). This AE was grade 2 in severity and considered probably related to DRV. The AE was not reported as SAE, and did not lead to treatment discontinuation. The increase occurred after dose adjustment and resolved without treatment or actions.

Hematologic Adverse Events

Three patients had an (one each) hematologic AE during the treatment period (anemia in 1, neutropenia in 2). One case of neutropenia (228-0018) was graded as Grade 3 in severity; however, this AE was present on Day 1 and resolved after 17 days while DRV/rtv was continued. This patient had previously been on zidovudine, nevirapine, and lamivudine until the study start at which time he was switched to abacavir. It is likely that both his anemia and his neutropenia were attributable to zidovudine. The other hematologic AEs were grade 1. None of the hematologic AEs were considered drug related.

No hematologic AEs were reported as an SAE, or led to permanent treatment discontinuation.

Glucose Related Adverse Events

One patient developed the AE of hyperglycemia, grade 2 in severity and considered not related to DRV. The AE was not reported as SAE, and did not lead to treatment discontinuation.

7.4 Supportive Safety Results

Common Adverse Events

NOTE: All of the Applicant's analyses and tables were independently confirmed by the medical reviewer using the adverse event dataset and jmp software.

Twenty-three of 27 patients (85%) reported an AE during the treatment period.

AEs were most frequently reported from the SOCs of Infections and Infestations (20 patients. 74%), Gastrointestinal Disorders (12 patients, 44%), Investigations, and Metabolism and Nutrition Disorders (both in 6 subjects, 22%).

By preferred term, the most frequent (> 3 patients, > 11.1%) AEs were upper respiratory tract infection (9 subjects, 33%), diarrhea (8 subjects, 30%), hypokalemia (5 subjects, 19%), alkalosis, cough and nasopharyngitis (all in 4 subjects, 15%).

The incidence of AEs before and after the dose adjustment was similar (19 patients, 70% before vs.17 patients, 65%).

Table 16
Common Adverse Events Reported in Greater than One Patient During Treatment Period

System Organ class Dictionary derived term n (%)	DRV/r		
	Overall N = 27	**Before Dose Adjustment N = 27**	**After Dose Adjustment N = 26**
Mean exposure (weeks)	30.5	12.8	18.4
Any AE	23 (85)	19 (70)	17 (65)
Blood and Lymphatic System Disorders	3 (11)	3 (11)	0
Neutropenia	2 (7)	2 (7)	0
Cardiac Disorders	2 (7)	2 (7)	0
Tachycardia	2 (7)	2 (7)	0
Eye Disorders	2 (7)	0	0
Gastrointestinal Disorders	12 (44)	11 (41)	1 (4)
Diarrhea	8 (30)	8 (30)	0
Vomiting	3 (11)	3 (11)	0
Infections and Infestations	20 (74)	12 (44)	12 (46)
Impetigo	2 (7)	2 (7)	0
Nasopharyngitis	4 (15)	0	4 (15)
Otitis Media Acute	2 (7)	1 (4)	1 (4)
Otitis Media Chronic	2 (7)	1 (4)	1 (4)
Pharyngitis	2 (7)	1 (4)	1 (4)
Pneumonia	2 (7)	1 (4)	1 (4)
Rhinitis	3 (11)	3 (11)	0
Tinea Capitis	2 (7)	1 (4)	1 (4)
URI	9 (33)	7 (26)	2 (8)
Investigations	6 (22)	3 (11)	4 (15)
Metabolism and Nutritional Disorders	6 (22)	6 (22)	0
Acidosis	3 (11)	3 (11)	0
Alkalosis	4 (15)	4 (15)	0
Hypokalemia	5 (19)	5 (19)	0
Hyponatremia	2 (7)	2 (7)	0
Respiratory, Thoracic and Mediastinal Disorders	5 (19)	5 (19)	2 (8)
Cough	4 (15)	4 (15)	0
Nasal congestion	2 (7)	1 (4)	1 (4)
Rhinorrhea	2 (7)	1 (4)	1 (4)
Skin and Subcutaneous Tissue Disorders	5 (19)	3 (11)	3 (12)

N = total # of subjects with data, n = # of observations

In study C112, 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%).

Laboratory Findings

Chemistry

There were no abnormalities for the selected liver-related laboratory parameters of interest. There were no patients meeting Hy's Law criteria (i.e., ALT or AST > 3 x ULN, in combination with total bilirubin elevation > 2 x ULN, or INR > 1.5). One Kenyan patient with local laboratory data developed a grade 2 increased AST (reported as an AE).

One patient developed an increased amylase (5%) and 2 an increased creatinine (9.5%). All aforementioned increases were Grade 1 and all resolved.

All lipid-and glucose-related laboratory abnormalities were grade 1 or 2 in severity. Grade 2 abnormalities for total cholesterol were observed in 5 patients (24%), and for LDL in 7 (33%). Grade 2 hyperglycemia was observed in 1 patients (4%).

There were no laboratory abnormalities for triglycerides and HDL.

Hematology

All, except 1 hematology laboratory abnormality, were grade 1 in severity. Grade 3 decreased neutrophils was observed in 1 patient (4%) at Week 24; this patient had grade 1 decreased neutrophils at screening, and marked fluctuations during treatment.

There were no laboratory abnormalities for total WBC and platelet count.

Vital Signs

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

Electrocardiograms (ECGs)

None of the observed mean changes in ECG parameters including QTc were statistically significant, and none were considered clinically relevant.

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

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 was focused on rash and liver enzyme tests (ALT, AST). No apparent relationship was shown between exposure and rash or liver enzymes.

Drug-Demographic Interactions

This sNDA evaluated use of darunavir in the 3 - < 6 years pediatric population. Clearance (per body weight) of darunavir appears to decrease toward adult values as age increases. The overall safety profile was similar between this youngest age group and the previously evaluated 6 – 18 years group and adult patients.

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 count and percentage have improved across all age groups after initiation of treatment with darunavir co-administered with ritonavir in combination with other ART.

Drug-Drug Interactions

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

7.6 Additional Safety Explorations

Human Carcinogenicity

Please refer to the original NDA reviews.

Human Reproduction and Pregnancy Data

Darunavir was previously categorized as Class B for use in pregnancy. Recently completed animal (rat) studies were significant for number of in utero deaths. The pregnancy labeling category has thus been changed to Class C. Please refer to the traditional NDA approval and Pharmacology/toxicology review for further details.

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 Week 24, within-group comparison for the changes from baseline showed an increase versus baseline for height (2.6 cm) and weight (0.8 kg). There was no mean change in BMI.

Clinical Study Report

Table 65: Mean Changes From Baseline at Week 24 for Growth and Development Parameters (Age-Adjusted Z-Scores)

Growth and Development Parameter	DRV/rtv				
	N	Baseline (SE)	N	Mean Change (SE)	p-Value[a]
Height (cm)	27	101.2 (1.43)	26	2.6 (0.30)	< 0.001
Age-adjusted z-score	27	-1.4 (0.20)	26	-0.01 (0.068)	0.8823
Weight (kg)	27	15.3 (0.40)	26	0.8 (0.10)	< 0.001
Age-adjusted z-score	27	-1.1 (0.18)	26	0.01 (0.056)	0.6852
BMI (kg/m^2)	27	14.9 (0.29)	26	0.0 (0.11)	0.9508
Age-adjusted z-score	27	-0.4 (0.24)	26	0.02 (0.094)	0.9312

N = number of subjects
a Exploratory p-value based on 2-sided Wilcoxon signed rank-test for comparison versus baseline
Source: Display SAF.37

Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions

As noted in section 4, in addition to trial C228 in pediatric patients, the Applicant also submitted the result of trial TMC114-C169, a Phase I, open-label, randomized, crossover trial in adult healthy subjects to compare the oral bioavailability of the suspension formulation of DRV (F051) to that of the registered tablet formulation (F016), in the presence of low-dose ritonavir, under fasted and fed conditions. This trial also assessed multiple dose pharmacokinetics of DRV formulated as this oral suspension, in the presence of low-dose ritonavir. The trial was divided into 2 parts that were conducted sequentially. Results from Part 1 were evaluated before the start of Part 2 of the trial. The dose and volume of suspension of DRV and food recommendations for DRV/rtv intake for Part 2 were based on the results of Part 1 of the trial.
In Part 1, 20 subjects were randomized to receive in 3 different sessions separated by a 7 day washout period:

- Treatment A: 100 mg rtv b.i.d. from Day 1 to 5 and a single dose of 600 mg DRV (F016, tablet) on Day 3 (fed);
- Treatment B: 100 mg rtv b.i.d. from Day 1 to 5 and a single dose of 600 mg DRV (F051, suspension) on Day 3 (fasted);
- Treatment C: 100 mg rtv b.i.d. from Day 1 to 5 and a single dose of 600 mg DRV (F051, suspension) on Day 3 (fed).

In addition to the 15 subjects who remained in the trial after having completed Part 1 of the trial, 3 additional subjects were enrolled to receive Treatment D in Part 2 of the trial, i.e.,

- Treatment D: 100 mg rtv b.i.d. from Day 1 to 9, and 600 mg DRV (F051) b.i.d. from Day 1 to 6 and an additional morning dose on Day 7 (fed).

Safety data were available for 23 subjects. Safety and tolerability were evaluated continuously throughout the trial.

No deaths or other serious adverse events (SAEs) occurred in this trial.

Four (17.4%) subjects discontinued study medication due an AE, 1 due to nausea and 3 due to rash.

Twenty (87%) subjects reported at least one AE during this trial.

There were no significant differences in incidences of AEs between treatment groups with a single dose of DRV except for dysgeusia, which was reported for 4 (23.5%) subjects following DRV intake in Treatment B (DRV suspension, fasted) compared to none of the subjects in Treatment A (DRV tablet, fed, i.e., reference) and Treatment C (DRV suspension, fed). Other AEs were reported in at most 3 subjects. The most frequent AEs reported following administration of multiple doses of DRV in Treatment D (DRV suspension, fed) were headache (4 subjects, 22.2%), diarrhea (3 subjects, 16.7%), and rash (3 subjects, 16.7%). All AEs were grade 1 or 2 in severity.

AEs considered related to DRV by the investigator were reported for 16 (69.6%) subjects. These were most frequently reported for dysgeusia and for headache, diarrhea, and rash following

Three (13%) subjects had a skin event of interest (rash). All three events started on the last day of ritonavir administration of Treatment D. None of the events was considered serious. Each was considered probably related to DRV and ritonavir by the investigator and led to permanent discontinuation (see above).

All laboratory abnormalities were grade 1 or 2 in severity. The most frequent abnormalities following DRV/rtv administration were increased low-density lipoprotein, increased total cholesterol, and high-density lipoprotein below normal. No laboratory abnormalities or abnormalities related to urinalysis were reported as an AE during this trial.

No clinically relevant changes in vital signs or ECG parameters were observed.

In conclusion, the results of this trial demonstrated that administration of the DRV suspension formulation in combination with low-dose rtv was relatively well tolerated with an adverse event profile consistent with that previously reported in both adult and pediatric subjects.

8 Postmarketing Experience

Darunavir has been approved for use in the pediatric patient population aged 6 years and above. The Applicant will continue to provide periodic safety updates in addition to providing full 48 week study report for Study TMC114-C228.

9 Appendices

9.1 Literature Review/References

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

2. NDA (Accelerated)
   NDA 21-976
   SN 000
   SC N
   Reviewer: Nevel , 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 patients, 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 patients, 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).

9.2 Labeling Recommendations

Primary labeling revisions were made to the Dosing and Administration section of the label *dated August 16, 2011* to reflect new dosing recommendations for pediatric patients ages 3 – 6 years. These changes can be found in section 6.1.9 and are also reproduced below:

(b) (4)

9.3 Advisory Committee Meeting

Not Applicable

MO by Patient Listing created in jmp

Patient ID	Baseline Weight	Week 24 Weight	Virologic Outcome
228-1	14.9	15.6	VIROLOGIC SUCCESS
228-3	16.5	17.5	VIROLOGIC FAILURE
228-5	13.9	14.5	MISSING DATA DURING WINDOW
228-6	13.3	14.0	VIROLOGIC FAILURE
228-7	19.4	20.3	VIROLOGIC SUCCESS
228-9	13.4	15.4	VIROLOGIC SUCCESS
228-10	16.8	16.8	VIROLOGIC SUCCESS
228-12	11.9	12.5	VIROLOGIC FAILURE
228-14	15.7	16.3	VIROLOGIC SUCCESS
228-15	16.7	17.5	VIROLOGIC SUCCESS
228-17	13.4	15.0	VIROLOGIC SUCCESS
228-18	12.3	12.4	VIROLOGIC FAILURE
228-19	14.9	15.9	VIROLOGIC FAILURE
228-20	17.5	18.1	VIROLOGIC SUCCESS
228-21	14.3	14.9	VIROLOGIC FAILURE
228-22	18.5	19.0	VIROLOGIC SUCCESS
228-25	16.3	16.8	VIROLOGIC FAILURE
228-26	16.0	17.5	VIROLOGIC FAILURE
228-27	16.8	17.4	VIROLOGIC SUCCESS
228-29	14.3	14.0	VIROLOGIC SUCCESS
228-30	19.8	19.8	DC AE
228-33	13.0	13.7	VIROLOGIC FAILURE
228-34	15.5	16.3	VIROLOGIC SUCCESS
228-38	13.3	14.9	VIROLOGIC SUCCESS
228-40	13.1	14.3	VIROLOGIC SUCCESS
228-41	14.7	16.5	VIROLOGIC SUCCESS
228-42	16.0	16.7	VIROLOGIC SUCCESS

REVISED SNAPSHOT EXCLUDING 3 Kenya (1 VF, 2 VS)

VS 58.3%, VF 33.3% or if all non success = failure 41.6%
DISCONTINUED DUE TO AE/DEATH - BEFORE WEEK 24 1
MISSING DATA DURING WINDOW - LAST VL AFTER WEEK 24 1
VIROLOGIC FAILURE - AT WEEK 24 8
VIROLOGIC SUCCESS - AT WEEK 24 14

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/s/

M R ALIVISATOS
01/04/2012

YODIT BELEW
01/04/2012

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/s/

M R ALIVISATOS
08/25/2011

YODIT BELEW
09/06/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-895 **Applicant: Tibotec** **Stamp Date: March 29, 2011**

Drug Name: Darunavir (Prezista) **NDA/BLA Type: Pediatric**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: TMC114-C228 Study Title: A Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low-dose ritonavir (DRV/rtv) in treatment-experienced HIV-1 infected children from 3 to < 6 years of age. Week-24 Primary analysis. Sample Size: N = 27 Arms: single arm Location in submission: Section 5	x			Ph 2 OL study of 27 pediatric patients performed to establish dosing. BE of or solution to marketed tablets previously in trial 169, efficacy and safety previou shown in adults and pediatric patients a 18
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			x	See above

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			The primary objective as previously agreed Agency include: To evaluate the pharmacok DRV/ rtv in children aged from 3 to < 6 yea weighing between 10 and < 20 kg. - To support dose recommendation of DRV used in this population by comparing the DRV exposure achieved in these treatm experienced HIV-1 infected children to that in HIV-1 infected adults and older chil weighing > 20 kg Primary endpoint is viral load at week 2 consistent with Agency policies
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	Previously submitted and reviewed as p original NDA application
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	Dosing currently extended to younger a (i.e. 3-6 years of age). Efficacy previou established. Safety being collected as p PWR in accordance with PREA
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Regina Alivisatos, MD — April 26, 2011

Reviewing Medical Officer — Date

Yodit Belew, MD — April 29, 2011

Clinical Team Leader — Date

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

/s/

M R ALIVISATOS
04/29/2011

YODIT BELEW
05/09/2011