CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-976

MEDICAL REVIEW

Deputy Office Director Memo

Applicant: Tibotec, Inc.

NDA #: 21-976

Drug: darunavir, tablets, 300 mg

Other names used during development: TMC114

Trade Name: PREZISTA™

Indication: PREZISTA, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

Dose: darunavir/ritonavir 600/100 mg twice daily

Date of Submission: December 23, 2005

Action Date: June 23, 2006

Recommended Regulatory Action:

Approval for NDA 21-976

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of PREZISTA (darunavir), co-administered with 100 mg of ritonavir for the treatment of HIV infection in antiretroviral experienced adult patients. For a detailed discussion of NDA 21-976, the reader is referred to the individual discipline specific reviews. In addition Dr. Marcus's Team Leader's Memo and Dr. Murray's Deputy Division Director's Memo review key issues in the NDA submission.

The chemistry for PREZISTA is discussed in Dr. Kambhampati CMC review and is found to be acceptable. The recommendation regarding CMC is for approval.

The recommendation from Dr. Farrelly and Dr. Verma with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. The approval of PREZISTA will

include a phase 4 commitment to complete the ongoing carcinogenicity studies in mice and rats.

The clinical pharmacology of PREZISTA is discussed in Dr. Arya's review. Darunavir is primarily metabolized by oxidative metabolism, and based upon findings from in vitro studies this is primarily by CYP3A. Darunavir is co-administered with 100 mg of ritonavir as a metabolic inhibitor. When darunavir is administered with ritonavir, darunavir was found to be 82% bioavailable. The product label provides a table with a listing of drug interactions based upon results of clinical studies or expected drug-drug interactions and information on dose and schedule for the listed medications, as appropriate. A list of contraindicated medications is also included in the PREZISTA label. As part of the phase 4 commitments, the Applicant will conduct drug interaction studies evaluating darunavir/rtv b.i.d with each of the following medications: rifabutin, buprenorphine/naloxone, and carbamazepine.

The microbiologic assessment of darunavir is discussed in Dr. Naeger's microbiologist's review. Darunavir is an HIV-1 protease inhibitor that inhibits the cleavage of the HIV encoded Gag-Pol polyproteins in infected cells. The mutations associated with decreased susceptibility of HIV to darunavir have been characterized and are summarized in the product label.

The results of the clinical trials evaluating the safety and efficacy of darunavir are discussed in detail in Dr. Gibbs's Medical Officer's Review, Dr. Hammerstrom's Statistical Review, and also in the reviews prepared by Dr. Marcus and Dr. Murray. The reader is referred to their reviews for a detailed discussion of safety and efficacy. In dose-finding studies 202 and 213, HIV positive patients who were at least 3-class experienced were randomized to either one of four doses of darunavir/rtv plus optimized background regimen or control which was ritonavir-boosted protease inhibitor(s) plus optimized background regimen. The mean viral load at the time of enrollment in the studies was approximately 4.5 $\log_{10}$ viral load copies/mL, the mean CD4+ cell count was approximately 300 cells/μL, and the mean number of years of duration of HIV infection was approximately 11 to 13 years. The primary endpoint in these studies is the proportion of subjects with a greater than one log drop in viral load at Week 24. In both studies, all darunavir treatment arms exhibited a statistically significant greater proportion of subjects achieving the primary endpoint compared with the control arm with a trend towards greater response in the patients receiving higher doses of darunavir up to the highest dose studied of 600 mg po BID. Additional analyses that evaluated response using the more stringent endpoints of proportion of subjects with viral load below 400 copies/mL and proportion of subjects with viral load below the limit of quantification of 50 copies/mL also corroborated these findings (please see Dr. Hammerstrom's review for the tabulation of these results). Evaluation of changes in CD4+ cell count demonstrated higher increases in patients receiving darunavir with a mean increase of 92 cell/μL compared to 17 cells/μL in control subjects. These data provide clear evidence of the effectiveness of darunavir in reducing HIV viral load and increasing CD4+ cell counts.

A total of 810 patients received the proposed dose of darunavir/rtv 600/100 mg for any length of time. Of these patients, 458 initiated therapy at the proposed dose and received it for a mean of 35.2 weeks. Darunavir was studied in a heavily treatment-experienced patient population on multiple concomitant medications and with limited treatment options; hence patients with limited treatment may have chosen to remain on darunavir therapy even if they experienced adverse events.

Darunavir appears to be associated with skin rash. The molecule contains a sulfa moiety and this may, in some cases, play a role in the observed rash events. In the clinical development program rash (regardless of causality and of any grade) was reported in 7% of subjects with treatment discontinuations in 0.3% of subjects. Most rashes were self-limited maculopapular skin eruptions of mild to moderate severity. However, there were also infrequent reports of more severe skin reactions including cases of erythema multiforme and Stevens-Johnson Syndrome. Some cases of rash have been accompanied by fever and elevations in transaminases. The PREZISTA label provides a WARNING about skin rash and also includes a section warning about sulfa allergy given that darunavir contains a sulfonamide moiety.

The most common adverse events reported with darunavir/rtv included gastrointestinal adverse events. Darunavir/rtv also exhibits adverse events similar to other protease inhibitors including effects on serum lipids. In dose-finding studies, treatment emergent moderate elevations in amylase and lipase were reported approximately twice as frequently in patients receiving darunavir/rtv as compared to control subjects. There were also three cases of pancreatitis reported in the clinical development program, one of which was fatal. However, these patients were all receiving didanosine in combination with tenofovir, with didanosine being a drug associated with development of pancreatitis.

Elevations in liver enzymes appeared similar in patients receiving darunavir and comparator with about one third experiencing any grade elevation in liver enzymes. Across the phase 2 studies there were eight patients receiving darunavir who experienced serious adverse events of liver dysfunction or liver enzyme elevations. Dr. John Senior was consulted for evaluation of the potential hepatic effects of darunavir. As noted in Dr. Marcus's review, Dr. Senior concluded that "no clear evidence of darunavir-induced liver toxicity is apparent in the data accrued so far. A couple of cases suggested possible contribution by darunavir to liver injury in patients with pre-existing liver problems, but definite attribution of causality is difficult in these patients with prolonged complex illnesses and exposure to many drugs. There is no indication at this time for special labeling of darunavir as causing clear cut liver injury."

The occurrence of death in the darunavir clinical trials was carefully evaluated by the clinical and statistical reviewers. In the original application it was noted that the deaths in the phase 2 studies were all in the pooled darunavir arms. (Randomization in studies 202 and 213 was 4:1 darunavir to control as there were four darunavir doses being studied.) In study 202 there were 11 deaths across the four darunavir arms (range of number of deaths per darunavir arm 2-4) and 0 deaths in the control arm. In the second study there were 6 deaths across the four darunavir arms (range of number of deaths per

darunavir arm 0-3) and 0 deaths in control arm. There was no apparent trend in dose response for mortality across the range of doses studied. The issue of deaths in the studies was evaluated extensively by the review team. There was no clear pattern to the cause of deaths; they appear to be causes that occur in patients with advanced HIV/AIDS. There are several other factors that may be contributing to the observed differences in the number of deaths that were observed in Studies 20 and 213 as follows. Patients were randomized four to one to darunavir versus control arm in accordance with the study design. Patients were more likely to remain on darunavir longer; in his review Dr. Hammerstrom performs an analysis which adjusts for person years of exposure and the difference in death rates for each of the arms is not statistically significantly different from the control arm. The number of patient years in the control arms are lower because the study design allows patients who are not achieving satisfactory viral suppression to receive alternative therapy rather than remaining on a failing regimen – a proviso necessary for safety reasons. Many of these patients who were on control and failed to respond were allowed to roll over into another study in which they could receive darunavir. Another potential contributing factor is that four times as many patients randomized to control (20/144) as compared to any darunavir arm (17/530) dropped out of the study prior to receiving study drug, perhaps reflecting that in this open-label study patients randomized to control elected to drop out in order to enroll in other clinical trials. The observed mortality rates in the darunavir study arms are similar to the mortality rates (per 100 patient years) observed in the clinical trials for tipranavir and enfuvirtide, two recently approved agents targeting a similarly advanced population of HIV positive patients. What is out of the range of past experiences is the absence of deaths in the control arms in studies 202 and 213.

To further evaluate the occurrence of deaths additional follow-up data was requested on patients enrolled in the studies up to the current time, including information on patients who were randomized but did not receive study drug and for subjects who discontinued for virologic failure but did not roll over to treatment with darunavir. These data were analyzed in an intent-to-treat analysis and also in an "as-treated" analysis for all patients. In the As-Treated Analysis, for all patients, the mortality rates were 4.0% (6/149) for control and 3.8% (38/992) for darunavir. For additional analyses, including the sensitivity analyses, the reader is referred to Dr. Hammerstom's Review.

Based upon all of the evaluations it appears that there are factors other than drug effect that are likely contributing to the apparent differences in observed mortality rates reported in the original NDA for studies 202 and 213.

The reader is also referred to Dr. Murray's Review that summarizes some of the recent discussions at the Antiviral Drugs Advisory Committee meeting. As Dr. Murray notes, we are not seeing mortality differences in contemporary trials of antiretroviral agents at 24-weeks in patients with advanced HIV/AIDS, likely because of efforts to have adequate safeguards in place and to ethically design clinical trials.

As additional data become available from the ongoing studies of darunavir, it will be important to continue to carefully review the findings with regards to mortality.

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name PREZISTA. Comments from DMETS and DDMAC have also been incorporated into the product labeling. The DSI inspections have been performed and did not identify any significant observations that would compromise the integrity of the data. Pediatric studies required under PREA have been deferred as noted in the approval letter.

Postmarketing Study Commitments

- Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. The following are the postmarketing study commitments related to approval under Subpart H.

1. By December 31, 2007, please submit final study reports and datasets for the 96-week data on the ongoing Phase 2b dose-finding studies TMC114-C202, TMC114-C213, TMC 114-C208 and TMC114-C215.

2. By December 31, 2007, please submit final the study reports for the 48 week data on the ongoing Phase 3 studies TMC114-C211 and TMC114-C214.

- Deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA)

3. 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:	by June 2008

4. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages less than 6 years. Please 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 old children in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

Protocol Submission:	by December 2008
Final Report Submission:	by June 2011

- Other postmarketing study commitments

Drug-Drug Interaction Trials

5. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and rifabutin.

6. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and buprenorphine/naloxone.

7. Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and carbamazepine.

Pharmacology/Toxicology

8. Complete ongoing carcinogenicity study in mice and submit final report.

9. Complete ongoing carcinogenicity study in rats and submit final report.

Pharmacokinetics

10. Please conduct a cocktail study to determine the effects of steady state Darunavir/rtv 600/100 mg b.i.d. on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.

Special Populations

11. Evaluate the pharmacokinetics of Darunavir/rtv in subjects with varying degrees of hepatic impairment in order to determine dosing recommendations.

12. Conduct a study of darunavir in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

Although not post marketing study commitments we have also requested the following information to be submitted:

Drug-Drug Interaction Trials

1. The following represent clinical drug-drug interaction studies that have been planned by Tibotec, Inc. to be conducted with darunavir. The Division acknowledges the following planned studies:

- TMC114-C127: drug-drug interaction study between Darunavir/rtv b.i.d. and methadone.
- [redacted]

Clinical

2. In addition to the required periodic adverse drug experience reports [21 CFR 314.80(c)(2)], please submit a separate periodic adverse drug experience report for rash.

Microbiology

3. Determine response rates based upon presence of specific cleavage site mutations at baseline and submit this analysis with the PREZISTA traditional approval application.

4. Determine the protease cleavage site mutations that occur most frequently (>10%) in virologic failure isolates and submit this analysis with the PREZISTA traditional approval application.

5. Determine if the most frequently occurring protease cleavage site mutations contributed to decreases in darunavir susceptibility through site-directed mutagenesis and submit this analysis with the PREZISTA traditional approval application.

Summary

I concur with the assessment of the review team that PREZISTA (darunavir) tablets, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor, under the subpart H accelerated approval regulations for serious or life-threatening illnesses (21CFR §314.510). The clinical studies show a clear effect on viral load and CD4 cell count and the safety profile based upon the available data is acceptable. The product labeling adequately describes the available information on PREZISTA. Approval under Subpart H is appropriate for PREZISTA given that it may provide meaningful treatment benefit over existing antiretroviral treatment options based upon its activity against clinical isolates resistant to multiple protease inhibitors in the treatment of patients with HIV/AIDS. As part of approval under Subpart H, the applicant will study the drug further to verify and describe its clinical benefit as described in the postmarketing study commitments under Subpart H listed above.

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/s/

Edward Cox
6/23/2006 03:45:31 PM
MEDICAL OFFICER

Team Leader's Memorandum

NDA:	21-976
Drug and Indication:	darunavir, co-administered with 100 mg ritonavir (darunavir/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor
Proposed Dose:	darunavir/ritonavir 600/100 mg twice daily
Dosage Form:	300 mg film-coated tablet
Letter Date:	December 22, 2005
Stamp Date:	December 23, 2005
Date of Memorandum:	June 23, 2006

Background

Darunavir (DRV, tradename Prezista) is a novel HIV protease inhibitor under development by the applicant (Tibotec, Inc.) for the treatment of HIV infection. This New Drug Application (NDA) was submitted in accordance with regulations and guidance for submission of drugs for accelerated approval; demonstration of efficacy of this drug is based on surrogate endpoint analyses of plasma HIV RNA and CD4+ cell counts in antiretroviral heavily treatment-experienced HIV-infected subjects after 24 weeks of treatment.

The clinical development package submitted to support the efficacy of DRV consists primarily of data from 4 controlled and 2 uncontrolled clinical trials. Two of these studies were 4-week randomized, controlled open-label proof-of-concept studies that were conducted in treatment-experienced HIV-infected subjects currently failing their antiretroviral regimen. One study evaluated DRV administered alone, and the other study evaluated DRV co-administered with a low dose (100 mg) of another protease inhibitor, ritonavir (rtv). In this combination, DRV is the active antiretroviral and rtv serves as a pharmacologic enhancer by inhibiting the metabolism of DRV via the CYP3A system, thereby increasing DRV concentrations. Based on the efficacy results of these proof-of-concept studies, the applicant chose to further develop DRV in combination with low dose rtv.

Two randomized, controlled, partially-blinded dose-finding Phase 2b trials of 3-class experienced HIV-infected subjects were then initiated to evaluate four different dosing regimens of DRV/rtv as compared to a control regimen containing one or two rtv-boosted protease inhibitors (PIs). All regimens were co-administered with an optimized

background of nucleoside reverse transcriptase inhibitors (NRTIs) with or without enfuvirtide (ENF). Statistically significantly higher rates of HIV viral load reduction were observed with all dosing regimens of DRV/rtv versus the control arm. Although not statistically significant, efficacy increased numerically with increasing dose. As a result, DRV/rtv 600/100 mg twice daily was chosen as the proposed dose.

Based on the robust efficacy demonstrated in these dose-finding studies, it was determined that further controlled clinical studies in highly treatment-experienced patients would not be required nor would they be ethical; however, additional safety data was required at the proposed dose. As a result, the applicant enrolled additional patients in an ongoing open-label rollover safety study. An additional 327 "*de novo*" patients were enrolled and started DRV/rtv 600/100 mg twice daily, resulting in a safety database of 458 patients who initiated DRV/rtv at the proposed dose.

Dose Selection

Two proof-of-concept dose-finding studies, studies TMC114-C201 (C201) and TMC114-C207 (C207), were first conducted in treatment-experienced patients failing their current antiretroviral (ARV) regimen. Patients substituted their current protease inhibitor (PI) with unboosted DRV in C201 and DRV/rtv in C207 for 14 days. Each study contained a control arm in which subjects continued their current regimen. Demographics, including baseline antiretroviral (ARV) resistance, viral load, CD4+ cell count, sex, age and CDC class, were generally similar between the two studies. About half of patients in each study had no susceptible PIs at baseline. In study C201, doses ranging from DRV 400 mg twice daily to 800 mg three times daily resulted in reductions of viral loads from 0.28 to 0.79 log10 copies/mL, respectively. In study C207, a dose of DRV/rtv 600/100 twice daily produced the largest observed reduction in viral load on either study of 1.38 log10 copies/mL.

To further explore optimal dose selection, the applicant then initiated two large Phase 2b dose-finding studies of highly treatment-experienced patients with limited to no treatment options, TMC114-C202 (C202) and TMC114-C213 (C213). Each study was a randomized, active-controlled partially-blinded (to DRV dose only) study comparing the following 4 DRV/rtv treatment groups to a control group: DRV/rtv 400/100 mg once daily, 800/100 mg once daily, 400/100 mg twice daily, and 600/100 mg twice daily. A dynamic central randomization was applied using biased coin techniques, so that all allocations were done randomly. Three stratification factors were applied for randomization: screening plasma viral load, use of ENF in the OBR and the number of primary PI mutations.

Subjects randomized to DRV/rtv treatment groups substituted their PI(s) with DRV/rtv and continued their same background NRTIs and ENF for 2 weeks (functional monotherapy phase). After the 2-week period, subjects continued their randomized DRV/rtv dose and changed the screening background regimen to an optimized background regimen (OBR) consisting of NRTIs with or without ENF. Subjects randomized to the control group changed their therapy at baseline to an investigator-

selected PI(s) regimen plus an OBR (NRTIs with or without ENF); these regimens were selected by the investigator prior to randomization.

The proposed dose of DRV/rtv 600/100 mg twice daily was selected and confirmed by a Week 16 analysis of the first 150 patients enrolled into each study, and a second analysis when 200 patients in each study had reached Week 16. The dose-finding portion of each study ended when the primary Week 24 analysis was performed. Immediately prior to the cut-off date of the primary analysis (February 1, 2005), the proposed dose was communicated to investigators and all subjects randomized to DRV/rtv were instructed to switch to 600/100 mg twice daily.

Because of their prior ARV experience, not all subjects had a PI to which their virus was susceptible. Therefore, subjects were considered early failures if they did not achieve a 0.5 log decrease in HIV RNA by Week 12. Early failures were allowed to roll over to an open-label DRV study. Of note, a similar early failure definition was used in both the "TORO" studies that formed the basis of approval of the ENF NDA and the "RESIST" studies that formed the basis of approval of the tipranavir (TPV) NDA. These studies also enrolled advanced populations for whom the open-label control for some subjects was expected in advance to be potentially ineffective.

Inclusion Criteria and Patient Demographics for Studies C202 and C213

C202 and C213 were conducted in different countries, although the two studies were otherwise identical in design. C202 enrolled patients at investigative sites in the United States and Argentina. C213 enrolled patients at sites in Austria, Belgium, France, Germany, Hungary, Italy, Portugal, Spain, Switzerland, United Kingdom, Canada, Brazil and Australia.

Eligible HIV-1 infected subjects were at least 3-class experienced, were on a stable PI-containing regimen at screening for at least 8 weeks, and had a plasma HIV-1 RNA > 1000 copies/mL. Three-class experience was defined as prior treatment with 2 or more NRTIs for at least 3 months in total and 1 or more NNRTIs as part of a failing regimen. In addition, all subjects had received at least 1 PI for at least 3 months in the past and had at least 1 primary PI mutation at screening (according to the IAS-USA list of March 2003). Prior use of ENF was allowed.

Demographics of patients enrolled in each study are summarized in the two following tables obtained from the Summary of Clinical Efficacy. Of note, just 70/596 (12%) enrolled subjects were female. Similar percentages of female patients were enrolled in the TORO and RESIST studies. In addition, just 44/596 (7.4%) patients were co-infected with hepatitis B or C. Low enrollment was likely due to the fact that co-infected patients were excluded from participation in C202 due to concerns about hepatotoxicity early in the development program.

Table 17: Demographic Data in TMC114-C202 and TMC114-C213

Parameter	TMC114-C202	TMC114-C213
Gender, n (%)		
N	278	318
Female	25 (9.0)	45 (14.2)
Male	253 (91.0)	273 (85.8)
Age (years)		
N	278	318
Mean (SD)	45.4 (7.31)	43.6 (8.72)
Ethnic origin, n (%)		
N	277	318
Black	53 (19.1)	34 (10.7)
Caucasian/white	176 (63.5)	256 (80.5)
Hispanic	38 (13.7)	12 (3.8)
Oriental/Asian	3 (1.1)	3 (0.9)
Other	7 (2.5)	13 (4.1)

N = number of subjects with data; n = subjects in class

Source: Summary of Clinical Efficacy, p. 52, NDA 21976

Table 18: Baseline Disease Characteristics in TMC114-C202 and TMC114-C213

Parameter	TMC114-C202	TMC114-C213
Log_{10} viral load (copies/mL)		
N	278	318
Mean (SD)	4.66 (0.76)	4.48 (0.78)
CD4+ cell count (10^6/L)		
N	278	315
Median (Range)	106 (1 - 1274)	179 (3 - 816)
Duration of HIV-1 infection (years)		
N	274	318
Mean (SD)	13.2 (3.94)	11.6 (4.20)
CDC class at time of diagnosis, n (%)		
N	274	315
A	94 (34.3)	102 (32.4)
B	68 (24.8)	73 (23.2)
C	112 (40.9)	140 (44.4)
Time since first ART initiation (months)		
N	278	318
Mean (SD)	114.3 (43.90)	112.0 (35.11)

N = number of subjects with data; n = subjects in class

Source: Summary of Clinical Efficacy, p. 53 NDA 21976

Comparator PIs and OBR

Determination of the number subjects with susceptible drugs at baseline was based on phenotypic data obtained from the Antivirogram® assay. Overall, 71% of the subjects in C202 and 63% of subjects in C213 were infected with virus resistant to all available PIs. The proportion of subjects susceptible to at least one NNRTI was 49% in C202 and 46% in C213; however, this is likely related to the fact that 84% of the subjects in C213 were not using an NNRTI in their screening regimen and for C202 the use of an NNRTI during the screening period was disallowed. The use of NNRTIs in the OBR was not allowed in both trials.

The choice of PI regimen in the control group was similar in both trials. Overall, almost all PI regimens (98%) were co-administered with low-dose ritonavir as a pharmacologic enhancer, of which 75% were single boosted and 23% double boosted. No subject used an unboosted PI-containing regimen. The most frequently used PI was lopinavir (38%) followed by saquinavir (35%), amprenavir (33%) and atazanavir (17%). Two subjects used indinavir.

The proportion of subjects susceptible to at least 1 NRTI was 94% for C202 and 97% for C213. More subjects in C213 received at least one NRTI to which they were susceptible (75%) as compared to C202 (65%). For both trials, the most susceptible NRTIs were stavudine (d4T, 84%), didanosine (ddI, 80%), and zalcitabine (ddC, 75%); however, in the OBR, ddI was used by only 37%, d4T by 16%, and ddC by 0.7% of subjects. In contrast, the least susceptible NRTIs were tenofovir (TDF) and lamivudine (3TC), yet they were the most commonly used NRTIs in the OBR; TDF was used by 86% of subjects and 3TC by 59%.

Overall, 47% of subjects used ENF in the OBR. ENF was more frequently included as part of the OBR in C202 than in C213 (55% versus 45%, respectively). A total of 11% of subjects had used ENF before and 36% of subjects used ENF for the first time. The percentage of subjects that used ENF for the first time during the trials was similar for both trials.

The optimization of and compliance with the background regimen for the control subjects is supported by the observation of the applicant that 38 of the 59 subjects (64%) in the control group that discontinued due to virologic failure initially showed a drop in viral load of at least 0.5 $\log_{10}$. In addition, monitoring of the serum levels of PIs demonstrated that the investigator-selected PI could be detected on average in 90% of control subjects.

Efficacy Analyses

The following section highlights the major findings of the statistical review of this NDA by Dr. Thomas Hammerstrom.

The specified primary endpoint of both studies was the proportions of subjects with a greater than 1 log drop in viral load at Week 24. In addition to analyses of this primary endpoint, analyses were performed on the more stringent endpoints of proportions of

subjects with viral load below 400 copies/mL, and proportions of subjects with viral load below the limit of quantification of 50 copies/mL. Change in CD4+ cell count was also evaluated.

In summary, all four doses of DRV/rtv were statistically significantly superior to the control arm. These findings remained significant after performance of multiple sensitivity analyses. The following tables summarize results of analyses of the primary endpoint, proportion of subjects with greater than 1 log drop in viral load at Week 24. In addition, analysis of the most stringent endpoint of reduction in viral load, the proportion of subjects with viral load <50 copies/mL, is also reported.

This FDA review defines response rates by the "Time to Loss of Virologic Response (TLOVR)". The TLOVR analysis is an intent-to-treat analysis that examines endpoints using the following definitions of treatment failure for patients who have achieved HIV RNA levels below the limit of quantification:

For all subjects with confirmed HIV RNA levels below an assay limit, the time to failure is the earliest time when a specific event had occurred. These events are

- Death
- Permanent discontinuation of the study drug or loss to follow-up
- Introduction of a new antiretroviral drug (unless a background drug is changed for reasons of toxicity or intolerance that are clearly attributable to that drug)
- Confirmed HIV RNA levels above or equal to an assay limit

PERCENTAGE OF SUBJECTS WITH ≥1 LOG DROP AT WK 24, TRIAL C202

Treatment Arm	Mean Diff	95% Limits Lower	Upper	Rates of Suppression DRV/r	Control	P-value
400 QD	34.6%	19.8%	49.4%	31/65=48%	8/61=13%	<.0001
800 QD	38.4%	23.6%	53.3%	33/64=52%	8/61=13%	<.0001
400 BID	47.2%	32.4%	62.0%	38/63=60%	8/61=13%	<.0001
600 BID	50.5%	36.2%	64.9%	42/66=64%	8/61=13%	<.0001

Source: Statistical review of NDA 21976, by Dr. Thomas Hammerstrom

PERCENTAGE OF SUBJECTS WITH ≥1 LOG DROP AT WK 24, TRIAL C213

Treatment Arm	Mean Diff	95% Limits Lower	Upper	Rates of Suppression DRV/r	Control	P-value
400 QD	41.7%	25.9%	57.5%	45/64=70%	18/63=29%	<.0001
800 QD	42.9%	27.1%	58.6%	45/63=71%	18/63=29%	<.0001
400 BID	42.9%	27.1%	58.6%	45/63=71%	18/63=29%	<.0001
600 BID	46.8%	31.5%	62.1%	49/65=75%	18/63=29%	<.0001

Source: Statistical review of NDA 21976 by Dr. Thomas Hammerstrom

PERCENTAGE OF SUBJECTS WITH <50 COPIES/ML AT WEEK 24

	Mean	95% Limits		Rates of Suppression		
Covariate	Diff	Lower	Upper	DRV/r	Control	P-value
TRIAL C202						
400 QD	18.1%	5.9%	30.2%	16/65=25%	4/61=7%	.0008
800 QD	18.4%	6.1%	30.7%	16/64=25%	4/61=7%	.0092
400 BID	30.0%	16.5%	43.4%	23/63=37%	4/61=7%	<.0001
600 BID	29.8%	16.6%	43.0%	24/66=36%	4/61=7%	<.0001*
TRIAL C213						
400 QD	26.3%	11.2%	41.4%	27/64=42%	10/63=16%	.0008
800 QD	33.3%	18.0%	48.6%	31/63=49%	10/63=16%	<.0001
400 BID	38.1%	22.8%	53.4%	34/63=54%	10/63=16%	<.0001
600 BID	41.1%	26.0%	56.1%	37/65=57%	10/63=16%	<.0001*

*indicated dose

Source: Statistical review of NDA 21976, Dr. Thomas Hammerstrom

As noted in the analysis above, viral load reduction increased with increasing dose and appeared to be highest with the DRV/rtv 600/100 mg twice daily dose. Importantly, doses greater than 600/100 mg twice daily were not explored because of less than dose proportional increase in exposure (AUC) with increasing dose; population pharmacokinetic analysis showed that a 50% increase in dose, from 400/100 twice daily to 600/100 mg twice daily, resulted in only a 29% increase in exposure. Based on PK/PD evaluation of data generated in the pivotal Phase IIb trials, the applicant determined that a 10-fold increase in exposure of DRV would be required to produce a clinically meaningful increase (> 0.5 log) in viral load reduction above that observed with the 600/100 twice daily dose.

The DRV package insert reports response rates for C202 and C213 for the 600/100 twice daily and control arms only. Because the two studies were identical, FDA allowed the applicant to combine the results of C202 and C213 in the package insert. Data from the three other DRV treatment arms were not presented because FDA does not allow inclusion of data from unapproved doses in the package insert. The following table reflects the efficacy data reported in the package insert. This data was confirmed by both this reviewer and Dr. Hammerstrom.

Efficacy Outcomes – Studies C202 and C213 Combined

Outcomes through Week 24 Studies C202 & C213 Combined	DRV/RTV 600/100 bid + OBR	Control PI + OBR
Treated	N=131	N=124
Responder - ≥1 log reduction	69.5%	21.0%
Responder - <50 copies/mL	45.0%	12.1%
Virologic failure	26.0%	71.0%
Lack of initial response[a]	9.9%	57.3%
Never suppressed[b]	6.9%	4.0%
Rebounded	9.2%	9.7%
Discontinued due to adverse event or death	3.9%	1.6%
Discontinued due to other reasons	0.8%	6.5%

[a]Patients without 0.5 log10 drop from baseline at Week 12
[b]Patients who never reached a confirmed 1 log10 drop in viral load before Week 24

The following analysis evaluates outcomes by number of susceptible drugs used by each subject (TSITOTAL) as determined by use of the Antivirogram® at screening. In this analysis subjects are classified as resistant to darunavir if the fold-change in susceptibility (FC) was greater then 10 relative to wild-type HIV isolates. In this analysis 81/123 patients were considered susceptible to darunavir and received 1 point in the TSITOTAL variable for darunavir use.

≥1 Log Drop at Week 24 ITT - Trials C202 and C213 Combined
DRV/RTV 600/100 mg Twice Daily

	Mean	95%_Limits		DRV/r	Control
TSITOTAL	Diff	Lower	Upper		
0	22.2%	-4.9%	49.4%	2/9=22%	0/18=0%
1	52.9%	35.8%	70.0%	22/38=58%	2/40=5%
2	47.0%	25.9%	68.1%	28/38=74%	8/30=27%
3	48.9%	25.6%	72.3%	29/34=85%	8/22=36%
4	15.7%	-22.7%	54.2%	6/7=86%	7/10=70%
5				2/2=100%	0/0
6				0/0	0/1=0%

Source: Dr. Thomas Hammerstrom

<50 Copies/mL At WK 24 ITT – Trials C202 and C213 Combined
DRV/RTV 600/100 mg Twice Daily

	Mean	95%_Limits		DRV/r	Control
TSITOTAL	Diff	Lower	Upper		
0	0.0%	0.0%	0.0%	0/9=0%	0/18=0%
1	36.8%	21.5%	52.2%	14/38=37%	0/40=0%
2	46.5%	26.2%	66.8%	24/38=63%	5/30=17%
3	36.4%	14.3%	58.5%	17/34=50%	3/22=14%
4	-7.1%	-55.1%	40.9%	3/7=43%	5/10=50%
5				2/2=100%	0/0
6				0/0	0/1=0%

Source: Dr. Thomas Hammerstrom

An analysis of outcome by use of ENF was also performed by Dr. Hammerstrom. In this analysis, use of ENF does not appear to add additional viral load reduction above what is achieved with use of DRV/rtv; however, an unexpected finding in this analysis is that it also does not appear to contribute significantly to the viral load reduction of control patients. Of note, naïve versus non-naive use of ENF was balanced between the treatment and control arms.

≥1 Log Drop At Wk 24 ITT – Trials C202 and C213 Combined
DRV/RTV 600/100 mg Twice Daily versus Control

	Mean	95%_Limits		DRV/r	Control
Covariate	Diff	Lower	Upper		
ENF Use					
N	46.0%	31.1%	60.9%	44/67=66%	13/66=20%
Y	51.0%	35.8%	66.3%	47/64=73%	13/58=22%

In contrast, an analysis of response rates by ENF use and baseline phenotype for DRV yielded more informative results and is discussed in the Microbiology section of this memorandum.

CD4+ Cell Count
At Week 24, the mean increase in CD4+ cell count was 92 cells/mm^3 in subjects receiving DRV/rtv 600/100 twice daily as compared to 17 cells/mm^3 in control subjects.

Microbiology/Resistance
The following summary is excerpted from Dr. Lisa Naeger's review of microbiology. Please see her review for additional details.

With data from studies C202 and C213, analyses were conducted to evaluate the impact of the type and number of baseline PI resistance-associated mutations on virologic response. In general, in these analyses, the response rate in all subgroups was higher in the DRV/rtv 600/100 twice daily group as compared to the control group. In addition,

analyses of outcome by the number of susceptible drugs in the OBR, and ENF use were conducted.

The presence at baseline of the mutations V32I, I47V, or I54L/M, was associated with a decreased virologic response and decreased susceptibility to DRV. In addition, a diminished virologic response was observed in patients with ≥7 protease inhibitor resistance-associated mutations (any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline.

Baseline darunavir phenotype (shift in susceptibility relative to reference wild-type HIV-1 isolates) was shown to be a predictive factor of virologic outcome. Analyses of data from studies C202, C213 and from C215 "de-novo" subjects, showed that response rates at Week 24 decreased when the baseline darunavir phenotype was >7-fold. Response rates by clinically relevant changes are displayed in the following table.

Response to PREZISTA/rtv 600/100 mg Twice Daily by Baseline DRV Phenotype: As-treated Analysis of Studies C202, C213 C215

Baseline DRV Phenotype n=340 (fold change ranges)	Proportion of subjects with ≥1 $\log_{10}$ decrease at Week 24	Proportion of subjects with <50 copies/ml at Week 24	Clinical Response Range
All ranges	70% 238/340	43% 147/340	
0-2	88% 119/136	60% 82/136	Higher than Overall Response
>2 - 7	73% 62/85	47% 40/85	Similar to Overall Response
>7 - 30	52% 33/63	24% 15/63	Lower than Overall Response
>30	43% 24/56	18% 10/56	Lower than Overall Response

The number of susceptible drugs in the optimized background regimen and ENF use affected DRV/rtv response rates. In Studies C202 and C213, patients with no susceptible NRTIs at baseline had lower response rates (38% with ≥1 $\log_{10}$ decrease and 13% with <50 copies/mL) than those with at least one susceptible NRTI. In addition, for patients with baseline darunavir phenotypes of >10 in studies C202, C213 and C215, response rates were 81% (13/16) with ≥ 1 log decrease when ENF was used for the first time concomitantly with DRV/rtv while response rates were 36% (27/74) for those who did not use ENF concomitantly.

In cell culture, DRV has a <10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir: viruses resistant to most PIs remain susceptible to DRV. In

studies C202 and C213, 60% (24/40) of patients with decreased susceptibility to tipranavir (fold change >3) at baseline demonstrated a 1 $\log_{10}$ or greater decrease from baseline at Week 24 on DRV/rtv and 45% (18/40) achieved <50 copies/mL serum HIV RNA levels. Results from C215 *de novo* subjects supported this finding.

DRV-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine DRV-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC_{50} values <3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from patients experiencing virologic failure on DRV/rtv 600/100 mg bid, greater than 50% were still susceptible to tipranavir while less than 5% were susceptible to other PIs (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir).

Safety Evaluation – Data Sources

Safety data from the following sources was reviewed:

- 35 completed pharmacokinetic and drug-drug interaction studies in healthy volunteers (748 subjects)
- 2 Phase 2a 14-day proof-of-concept studies in PI-experienced subjects (C201 and C207) (84 subjects)
- 2 ongoing Phase 2b randomized, controlled, 96-week dose-finding studies in heavily treatment-experienced subjects (C202 and C213) (637 subjects)
    - 513 subjects received DRV/rtv at one of four doses
    - 124 subjects received control regimens
- 2 ongoing open-label, non-randomized, long-term trials enrolling both subjects from prior DRV studies and *de novo* heavily treatment-experienced subjects who initiated DRV/rtv at the proposed dose (C208 and C215) (460 subjects)
    - 327 subjects initiated DRV/rtv at the proposed dose
    - 59 subjects rolled over from control groups to receive DRV/rtv
    - 74 subjects rolled over from a DRV arm of any Phase 2 study to receive DRV/rtv
- Serious adverse event (SAE) data from all other ongoing trials

A total of 810 subjects received DRV/rtv at the proposed dose for any length of time. These subjects include:

De novo subjects who initiated therapy at the proposed dose of DRV/rtv 600/100 mg twice daily:

- 131 subjects in dose-finding studies C202 and C213
- 327 subjects in studies C208 and C215

Subjects who switched from a lower DRV dose to the proposed dose of DRV/rtv 600/100 mg twice daily at the Week 24 interim analysis of studies C202 and C213:

- 352 subjects in studies C202, C213 and C215

The mean duration of treatment (MDT) of all *de novo* subjects was 35.2 weeks. The MDT of *de novo* subjects enrolled in dose-finding studies C202 and C213 was 62.3 weeks. The MDT of control subjects enrolled in C202 and C213 was 31.5 weeks; the shorter duration of treatment is attributed to the higher dropout rate of control subjects due to virologic failure. Overall, 11% of *de novo* subjects and 81% of control subjects discontinued from clinical trials. In order to compensate for the higher dropout rate of control subjects and the lower mean duration of treatment, the applicant conducted analyses of safety data both by incidence and by patient years of exposure.

Overall Safety Summary

Darunavir was evaluated in a heavily treatment-experienced population of HIV-infected patients who had many concomitant medical illnesses and heavy concomitant medication use. In addition, optimized background therapy (OBR) was individualized for each subject, resulting in wide variability in background ARV use. Furthermore, subjects with few or no remaining treatment options may have elected to continue darunavir despite adverse events. For these reasons, assessment of tolerability of darunavir and attributability of adverse events (AEs) is somewhat difficult.

Despite these confounding variables, darunavir appeared to be well-tolerated. In the controlled dose-finding studies C202 and C213, no relationship of the incidence of any adverse events with increasing dose was apparent, with the exception of grade 4 increases in triglycerides. The most commonly reported treatment-emergent adverse events, aside from injection site reactions related to ENF use, were diarrhea, headache, nausea and fatigue. In the non-randomized clinical trials, diarrhea and nausea were the most common treatment-emergent AEs. In multi-dose healthy volunteer studies, headache, nausea, and diarrhea were also the most commonly reported.

Discontinuations due to AEs were infrequent in all of the trials. AEs were listed as the reason for discontinuation in 7% of DRV-treated subjects as compared to 5% of control subjects in dose-finding trials C202 and C213 combined, and in 3% of subjects in studies C208 and C215 combined. Notable AEs leading to discontinuation included rash (3 subjects), diarrhea (3 subjects), elevated hepatic transaminases and/or GGT (7 subjects), elevated amylase and lipase (4 subjects), and pancreatitis (1 subject).

Rash-Related Events

A causal association between DRV use and serious rash leading to discontinuation of DRV appears compelling. DRV has a sulfonamide moiety, which is well known to be associated with drug allergy and rash. In healthy volunteer studies, rash appeared to be dose related (when DRV was administered alone in dose escalation studies) and occurred more frequently in women. The incidence of rash was lower when DRV was co-administered with rtv. Median time to onset was about 9 days. Of note, in a preliminary report of an oral contraceptive (OC) drug-drug interaction study, rash was reported in 4/16 patients after initiation of DRV/rtv and 5 subjects discontinued the study for rash or hypersensitivity reaction. In all other healthy volunteer studies, 3 subjects receiving DRV (7%) and 1 subject receiving DRV/rtv (<1%) discontinued for grade 3 or greater rash. One subject who developed rash required hospitalization.

In dose-finding studies C202 and C213, the incidence of rash was similar between DRV-treated subjects and control subjects, about 8%. In these two studies, the incidence of rash appeared to be similar between subjects reporting a sulfonamide allergy as compared to those who did not. In *de novo* subjects, rash was reported more frequently in subjects reporting a sulfonamide allergy as compared to those who did not (9% versus 5%).

Importantly, three subjects in the clinical development program discontinued for development of rash and one subject enrolled in a treatment-naïve study was reported to have Stevens-Johnson syndrome. Fever and transaminase elevations were reported in association with the rash in some cases. One subject developed erythema multiforme four months after initiating DRV/rtv; study drugs were discontinued and the patient was treated with prednisone. One subject developed a severe rash and discontinued medication about two weeks after initiating DRV/rtv. This subject also required treatment with prednisone. A third subject was diagnosed with a drug-induced rash that resulted in discontinuation of study drug 11 days after initiating DRV/rtv; skin biopsy was reported as consistent with drug-induced rash/erythema multiforme. And recently, a Medwatch report was received of biopsy confirmed Stevens-Johnson syndrome that was diagnosed four days after initiation of DRV/rtv in a subject enrolled in a treatment-naïve trial. DRV/rtv was discontinued and the patient was placed in an intensive care unit for monitoring. Concomitant medication use in this patient included dapsone and amoxicillin/clavulanate.

Information about rash and sulfa allergy were placed in the warning section of the package insert.

Hepatotoxicity and Liver Enzyme Elevations

In controlled clinical trials C202 and C213, any grade of liver enzyme elevation was observed in about one-third of darunavir-treated subjects and in similar numbers of control subjects. No relationship to dose of DRV/rtv was observed for liver enzyme elevations. Elevations in bilirubin were more common in control subjects, likely due to atazanavir use. Grade 3-4 elevations of liver enzymes were infrequent.

Across all phase 2 studies, eight DRV-treated subjects had liver dysfunction or enzyme elevations reported as SAEs. One subject with a history of hepatic steatosis died secondary to port-a-cath sepsis, atypical mycobacterial infection and hepatic failure. One subject died with liver enzyme elevations, pneumonia and end-stage AIDS. One subject with chronic hepatitis B/C had a scheduled liver biopsy consistent with chronic hepatitis. One subject had liver enzyme elevations that resolved with a change to lipid-free TPN. One subject had temporary interruption of study medication for elevated enzymes related to viral meningitis/orchitis/hepatitis. The remaining three subjects reported as SAEs, who all underwent liver biopsy, are discussed below.

Six subjects in the clinical development program discontinued treatment due to transaminase elevations and/or GGT elevations. Four subjects without evidence of liver dysfunction had no further evaluation. The other two subjects, reported as SAEs,

underwent liver biopsies. One biopsy showed evidence of alcoholic or non-alcoholic steatohepatitis. The other biopsy, in a subject with a clinical picture suggestive of cirrhosis and mild elevations of transaminases eight months after initiating study medication, showed multifocal bile duct degeneration/loss and parenchymal Kuppfer cell aggregates, suggestive of prior hepatocellular necrosis.

One subject participating in a proof-of-concept study developed evidence of drug-induced hepatotoxicity two weeks after completing a 14-day course of DRV/rtv. The subject, also known to consume alcohol, developed grade 4 elevations of transaminases and bilirubin 14 days after receiving DRV/rtv 600/100 mg twice daily for 14 days. A liver biopsy showed "a histologic image compatible with an acute hepatitis of medicamentous origin".

Dr. John Senior, a hepatologist at FDA, was consulted for evaluation of the above-mentioned potential cases of drug-induced liver injury, as well as other liver enzyme data and subject narratives. Please see Dr. Senior's consult for his full review. In summary, Dr. Senior concluded that no clear evidence of darunavir-induced liver toxicity is apparent in the data accrued so far. A couple of cases suggested possible contribution by darunavir to liver injury in patients with pre-existing liver problems, but definite attribution of causality is difficult in these patients with prolonged complex illnesses and exposure to many drugs. There is no indication at this time for special labeling of darunavir as causing clear cut liver injury.

Elevations of Amylase and Lipase and Pancreatitis

Use of protease inhibitors is known to be associated with hypertriglyceridemia (HTG), and is thought to increase risk for complications associated with HTG, in particular cardiovascular disease and pancreatitis. An association of PIs with asymptomatic elevations in amylase and lipase and pancreatitis independent of HTG has not been described. NRTIs as a class are known to be associated with asymptomatic increases in amylase and lipase as well as the development of pancreatitis, particularly stavudine (d4T) and didanosine (ddI).

In controlled studies C202 and C213, treatment emergent Grade 2-4 elevations of amylase and lipase occurred about twice as frequently in subjects receiving DRV/rtv 600/100 twice daily as compared to control subjects. The incidence of Grade 2-4 elevations was also higher in other DRV treatment arms. Elevations of amylase and lipase occurred less frequently in uncontrolled study C215, however, the incidence was still slightly higher as compared to control subjects from C202 and C213.

Three cases of pancreatitis were reported in clinical trials, including one fatal case. This occurred in a patient with a baseline CD4+ cell count of 6 cells/mm3. The patient was initially admitted to hospital for *E. coli* sepsis and subsequently developed pancreatitis on study Day #55. Study medications, including DRV/rtv/ddI/TDF were discontinued, however, the patient died. Two other cases of pancreatitis resulted in temporary discontinuation of medications. One patient was receiving ddI/TDF as part of OBR and the other patient received ddI/TDF/3TC.

Four subjects permanently discontinued study for asymptomatic grade 3-4 elevations of amylase and/or lipase. The subjects were receiving the following NRTIs as part of the OBR: ddI/TDF/3TC/ZDV; ddI/TDF; TDF/ZDV; and 3TC/TDF. A fifth patient temporarily discontinued ARV including DRV/rtv/ddI/TDF for amylase and lipase elevations and restarted DRV/rtv/3TC/ZDV after resolution. Two subjects who experienced grade 4 elevations, but had no action taken on study drug were receiving ddI/TDF and 3TC/TDF.

In summary, while asymptomatic Grade 2-4 elevations of amylase and lipase appeared to occur somewhat more frequently in subjects receiving DRV/rtv 600/100 mg twice daily and also occurred in healthy volunteer studies, clinical events or laboratory abnormalities leading to study drug interruption or discontinuation appeared to be associated with other risk factors, most noticeably, use of ddI. At this time, a causal association with use of DRV/rtv is not evident, but will be further evaluated when results from the ongoing treatment-naive and treatment-experienced studies are available.

Lipid and Glucose Abnormalities

In dose-finding studies C202 and C213, the mean change from baseline of total cholesterol (TC) and LDL decreased in subjects receiving DRV/rtv 400/100 mg once daily, while increases were observed in subjects receiving DRV/rtv 600/100 mg twice daily. The mean change from baseline of TC and LDL was also observed to increase in *de novo* subjects enrolled into study C215. Decreases were observed in controls. HDL increased in all treatment groups.

In contrast, DRV/rtv-treated subjects in studies C202 and C213 showed reductions in triglycerides, particularly in those subjects who had been receiving lopinavir (LPV)/rtv at the time of enrollment. These changes were consistent whether subjects were receiving lipid-lowering drugs at baseline or not. Despite overall mean decreases in triglycerides, some patients showed increases in triglycerides in these studies. The incidence of grade 4 triglyceride elevations was slightly higher in the DRV/rtv twice daily dose groups as compared to the once daily treatment arms, and was highest in the 600/100 mg twice daily group (5%).

Although similar proportions of patients in all treatment groups of the dose-finding studies were reported as using lipid lowering agents (about 1/4), FDA review of data on use of lipid-lowering agents indicated that about 20% of DRV subjects initiated lipid lowering drugs while on study, with more subjects on DRV/rtv 600/100 mg (21%) initiating treatment as compared to the other DRV-treatment arms (10-15%) and controls (8%). No subjects discontinued studies for lipid elevations.

Any emerging grade of hyperglycemia observed during the treatment in dose-finding studies C202 and C213 combined was reported in 21% of subjects receiving any dose of DRV versus 17% of controls. Diabetes was reported as an AE in four DRV-treated subjects and one control. Worsening of diabetes was reported in five subjects receiving DRV.

Deaths

A total of 25 out of 924 patients treated with DRV/rtv at any dose died on or by the data cutoff for original NDA submission. The overall mortality for any patient treated with DRV at the time of NDA submission was 3.0 per 100 patient-years of follow-up. A total of 11 deaths occurred in the 458 patients who initiated treatment with DRV/rtv at the proposed dose of 600/100 mg twice daily, reflecting a mortality rate of 3.6 per 100 patient-years of follow-up. In the two controlled studies, C202 and C213, 17 of 513 subjects treated with DRV/rtv at any dose died up to the date of data cutoff, reflecting a mortality rate of 3.9 per 100 patient-years of follow-up.

The reported causes of death were generally similar to those observed in advanced populations of patients. Most of the adverse events leading to death were related to infectious illnesses (15 of 25 subjects) and included 4 cases of new AIDS-defining illnesses. Four deaths were due to neoplasms, specifically anal cancer, lymphoma, acute myeloid leukemia, and adenocarcinoma of the lung. Please refer to the review of Dr. Neville Gibbs for a complete listing of the causes of death.

Deaths in Controlled Studies

In the two controlled trials C202 and C213, 17 of 513 DRV/rtv-treated subjects died on study up to the time of data lock for NDA submission. In contrast, only 1 of 124 control subjects died; however, this death occurred after the designated follow-up period for discontinuations and was not included in the initial analysis of deaths. One subject receiving DRV/rtv on study C213 who had rolled over to C215 also died; this subject was also not included in the initial analyses. No relationship with dose and mortality was observed.

Analysis of the demographic information of subjects who died on study revealed a more advanced sub-group of patients relative to all subjects enrolled. Select demographic data of the subjects who died as compared to all subjects is displayed in the following table.

Select Patient Demographics of Subjects Who Died During C202 and C213

	Deaths N=17	DRV-Trt'd Subjects N=496	Control Subjects N=124
Mean age	49.3 yrs	44.3 yrs	44.3 yrs
Mean baseline VL	4.97	4.56	4.48
Mean last VL	3.48	2.99	4.08
Mean baseline CD4+	105	174	217
Median baseline CD4+	72	137	162
Proportion baseline CD4+ <50	48%	26%	24%
Mean last CD4+	139	274	240

An analysis of the mortality rate per 100 patient years for the first 24 weeks of the study was also performed and compared to the mortality rates observed in studies enrolling similar patient populations of highly treatment-experienced patients. These studies were the "TORO" studies which evaluated enfuvirtide (ENF) and the "RESIST" studies which evaluated tipranavir (TPV). The results of these analyses are reported in the following table.

Comparison of Mortality per 100 Patient-Years of Follow-up in Clinical Trials

ENF Mortality at Wk 24 analysis of TORO trials		*TPV/RTV Mortality at Wk 24 analysis of RESIST trials*		*DRV/RTV Mortality at Wk 24 analysis of C202 and C213*	
ENF+/- OBR	*OBR*	*TPV/RTV+/- OBR*	*CPI/RTV +/- OBR*	*TMC/RTV+/- OBR*	*CPI/ RTV+/- OBR*
10/663 (1.5%)	*5/334 (1.5%)*	*12/582 (2.0%)*	*7/577 (1.2%)*	*6/513 (1.2%)*	*0/124 (0 %)*
Mortality rate = 3.3	*Mortality rate = 3.3*	*Mortality rate = 4.5*	*Mortality rate = 2.6*	*Mortality rate = 2.6*	*Mortality rate = 0.0*

Source: Data on ENF and TPV trials reprinted from Dr. Andrea James review of NDA 21-814

Dr. Hammerstrom analyzed the deaths by person-years of exposure for each of the five arms separately and for all four DRV arms pooled. The following table provides the deaths, person-years of exposure, and death rates per person-year of exposure for each of the five arms in each trial and for all four DRV arms pooled. It also includes the difference in rates between DRV arm and control, together with 95% confidence limits on the difference in the death rates and the p-value for the difference between DRV and control arms.

DEATHS, EXPOSURE, DEATH RATES
TRIALS C202 AND C213

				Difference in Rates			
		Per-yrs	Death	DRV-	95% Limits		
Arm	Deaths	Exp	Rate	Control	Lower	Upper	P-value
Trial 202							
Control	0	33.0	0.000				
600 bid	3	49.8	0.060	0.060	-0.042	0.163	.14
400 bid	2	46.9	0.043	0.043	-0.044	0.129	.22
800 qd	2	48.7	0.041	0.041	-0.044	0.126	.23
400 qd	4	46.5	0.065	0.064	-0.041	0.170	.08
Any DRV	11	192.0	0.057	0.052	-0.043	0.147	.15
Trial C213							
Control	0	45.8	0.000				
600 bid	2	63.8	0.031	0.031	-0.034	0.097	.23
400 bid	3	57.3	0.052	0.052	-0.032	0.137	.12
800 qd	0	59.5	0.000				
400 qd	1	60.2	0.017	0.017	-0.031	0.064	.38
Any DRV	6	240.8	0.025	0.025	-0.033	0.083	.29

Source: Statistical review of NDA 21976 by Dr. Thomas Hammerstrom

When compared to the TORO and RESIST studies, mortality rates of darunavir-treated patients clearly fall within the range of rates observed in studies enrolling similarly advanced patients. What is notable in trials C202 and C213 is the absence of deaths of control subjects, not an excess of deaths of darunavir-treated subjects.

As noted above, comparison of subjects who died with those who did not in C202 and C213 revealed that these patients had relatively more advanced disease, as reflected by lower baseline and last on-study CD4+ cell counts and higher viral loads. CD4+ cell count is a known risk factor inversely correlated with all-cause mortality in HIV-infected individuals. Another variable likely contributing to the imbalance is time spent on study by DRV-treated subjects as compared to controls. Mean time on study was six-fold higher for DRV-treated subjects as compared to control due to both unequal randomization (4:1 DRV:control) and due to more early dropouts of control subjects for virologic failure. As observed in Dr. Hammerstrom's analysis, after adjusting for exposure on the different treatment arms, the difference in death rates is not statistically significant.

Because of persistent concerns regarding the difference in mortality rates on control versus DRV treatment arms, additional follow-up on enrolled subjects up to the present time was obtained. In addition to subjects currently enrolled in C202, C213 and rollover studies, all available follow-up was obtained for subjects who were randomized to any treatment arm, but did not receive study medication and for subjects who discontinued for virologic failure but did not rollover to another DRV trial. In total, 5.5% (29/530) of subjects randomized to DRV-treatment arms and 4.9% (17/144) of subjects randomized

to control arms died. These numbers include 2/17 subjects randomized to DRV arms who did not receive study medication and 3/20 subjects randomized to control arms who did not receive study medication. The following analyses are excerpted from Dr. Hammerstrom's review: these analyses also include all deaths occurring in open-label non-randomized trial C215.

The following table shows the death rates for the three major DRV trials completed so far (randomized controlled trials C202 and C213 and single arm trail C215) together with the requested long range follow-up. The table provides the death rates on control and DRV, together with the point estimate and 95% confidence limits for control rate minus DRV rate. In this analysis, because all subjects were followed up, as thoroughly as possible, until June 2006, differences in person years of exposure were approximately proportional to number of subjects and thus rates are computed per person rather than per person-year. If subjects tended to leave control arms earlier in order to enter DRV rollover trials, the person-years would be relatively smaller for control and the rate per person-year would be relatively higher for control, relative to DRV. Thus, the analyses below are slightly biased against DRV.

DEATH RATES IN TRIALS C202, C213, AND C215 COMBINED INCLUDING LONG-TERM FOLLOW-UP

	Mean Diff	95% Limits Lower	Upper	Control	DRV/r
Intent-to-Treat Analyses					
All	0.8%	-2.9%	4.5%	7/144=4.9%	37/912=4.1%
Status					
Trted	-0.6%	-3.9%	2.8%	4/124=3.2%	34/895=3.8%
No Drug	-2.6%	-26.6%	21.3%	3/20=15.0%	3/17=17.6%
As-Treated Analyses					
All	0.2%	-3.2%	3.6%	6/149=4.0%	38/992=3.8%
Status					
Trted	-2.1%	-4.6%	0.5%	2/124=1.6%	36/980=3.7%
No Drug	-0.7%	-26.2%	24.9%	4/25=16.0%	2/12=16.7%

There are four analyses in the table, two of them being ITT analyses and two being as-treated analyses. One of each pair groups all subjects together, the other stratifies by whether the subjects took their initially assigned drug or did not take their assigned drug, either leaving Tibotec studies entirely or rolling over into another Tibotec trial. As expected, a decision not to take the assigned drug appears to be associated with an initial poor prognosis (15-17.6% death rate versus 3.2-3.8%).

The difference between the ITT analyses and the as-treated analyses is as follows. The ITT analyses count subjects randomized to control arms in trials C202 and C213 as control, even if they subsequently enroll in the DRV arm of trial C215. The as-treated analyses reclassify subjects from their initially assigned arm as follows. A subject who is

randomized to DRV and starts drug is a DRV subject. A subject who is randomized to DRV but never starts drug and never rolls over into another Tibotec trial becomes a control subject. A subject who is randomized to control but never starts drug and rolls over into trial C215 or another Tibotec trial becomes a DRV subject. A subject who is randomized to control and starts drug is a control subject. Finally, if that subject subsequently discontinues control and rolls over into trial C215 or another Tibotec trial, that subject counts as a two subjects, one on control from randomization to rollover and the other on DRV from rollover to last observation.

The FDA statistical reviewer considers the as-treated analyses as more appropriate for safety endpoints than the ITT analyses. If DRV actually increase death rate, then counting deaths on DRV in a rollover trial as deaths on control would be misleading. None of the analyses showed a statistically significantly higher death rate for DRV.

The FDA reviewer also conducted a sensitivity analysis with respect to the requested long-term follow-up. In this analysis, subjects who were lost to follow-up as of July 1, 2005, are counted as deaths if they were on DRV, as alive if they were on control. Even under this unfavorable assumption about DRV, one gets an as-treated analysis with all subjects showing death rates of 5.4% for DRV and 4.0% for control with the DRV rate being between 4.9% higher and 2.0% lower based on the 95% confidence limits.

SENSITIVITY ANALYSES ON MISSING DATA IN FOLLOW-UP

	Mean Diff	95%_Limits Lower	Upper	Control	DRV/r
ITT	-1.6%	-5.5%	2.3%	7/144=4.9%	59/912=6.5%
As trt	-1.4%	-4.9%	2.0%	6/149=4.0%	54/992=5.4%

Dr. Hammerstrom also compared DRV to control with respect to rates of serious adverse events, events requiring or prolonging hospitalization, and events producing persistent disability. None of these endpoints showed any particular discrepancy in rates.

The excess deaths in the DRV arms likely reflect in part the preference for the most ill patients at baseline to discontinue if they are randomized to a control arm. The Division considers the open-label design that likely introduces this type of bias as appropriate for this most seriously ill population of HIV-infected patients so that they can make informed decisions about their healthcare. The excess deaths observed in the DRV arms also likely reflect the longer follow-up on DRV arms and rollover studies in the initial submission.

Never-the-less, deaths in other clinical trials of DRV/rtv will be monitored closely for any potential imbalances in treatment arms. Currently or recently enrolled studies of interest include study C211, a study of treatment-naïve patients, study C214, a study of treatment-experienced patients, and two studies comparing DRV/rtv alone to DRV/rtv with TMC125, an investigational NNRTI, in heavily treatment-experienced patients. In study C214, a study comparing DRV/rtv to LPV/rtv in treatment-experienced patients who have never received LPV/rtv, a total of 604 patients have been randomized; enrollment closed to this study in December 2005. One death of a DRV-treated patient

enrolled in C214 has been reported to date while two deaths of subjects receiving LPV/rtv have been reported.

Conclusion

I agree with the primary reviewer's conclusion. DRV/rtv 600/100 mg twice daily is a safe and effective regimen, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. The risks associated with taking this medication, in particular rash and hyperlipidemia, are balanced by the robust efficacy observed in this population of patients with few or no remaining treatment options. DRV/rtv is not indicated for treatment-naïve patients or for pediatric patients.

Kendall A. Marcus, M.D.
Medical Team Leader

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/s/

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6/23/2006 01:33:08 PM
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CLINICAL REVIEW

Application Type	NDA 21976
Submission Number	21976
Submission Code	000
Letter Date	December 23rd 2005
Stamp Date	December 23rd 2005
PDUFA Goal Date	June 23rd 2006
Reviewer Name	Neville A Gibbs MD, MPH
Review Completion Date	June 23nd 2006
Established Name	Darunavir (DRV/TMC114)
(Proposed) Trade Name	Prezista
Therapeutic Class	Protease-Inhibitor
Applicant	Tibotec Inc
Priority Designation	P
Formulation	300 mg film coated tablet
Dosing Regimen	TMC 600 mg/Ritonavir100 mg bid
Indication	Treatment of HIV infection, in combination with 100 mg ritonavir (RTV), and with other antiretroviral agents in patients
Intended Population	HIV-1 protease inhibitor-experienced adult infected subjects

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends the accelerated approval (21 CFR 314 subpart H) of darunavir (abbreviated TMC114 or DRV) and with the trade name Prezista, at a dosage of 600 mg bid and boosted by 100 mg of ritonavir (RTV) for use in a highly treatment-experienced, multiple PI resistant, HIV-1 infected patient population with evidence of ongoing HIV replication, who are in need of darunavir to construct a viable antiretroviral regimen. This recommendation is based on review of the efficacy and safety data submitted by Tibotec Pharmaceutical, Inc for this New Drug Application (NDA). This highly treatment-experienced patient population is in desperate need of treatment alternatives and the need outweighs any currently identified risk associated with DRV/rtv use.

This reviewer's recommendation is made without reservation after thorough investigation of the apparent discordance in mortality rate in the controlled trials. In the controlled pivotal trials, at Week 24 of study, the mortality rate on the DRV arm was 2.6 per 100 patient years as compared to a mortality rate of zero in the control arm. This DRV adjusted mortality rate per 100 years patient exposure is comparable to that of enfurvitide and tipranavir, the two most recently approved ARV drugs for highly treatment-experienced patients; it is the apparent paucity of deaths in the *control arm* of the pivotal studies that is bothersome, with 13% of control subjects and 3.4% of study subjects withdrawing from these partially blinded studies between randomization and first dose of drug. Analysis of long-term follow-up data confirmed that the excess deaths on the DRV arm reflected mainly the preference of the most ill patients at baseline to discontinue the controlled trial if they failed to be randomized to the experimental drug, and the longer duration of follow-up on the DRV arms. (See Section 7.1.1)

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

Darunavir was studied primarily in two adequate and controlled Phase IIb clinical trials TMC114-C202 and TMC114-C213 enrolling nearly identical highly treatment-experienced, multiple PI resistant patient populations. Additionally the applicant submitted the results of 37 supportive clinical studies (including 18 clinical pharmacology studies).

Independent FDA review analyses confirmed the applicants conclusion that DRV/rtv was superior to a comparator PI control arm (in achieving the primary composite endpoint of the proportion of patients with a confirmed HIV-1 RNA viral load measurement > 1 $\log_{10}$ below baseline without prior evidence of confirmed virological failure, introduction of a new ARV for reasons other than toxicity or intolerance, permanent study drug discontinuation, death or loss to follow-up through Week 24. In general, there was a consistent pattern of increasing efficacy as one moved from a dose of DRV/rtv 400/100 mg qd, to the proposed dose of 600/100 mg bid, in both the primary and secondary efficacy endpoints. (See Table 6.1.4.1.H/I). The DRV/rtv 600/100 mg bid achieved a 62% 1 log drop in VL compared to baseline versus a 14 % 1 log

drop in the control arm of Trial TMC114-C202 while in Trial TMC114-C213 the 600/100 mg bid study arm achieved 82% versus 14% 1 log drop in VL from baseline in the comparator arm.

Multiple secondary end point analyses also supported the conclusions of efficacy over 24 weeks of dosing. For example, the proportion of patients who achieved and maintained HIV RNA < 50 copies/mL was 36% for the DRV/rtv 600/100 mg bid versus 7% in the control arm of Trial TMC114-C202 and 57% in the 600/100 mg bid group versus 16% in control group of Trial TMC114-C213 at Week 24. Analysis of the proportion of patients who achieved and maintained HIV- RNA < 400 copies/mL also demonstrated that DRV/rtv provided a treatment benefit compared to comparator PI control arm.

The mean difference in change in CD4 count from baseline to Week 24 using the DRV/rtv 600/100 mg bid treatment arm as compared to control was 56 cells/mm^3 in the Trial TMC114-C202 and 100 cells/mm^3 the Trial TMC114-C213. These diffeerences were considered to be statistically significant.

This treatment effect was consistent across gender, race, age, geographic region, use or non use of enfurvitide and important HIV baseline disease characteristics.

The FDA review of the DRV/rtv safety data found DRV/rtv safe for its intended use in a highly treatment-experienced patient, in combination with other active ARV agent. In general DRV/rtv had an overall safety profile that was similar to other commercially available ARV's in the protease inhibitor class. The overall type and incidence of adverse events (AE) profile, SAEs and the rate of discontinuation due to AEs did not differ relevantly or systematically for the subgroups by age, gender, race and geographic region.

A major safety concern identified during the safety review of DRV/rtv was the imbalance in the death rate in the controlled clinical trials, with 17 subjects dying on the DRV arm and 0 deaths occuring on the control arm, (when measured at the time of the September 25th 2005 data base lock) and the development of a maculopapular rash. Additionally, DRV is a sulfonamide and may be associated with the developoment of erythema multiforme and Stevens-Johnson Syndrome. Other safety concerns include hyperlipidemia.

DRV/rtv has a moderate drug interaction profile. Detailed drug-drug interaction data for DRV/rtv with certain drugs is available, and in general, the data provide adequate direction for use. The potential for interactions to occur when DRV/rtv is co-administered with other drugs is moderate.

The overall relative short term (24-week) virologic and immunologic benefits of DRV/rtv potentially outweigh the risk of DRV/rtv in this treatment-experienced population especially when DRV is combined with other active ARV and patients are monitored for toxicities and other untoward side effects of the drugs. The virologic and immunologic benefits of DRV/rtv exceeds the risks, when this drug is used in a highly treatment-experienced patient population.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Although Tibotec Inc did not submit a formal risk management plan there are many risk management activites planned for DRV/rtv post accelerated approval. As a requirement of traditional approval under 21 CFR 312 subpart H the applicant must submit:

1) The 96 Week data for their three pivotal Phase IIB trials, which will provide more safety data for analysis of known and unknown DRV/rtv related toxicities.
2) As a requirement of accelerated approval under 21 CFR 312 subpart H the applicant must submit periodic safety reports for review. The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.

Additionally, the Office of Drug Safety has been involved with this NDA submission, and if warranted will be consulted formally to evaluate any new or increased post marketing safety signals.

1.2.2 Required Phase 4 Commitments

1) Submit Week 96 safety and efficacy data on TMC114-C202, TMC114-C213, TMC114-C215 and TMC114-C208 by December 31, 2007 to support the traditional approval of DRV/rtv.

2) Submit Week 48 data for ongoing Phase III studies TMC114-C214 and TMC114-C 211 in order to support the traditional approval requirements for darunavir.

Pediatric Studies

3) 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:	by June 2008

4) Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 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 old children in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

Protocol Submission:	by December 2008
Final Report Submission:	by June 2011

Drug-Drug Interaction Trials

5) Conduct an *in vivo* drug-drug interaction study between darunavir/rtv bid and rifabutin.

Protocol Submission: by July 2006
Final Report Submission: by June 2007

6) Conduct an *in vivo* drug-drug interaction study between darunavir/rtv bid and buprenorphine/naloxone.

Protocol Submission: by December 2006
Final Report Submission: by January 2008

7) Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and carbamazepine.

Protocol Submission: by December 2006
Final Report Submission: by January 2008

Pharmacology/Toxicology

8) Complete ongoing carcinogenicity study in mice and submit final report.

Protocol Submission: Completed
Final Report Submission: by December 2007

9) Complete ongoing carcinogenicity study in rats and submit final report.

Protocol Submission: Completed
Final Report Submission: by December 2007

Pharmacokinetics

10) Please conduct a cocktail study to determine the effects of steady state Darunavir/rtv 600/100 mg bid on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.

Protocol Submission: by December 2006
Final Report Submission: by January 2008

The following studies are *not* postmarketing study commitments, however in an accelerated approval letter dated June 23, 2006 the Division requested the following information to be submitted:

Drug-Drug Interaction Trials

1. The following represent clinical drug-drug interaction studies that have been planned by Tibotec, Inc. to be conducted with darunavir. The Division acknowledges the following planned studies:

- TMC114-C127: drug-drug interaction study between Darunavir/rtv b.i.d. and methadone.

Clinical

2. In addition to the required periodic adverse drug experience reports [21 CFR 314.80(c)(2)], please submit a separate periodic adverse drug experience report for rash.

Microbiology

3. Determine response rates based upon presence of specific cleavage site mutations at baseline and submit this analysis with the PREZISTA traditional approval application.

4. Determine the protease cleavage site mutations that occur most frequently (>10%) in virologic failure isolates and submit this analysis with the PREZISTA traditional approval application.

5. Determine if the most frequently occurring protease cleavage site mutations contributed to decreases in darunavir susceptibility through site-directed mutagenesis and submit this analysis with the PREZISTA traditional approval application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Darunavir (DRV) is a new molecular entity (NME), a non-peptidic protease inhibitor (PI). DRV 600 mg, co-administered with 100 mg of ritonavir (RTV) twice daily
is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with

evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. This indication is based on the analyses of Week 24 data from the two pivotal Phase IIb studies, (TMC114-C202 and TMC114-C213).

These two pivotal studies were supported by two additional, non-randomized roll-over studies TMC114-C215 and TMC-C208. All 4 studies were multi-national trials in which 924 subjects were enrolled, resulting in a total patient years exposure of **828.4**. Of this total exposure, **438.7** patient years exposure were obtained in the dose-finding part of the controlled trials TMC114-C202 and TMC114-C213 during treatment of 513 subjects with 4 different doses of DRV/rtv (400/100 mg qd, 800/100 mg qd, 400/100 mg bid, and 600/100 mg bid) in addition to an individually optimized background ARV regimen.

The control groups in these trials consisted of 124 subjects who received an investigator-selected PI regimen in addition to an individually optimized background ARV regimen. Total patient years exposure in the **control** group was **75.1**.

Both pivotal trials were conducted in clinically advanced, 3-class antiretroviral treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The studies were designed to continue through 96 weeks. At Week 12, with virological confirmation at Week 16, patients in the CPI/r group, who had a lack of initial virologic response (defined as a < 0.5 $\log_{10}$ decrease) were allowed to enroll in the non-randomized roll-over trial, TMC114-C215 where all patients received DRV/rtv 600/100mg bid.

The pooled safety data of the dose-finding part of these trials, indicated that all doses of DRV/rtv were generally safe and well tolerated and showed a safety profile comparable to the control group. No relationship with DRV/rtv dose was observed for safety findings. The evaluation of efficacy and safety data led to the selection of 600/100 mg bid DRV/rtv as the recommended dose. Following selection of the recommended dose, all subjects in the lower dose groups of ongoing Phase IIb trials were instructed to switch to the recommended dose. This dose switch also implied a switch from the clinical trial tablet formulations of darunavir (F001/F002) to the commercial tablet formulation (F016) for all subjects randomized to DRV/rtv, including those already receiving 600/100 mg bid. Although the formulation switch resulted in an increase in darunavir exposure, comparison of safety data before and after switch did not reveal an increased incidence of safety findings, nor were there any indications of new safety findings after switch to the new formulation.

In addition to the two pivotal efficacy and safety trials, the applicant submitted 35 pharmacokinetic and drug-drug interaction studies, and 2 Phase 2a 14-day proof-of-concept trials that provided supportive safety data.

The size of the safety database is consistent with ICH Guidance Document for the determination of safety, and is not dissimilar in size to previously approved drugs at the time of accelerated approval.

1.3.2 Efficacy

Independent FDA statistical analysis confirmed the applicant's analysis of the primary efficacy endpoint. In general there was a consistent pattern of increasing efficacy as one moved from a dose of DRV/RTV 400/100 mg qd, to the proposed dose of 600/100 mg bid, in both the primary and secondary efficacy endpoints. (See Table 6.1.4.1.H/I). The proposed dose of DRV/rtv 600/100 mg bid achieved a 62% 1 log drop in VL compared to baseline versus a 14 % 1 log drop in the control arm of Trial TMC114-C202 while in Trial TMC114-C213 study arm achieved 82% versus 14% 1 log drop in VL from baseline in the comparator arm.

Multiple secondary endpoint analyses also supported the conclusions of efficacy over 24 weeks of dosing. For example, the proportion of patients who achieved and maintained HIV RNA < 50 copies/mL was 36% for the DRV/rtv 600/100 mg bid versus 7% in the control arm of Trial TMC114-C202 and 57% in the 600/100 mg bid group versus 16% in control group of Trial TMC114-C213. Analysis of the proportion of patients who achieved and maintained HIV- RNA < 400 copies/mL also demonstrated that DRV/rtv provided a treatment benefit compared to comparator PI control arm. The mean difference in change in CD4 count from baseline to Week 24 using the DRV/rtv 600/100 mg bid dose, and compared to control was 56 cells/mm^3 in Trial TMC114-C202 and 100 cells/mm^3 the Trial TMC114-C213. These differences were considered to be statistically significant.

The FDA's Statistical Reviewer verified the statistical significance of the observed dose response relationship by fitting logistic regressions to the three efficacy percentages, and performed sensitivity analyses to explore potential open label biases. The conclusion of darunavir's efficacy was confirmed.

The observed difference in the primary and secondary end point analysis between the two pivotal studies was likely a function of the baseline differences between the two study populations, with subjects in Trial TMC114-C213 being less advanced than the study population of Trial TMC114-C202.

An issue that may have affected the efficacy analysis was the partially blinded study design of the pivotal trials; this type of study design, allowed large number of study control subjects to discontinue a regimen perceived to be less desirable and /or efficacious. The FDA Statistical Reviewer conducted a series of sensitivity analyses to assess the impact of this issue on the study results. These sensitivity analyses confirmed the superiority of DRV/rtv.

The microbiology evaluation for emergence of resistance found that the most common protease mutations that developed in isolates from treatment-experienced patients who failed on DRV/rtv 600/100 mg bid included the following: *V11I, V32I, I15V, K20R, F53L, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, and L89V.* These mutations were identified to be associated with a decreased virologic outcome. Among these, *V11I, V32I, I47V, and I54L or M,* were identified by all 3 measures of virologic response.

Virologic outcome was dependent on the following:
1) Baseline phenotype – Virological response rates were greatest when baseline DRV phenotype was below 10. In Studies TMC114-C202 and TMC114-C213, the median baseline phenotype of

responders was 2.1 (n=85) and the median baseline phenotype of virologic failures was 17 (n=40).
2) Baseline DRV Fold change (FC) was shown to be the most predictive factor of virologic outcome
3) Activity of the Optimized Background Regimen (OBR) and the *number of active ARV agent* contributed to the efficacy of DRV/rtv containing regimens. Response (HIV-RNA < 50 copies/mL at Week 24 of the DRV/rtv containing regimen with ≥ 1 susceptible NRTIs in OBR was 48% and without susceptible NRTIs was 30%; in patients who used enfuvirtide (ENF) for the first time 50%; in those who did not use ENF 44%. Similarly, the efficacy of DRV/rtv containing regimens was greatest in patients who received more active antiretrovirals, and this was most pronounced in patients with higher FC. For example, for patients with darunavir FC < 10 the percentage of patients with virologic response measured as a decrease in viral load to < 50 copies/mL, with and without ENF were 53% and 52%, respectively. For patients with darunavir FC > 10 these percentages were 43% and 14%, respectively.

1.3.3 Safety

A total of 1783 healthy volunteers and HIV-1 infected subjects were exposed to DRV. A total of 810 subjects were exposed to the DRV/rtv 600/100 mg bid recommended dose.

The most commonly reported clinical AEs included: nausea, vomiting, headache, and diarrhea. Most of these AEs were mild or moderate in severity (Grade 1 or 2). Adverse events (AEs) that were judged to be severe or life-threatening (Grade 3 or 4) were proportionally similar in study and control arms. A review of SAEs and other AE's of special interest revealed few differences between the safety profiles of the treatment arms. The rate of serious AEs was similar between the treatment arms.

Similar proportions of patients in each treatment group experienced a post-baseline Grade 3 or 4 laboratory abnormality while receiving their assigned study drug.

The extent of exposure was six times greater in the study arms of TMC114-C202 and TMC114-C213 as compared to the control arm of these studies. The mean duration of exposure of subjects on the 600/100 mg bid study arm was 63.5 weeks versus a mean exposure of 31.5 weeks for subjects on the control arm. The control group exhibited a high attrition rate due to virologic failure (65% on control vs 12% on DRV/rtv arm), which had an impact on exposure and biased the safety data presented in this report in favor of the control group. In attempting to account for this bias, the incidence of AEs was corrected for the difference in exposure by performing analyses per 100 patient years of exposure. The reviewers also noted a disproportionate withdrawal of control subjects between randomization and first dose of drug, with the control arm losing 13% subjects prior to receiving first drug, and the study arm losing 3.4% subjects prior to first dose of drug. It is not unreasonable to believe that these unblinded control subjects may have opted for a perceived more efficacious drug option, prior to receiving first dose of drug when they discovered that they were randomized to the comparator arm.

The high rate of early discontinuations in the comparator/control arm may also have impacted the incidence of mortality between study and control arms, resulting in the imbalance of the mortality rate between DRV/rtv and the control arm.

Skin Rash

During the clinical development program, severe skin rash, including cases of erythema muliforme and Stevens-Johnson syndrome have been reported. In some cases, fever and elevations of transminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of subjects treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

DRV contains a sulfonamide moiety. DRV should be used with caution in patients with a known sulfonamide allergy. In controlled studies, darunavir-treated subjects with sulfonamide allergy reported rash at approximately twice the frequency of darunavir-treated subjects who did not report sulfonamide allergy.

Deaths

In the controlled pivotal trials, at Week 24 of study, the mortality rate on the DRV arm was 2.6 per 100 patient years as compared to a mortality rate of zero in the control arm. This adjusted mortality rate in the DRV arm was not grossly different from the mortality rate observed at Week 24 in the two most recently approved drugs for the treatment-experienced population, namely, enfurvitide (ENF) at Week 24 (3.3 in ENF versus 3.3 in control) and tipranavir (TPV) 4.5 versus 2.6 per 100 patient years in the control arm.

The difference between the adjusted mortality rates in these 3 "treatment-experienced" NDA submissions, was the *relative paucity of deaths on the DRV control arm.* FDA reviewers noted that disproportionately larger proportions of control subjects withdrew from these open-label trials between randomization and first drug dose, with the control arm losing 13% (17/133) subjects before starting drug, while the DRVarm lost 3.4% (17/495). It is not unreasonable to believe that these unblinded control subjects may have deliberately opted to go for a perceived potentially more efficacious drug option, prior to first dose of drug.

In pursuing the above hypothesis, the Division asked for additional information on the vital status of ALL subjects who were randomized to study or control arm, but never received medication, and subjects who received control or study drug, but discontinued from one of the controlled trials and did not rollover into TMC114-C215. This data showed that the incidence of death in DRV- treated and/or randomized subjects was 5.5% (29/530), while the incidence of death in control treated and/or randomized subjects was 4.9 % (7/144). These proportions are similar. (These numbers included the 2/17 DRV randomized and the 3/20 controls who were randomized but not treated).

The FDA reviewers directly compared deaths with survivors on several baseline covariates, including CD4 count, serum HIV RNA level, virologic suppression response at 24 weeks, baseline phenotype, neutrophil count during treatment, duration of prior ARV therapy, and age. The only covariate that seemed to be a good predictor of death was CD4 count.

1.3.4 Dosing Regimen and Administration

Darunavir is appropriately dosed by administering DRV/rtv 600/100 mg bid with food. This reviewer concur's with the above dosage as recommended by the sponsor.

1.3.5 Drug-Drug Interactions

Both DRV and rtv are both inhibitors of CYP3A4. Coadministration of DRV/rtv, with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events. The label and the body of this report provides a list of drugs should not be co-administered with DRV/rtv. The following drug interactions of DRV/rtv have not been studied; coadministration of DRV/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir have not been studied. Therefore, such coadministration is not recommended.

1.3.6 Special Populations

Data in the *elderly population* (that is, those aged 65 years and above) were obtained from 8 subjects who initiated treatment with DRV/rtv 600/100 mg bid; however, this data is too limited to draw any conclusions. The analysis by subgroups (age <40 years; 40 to ≤50 years or >50 years of age) did not reveal any age-related trends in the safety profile of darunavir.

Children and Adolescents- No data is currently available on the pediatric and adolescent population. A pediatric development program is in progress, and enrolling subjects ages 6 to 18 years.

Subgroup analyses by ***gender*** and by ***race*** demonstrated no clear differences in the safety profiles of these subgroups. There are no adequate and well controlled studies with DRV/rtv in pregnant women.

Hepatic impaired subjects - DRV is primarily metabolised in the liver, and caution should be exercised when DRV/rtv is given to patients with hepatic impairment, because increased plasma concentrations are expected in patients with varying degrees of hepatic impairment. However, the incidence of AE's and clinical chemistry abnormalities in the limited number of subjects co-infected with Hepatitis B and/or C virus who were exposed to DRV/rtv is no different from other clinical trial subjects. There is no data regarding the use of DRV/rtv in patients with varying degrees of hepatic impairment. The Sponsor has planned a hepatic impairment study and will submit results when available.

Renally impaired subjects- There are no adequate and well controlled studies with DRV/rtv in renally impaired subjects. Population PK analysis showed that the PK of DRV is not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no PK data available in HIV-1 infected patients with severe renal impairment or end stage renal disease.

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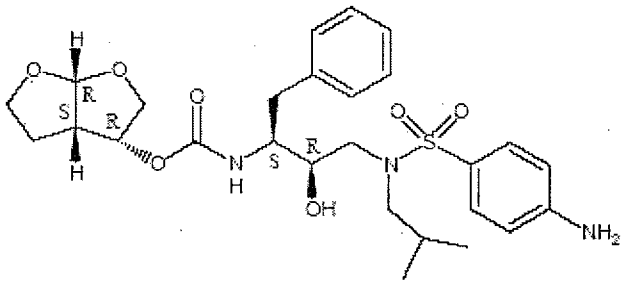
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established name:	Darunavir (DRV/TMC114)
Trade Name:	Prezista
Chemical (Molecular formula):	$C_{27}H_{37}N_3O_7S$
Chemical name:	[(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.
Molecular weight:	547.66
Class:	Protease inhibitor
Proposed indication:	Treatment of HIV-1 infection
Dose and regimen: adults-	Darunavir 600mg boosted by 100 mg ritonavir (DRV/RTV) orally twice daily
Dosage form:	300 mg tablet

Figure 1: Structural formula darunavir



Darunavir (DRV/TMC114) is a protease inhibitor (PI) selected for its high potency against wild-type (WT) and most PI-resistant human immunodeficiency virus (HIV). It selectively inhibits the cleavage of HIV encoded gag-pol polyproteins in virus-infected cells, thereby preventing the formation of mature and infectious progeny virus particles.

Darunavir has an EC_{50} (50% effective concentration in cell-based assays) value ranging from 1.2 nM (0.7 ng/mL) to 6.3 nM (3.4 ng/mL), and a median EC50 value ranging from 2.8 nM(1.5 ng/mL) to 16.4 nM (9.0 ng/mL) against WT HIV-1, and a CC_{50} (50% cytotoxic concentration in cell-based assays) value > 100 μM. With a selectivity index (SI) > 26000, darunavir is a potent and selective HIV inhibitor. Comparable EC_{50} values were found for darunavir against WT HIV-1 in cell lines, freshly isolated peripheral blood mononuclear cells and monocytes/macrophages. Darunavir binds very tightly to the HIV-1 protease at numerous atoms positions, through mainchain atoms interactions. The commercial formulation will be a 300 mg orange oval shaped film-coated tablet. Inactive ingredients are: microcrystalline cellulose, colloidal [redacted] silica, crospovidone, magnesium stearate and Opadry orange.

2.2 Currently Available Treatment for Indications

Darunavir, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.
Low-dose RTV is used as a pharmacokinetic enhancer of darunavir. The recommended dosage of darunavir is 600 mg twice daily (bid) taken with RTV 100 mg bid and with food. The type of food is not important.

There are now 22 drugs approved for the treatment of HIV-1 infection (this list does not include fixed dose combinations or different formulations). These drugs fall into four classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion/entry inhibitors (Table 2.2 A).

TABLE 2.2A: SHOWING CURRENTLY APPROVED ANTIRETROVIRALS AGENTS(ARV) FOR THE TREATMENT OF HIV-1 INFECTION

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT) Didanosine (ddI) Zalcitabine (ddC) Stavudine (d4T) Lamivudine Abacavir Tenofovir Emtricitabine (FTC)	Retrovir Videx Hivid Zerit Epivir Ziagen Viread Emtriva
NNRTI	Delavridine Nevirapine Efavirenz	Rescriptor Viramune Sustiva
PI	Indinavir Ritonavir Saquinavir (hard gel) Saquinavir (soft gel) Nelfinavir Amprenavir fos-amprenavir Atazanavir lopinavir/ritonavir Tipranavir	Crixivan Norvir Invirase Fortavase Viracept Agenerase Lexiva Reyataz Kaletra Aptivus
Fusion/Entry Inhibitor	Enfuvirtide (T20)	Fuzeon

According to the 2003 DHHS HIV-1 Treatment Guidelines "treatment goals should be maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality". Obstacles in achieving these goals include drug side effects, drug intolerance and drug resistance. The use of antiretroviral drugs in combination has decreased the morbidity and mortality of HIV disease. However, treatment with combination therapy is often associated with significant drug toxicities such as fat redistribution, hyperglycemia, pancreatitis, and lactic acidosis. In addition, drug intolerance, drug adherence and drug resistance play major roles in the success of these antiretroviral drug combinations.

The prevalence of drug resistance in HIV-positive, treatment-experienced patients and the incidence of drug resistance in treatment-naïve patients are increasing. TMC's development specifically targeted a highly resistant, highly treatment experienced population with very limited treatment options.

2.3 Availability of Proposed Active Ingredient in the United States

Darunavir is a new molecular entity that is not yet approved or marketed in the U.S.

Tibotec developed DARUNAVIR (DRV) to be used in conjunction with low dose ritonavir (RTV). RTV is an approved PI that is marketed world wide, and is "indicated in combination with other antiretroviral agents for the treatment of HIV-infection" (NORVIR package insert) when used as an antiretroviral. However, RTV is most commonly used at a low dose of 100-200 mg to "boost" the therapeutic levels of other PIs by increasing drug exposure and prolonging serum half-lives of the active PIs, inhibiting drug-transporting proteins such as Pglycoprotein and decreasing the rate of elimination by inhibition of cytochrome P(CYP)450 in the liver. The primary drawbacks of adding low-dose RTV to protease inhibitors include increased risk of hyperlipidemia, increased liver enzymes and more drug-drug interactions.

2.4 Important Issues With Pharmacologically Related Products

Darunavir and rtv are both protease inhibitors (PIs) and as such are associated with acute and chronic side effects observed throughout the PI class, namely, lipodsytrophy, hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, and increased bleeding in hemophiliacs. There were significantly higher increases in cholesterol and LDL, and somewhat lower increases in fasting triglycerides, while increases in HDL were significantly higher in the DRV arm versus the PI comparator arm. (Please see section 7.1.3.3. for a detailed review of DRV's associated adverse events).

2.5 Presubmission Regulatory Activity

The early IND work on this drug was performed in Europe. After an initial Pre-IND Consultation in October 2001, the initial Investigational New Drug Application (IND 62,477) for DRV was submitted to the Agency on December 19th 2002. The Sponsor interacted with the FDA on June 2003, regarding the acceptability of the proposed bridging toxicology program.

In August 6, 2003 the Division again met with the Sponsor , discussing the adequacy of the overall developmental plan, and more specifically on the design of the Phase IIb dose-finding studies, TMC114-C202 and TMC114-C213. The safety and efficacy, as well as the pharmacokinetic results of the 16 week combined interim analyses were discussed. These results were intended to support discussions with the Regulatory Agencies in preparation of future trials and to serve for the selection of the dosage to be used in further development.

A Type C Meeting was held between the Division and Tibotec Inc. on November 3rd 2004 to discuss the clinical development of DARUNAVIR, and to determine the eligibility for early NDA submission to support Accelerated Approval based on the Phase IIb study results. At this meeting, Tibotec Inc provided a brief presentation of DARUNAVIR development plan, the

results of the Week 16 interim analysis results, and sought the Division's concurrence on plans to submit TMC114-C202 and TMC114-C213 as the two adequate and well controlled studies supporting accelerated approval of DARUNAVIR, along with overall microbiology, non-clinical, pharmacokinetic.The Division agreed that the studies provided substantial evidence of efficacy, but requested that additional safety data be obtained at the proposed dose. As a result study C215 enrolled an additional 327 subjects.

On November 15th 2004, the Division granted Fast Track designation for the use of DARUNAVIR for the treatment of HIV infection, and concurred with Tibotec's request for the step-wise submission of sections of the NDA in September 2005 (Clinical), November 2005 (Quality and Nonclinical) and December 2005 (Clinical and Non Clinical).

On December 8th 2004, a CMC EOPII meeting was held to discuss the specific Chemistry, Manufacturing, and Control (CMC) aspects of the pharmaceutical development of DARUNAVIR and the potential submission of a New Drug Application (NDA). The Division found Tibotec's proposal to be acceptable. The proposed pediatric formulation development program was also discussed.

In February 2005, all subjects in TMC114-C202 and TMC114-C213 and open label studies TMC114-C215 and TMC114-C208 were converted to the recommend dose of DARUNAVIR/RTV 600/100 mg bid. The Week 48 end point for studies TMC114-C202/C213 was amended to become "time to virological failure".

At a Pre-NDA Meeting held on June 7th 2005, the proposed content and format of the accelerated NDA, were discussed and agreed to. The following submission dates were agreed to:

On September 23rd 2005, the Sponsor submitted the first section of the NDA which included the following Clinical Information:

- Clinical Pharmacology and Biopharmaceutics
- In vitro Virology and Clinical Virology
- The clinical efficacy and safety data from the 24 week primary analyses of two Phase IIB trials TMC114-C202 and TMC114-C213 (prior to the February 1st , 2005 dose switch)
- The results of the two completed Phase IIa Proof of Principle trials (TMC114-C201 and TMC114-C207
- 33 completed Phase I trials.

On November 4th 2005 the following was submitted to the Division:

- Complete chemistry, manufacturing and controls (CMC) information related to the drug product.
- All non clinical information (excluding the Non Clinical Overview)

On December 23rd , 2005, the submission to DAVP included

- Non clinical Overview
- Clinical Overview

- Clinical Summary, including the Summary of Biopharmaceutic Studies and associated analytical methods, Summary of Clinical Pharmacology Studies, Virology Summary, Summaries of Clinical Efficacy and Clinical safety
- Nonclinical Study Reports TMC114-NC213, and TMC-NC249
- Study reports from three Phase I trials (TMC114-C114, C116 and C153
- Population PK analysis report
- Virology research report
- Statistical analysis output and supportive datasets for clinical summaries

On March 29th 2006, a safety update review was submitted. This update included safety data collected from the open label safety study TMC114-C209 up to December 1st 2005, and an update on deaths and serious adverse events (SAE's) reported from ongoing TMC 114 trials from the final cut off date, up to January 13th 2006. Case report forms for all deaths and discontinuations due to AE's were included in this submission.

Other Relevant Background Information

At this time the marketing application for DARUNAVIR is currently under review by the [redacted] however, because of the lengthier review process in these countries, the approval is not anticipated in these countries prior to the FDA's, June 23rd 2006 PDUFA date.

Submissions to additional countries: [redacted]

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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology)

Please refer to Dr. Rao's CMC review for a detailed analysis of DRV's chemistry, manufacturing and controls. There were no CMC issues that are pertinent to the clinical review:

3.2 Animal Pharmacology/Toxicology

Please refer to Dr. James Farrelly's Animal Pharmacology/Toxicology Review for a detailed analysis of the DRV's pharmacology and toxicology data. Darunavir is a sulfonamide drug, which in general causes a number of toxic effects, of which the most worrisome is hypersensitivity. The key target organs identified in the toxicology studies were the hematopoetic system, the blood coagulation system, liver and thyroid. This was not confirmed in humans. The following is a summary of Dr. Farrelly's findings:

General toxicology-

In single- and repeated-dose toxicity studies, there were only limited effects of treatment with darunavir. In dogs, no major findings were identified. Key target organs or systems identified in rodents were the hematopoietic system, the blood coagulation system, liver, and thyroid. Single and multiple dose studies conducted in combination with RTV showed an additive effect on red blood cell parameters, liver, and thyroid in rats; these changes appeared to reflect the sustained systemic exposure to darunavir in the presence of RTV but were not of a different order of magnitude with each compound alone. The effects seen in the liver and thyroid (cellular hypertrophy with increase in organ weight) were consistent with the liver enzyme inducing properties of DRV, and an adaptive response to an induction of cytochrome P450.

Genetic toxicology - A series of in vitro and in vivo tests showed darunavir to be free of genotoxic potential.

Carcinogenicity - Rat and mouse carcinogenicity studies are ongoing and there is no information on the potential carcinogenic risk available at this time.

Both mouse and rat carcinogenicity studies will be conducted for two years. An additional dose will be administered with in combination with ritonavir. The complete results of the Carcinogenic Studies will be submitted as a Phase IV Commitment.

Immune function – Local lymph node assay (TMC114-NC245) in the mouse model showed that DRV/rtv was unlikely to have the potential to cause skin sensitization. Four (**4**) Week immunotoxicity study with DRV/rtv by daily gavage in rats did not reveal evidence of an immunotoxicological response.

(See Section 7.1.10 for further details on these immunogenicity studies).

Reproductive toxicology- Segment I, Segment II and III studies were unremarkable. Darunavir did not affect fertility and early embryonic development in rats and has shown no teratogenic potential in mice, rats and rabbits. However, exposure levels in these studies were below human exposure.

Safety Pharmacology Studies

i) Neurological effects- No neurological effects were noted in rats in a single dose up to 2000 mg/kg, without any overt changes in behavior or reflexes.

ii) Cardiovascular Effects - Darunavir showed no effect on the ***in vitro*** HERG transfected HEK293 cells and the Sheep isolated Purkinje fibre cardiac action potential study and ***in vivo*** cardiohemodynamic parameters and ECG in conscious telemetered dogs.
iii) Pulmonary effects- no effects were noted in respiration in rats in doses of up to 2000 mg/kg
iv) Gastrointestinal effects – no effects were noted in gastrointestinal transit time in rats.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is primarily based on data from the two pivotal Phase IIb studies, POWER 1 and POWER 2 conducted by Tibotec Inc.. Additionally, data from pooled roll-over studies, TMC114-C208 and TMC114-C215 were reviewed for additional safety and efficacy. (See Table 4.1.1 below).
The Clinical Reviewer, Neville A Gibbs MD, MPH was responsible for the overall clinical review process, for writing an overview of the review, the executive summary, the review of the pivotal/ registrational trials, plus the review of the integrated review of efficacy and the integrated review of safety. This clinical reviewer was supported by Anitra Denson M.D., who reviewed the Phase I supportive trials in healthy volunteers, the single and multiple dose bioavailability and other pharmacokinetic studies, and the drug interaction studies.
The scientific literature was reviewed to assess the prevalence and management of HIV and Hepatitis B and C co-infection and the current mortality rate of advanced HIV-1 infected adults in economically developed countries in the post HAART era. DAVP's clinical trials database was reviewed to assess the mortality rate of HIV-1 infected patients in registrational clinical trials.

TABLE 4.1.1 SHOWING THE CLINICAL DEVELOPMENT PROGRAM OF DARUNAVIR

Study Phase (Country)	**Design** **Study Objectives**	**Subjects** **N**	**Dosage Regimen** **Duration of Rx**	**Relevance to safety and /or efficacy review**
TMC114-C202 Phase IIb (US, Argentina)	Two-part hybrid: randomized, partially-blinded Dose-finding study in 3 class experienced	3-class experienced HIV-1 infected N= 278	DRV/RTV • 400/100 mg qd • 800/100 mg qd • 400/100 mg bid • 600/100 mg bid • Control: OBR 96 weeks	24 week Interim efficacy & safety analysis
TMC114-C213 Phase IIb (Australia, UK, Austria, Belgium, Brazil, Canada, France Germany, Italy, Hungary, Switzerland, Spain, Portugal)	Two-part hybrid: Randomized, controlled, partially blinded Dose-finding study in 3 class experienced	3-class experienced HIV-1 infected N= 318	DRV/RTV • 400/100 mg qd • 800/100 mg qd • 400/100 mg bid • 600/100mg bid • Control: OBR 96 weeks	24 week Interim Efficacy & safety analysis
TMC114-C215 (Roll-over study) Phase IIb (Australia, UK, Austria, Belgium, Brazil, Canada, France, Germany, Italy, Hungary, Switzerland, Spain, Portugal, US, Argentina)	Open Label 96-week trial roll-over study of subjects failing TMC114-C202 or -C213, or who may derive benefit of DRV/RTV. Further evaluates the safety or efficacy of the recommended dose of DRV/RTV	3-class experienced HIV-1 infected 120 + 200 subjects who did not participate in TMC114-C202 or -C213 N=431	DRV/RTV 400/100 mg bid → TMC/114/RTV 600/100 mg bid + OBR 2≥ ARV's NRTI's +/- ENF	Clinical Efficacy & Safety included in 12/05 submission- (including additional subjects included @ recommended dose)

Study Phase (Country)	Design Study Objectives	Subjects N	Dosage Regimen Duration of Rx	Relevance to safety and /or efficacy review
TMC114-C201 (unboosted) Phase IIa (Proof-of-principle) Austria, Germany, Great Britain, Italy, Poland, Russia, Switzerland)	Randomized, open-label, controlled, dose-finding trial To investigate the antiviral activity of DRV administered as an [redacted]	HIV-1 Infected, PI-experienced N=34 analyzed (60 planned)	• DRV 400 mg bid • DRV 800 mg bid • DRV 800 mg tid • DRV 1200 mg tid • Control – remained on failing regimen TF019 ; Oral formulation; Fasted, conditions 14 days with 6 week follow up	Demonstrated Intrinsic antiviral activity of DRV in subjects with multiple PI-resistant virus
TMC114/RTV-C207 (boosted) Phase IIa (Proof-of-principle) Germany, Belgium, Italy, Poland, Great Britain, Austria, Switzerland	Randomized, open-label, controlled, dose-finding trial To investigate the antiviral activity of DRV administered as an [redacted] co-administered with low-dose RTV in subjects multiple PI-resistant strains	HIV-1 infected, PI-experienced N= 50 analyzed	• DRV/RTV 300/100 mg bid • DRV/RTV 600/100 mg bid • DRV/RTV 900/100 mg bid • Control-remains on failing regimen 14 days	Demonstrated that VL reductions were greater when combined with low-dose RTV. Validated decision to develop in combination with low-does RTV.
TMC114-C208 (Roll-over study) Phase IIb (International, multicenter)	Open-Label trials for subjects randomized to -C201 or -C207 or From Sponsor selected Phase I trials & who may derive benefit DRV - to assess long term safety & tolerability	HIV-1 infected, PI-experienced N= 29	DRV/RTV 400/100 mg bid → 600/100 mg bid + OBR (≥2 ARV's, incl. NRTI's/NtRTI, NNRTI's/ &-or ENF)	Clinical Efficacy & Safety included in 12/05 submission (including additional subjects included @ recommended dose)

Study Phase (Country)	Design Study Objectives	Subjects N	Dosage Regimen Duration of Rx	Relevance to safety and /or efficacy review
TMCC114-C214 Phase III (International, multicenter)	Randomized, controlled LPV/RTV, open label Primary objective to demonstrate non-inferiority with TMC114/RTV vs LPV/RTV in virologic response (confirmed plasma VL <400 copies/mL @ 48 weeks)	Treatment - **experienced** (i.e on HAART for > 12 weeks) HIV-1 infected subjects N= 500	• DRV/RTV, 600 mg bid for 96 weeks vs • LPV/RTV 400/100 mg bid (or 533/133 mg bid when NNRTI used in OBR + OBR of > 2 ARV's (NRTI with or without NNRTI 96 weeks	SAE's reports included in "Open-Label Data" Submission Traditional Approval
TMC114-C211 Phase III (International, multicenter)	Randomized, controlled LPV/RTV, open label Primary objective to demonstrate non-inferiority with DRV/RTV vs LPV/RTV in virologic response (confirmed plasma VL <50 copies/mL @ 48 weeks)	Treatment-**naïve** HIV-1 infected subjects N= 660	• DRV/RTV, 800 mg qd for 96 weeks vs • LPV/RTV 800/200 mg or • 400/100 mg bid for 96 weeks + Fixed background of tenofovir + emtricitabine, 300/200 mg qd 96 weeks	SAE's reports included in "Open-Label Data" Submission Traditional Approval

Source: Medical Officers' Compilation of Clinical Efficacy and Safety Studies contributing to Accelerated approval

4.2 Tables of Clinical Studies

The darunavir clinical development program consisted of thirty-five Phase I trials involving 748 healthy subjects, and one Phase I trial in 19 HIV-1 infected subjects. Two clinical Phase IIa proof-of –principle trials TMC114-C201 and TMC114-C207 were conducted in treatment experienced subjects, and provided the guidance for design of the two Phase IIb trials. Trials TMC114-C202 and TMC114-C213 were the dose-finding trials, and also provided the basis for accelerated approval.

COMPREHENSIVE TABULAR LISTING OF ALL CLINICAL STUDIES SUBMITTED BY THE SPONSOR grouped by Biopharmaceutic; Human pharmacokinetic studies; Human Pharmacodynamic studies; Clinical Efficacy and Safety Studies

5.3.1 Biopharmaceutic Studies Bioavailability Study Reports				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C102 (Belgium)	Open-label, randomized, 2-way crossover Effect of food on relative bioavailability of TMC114	Healthy volunteers 12	- TMC114, [redacted] single dose, 800 mg - Fasted - Fed
I	TMC114-C114 (France)	Open-label, randomized, 4-way crossover Intravenous study to establish absolute bioavailability of TMC114	Healthy volunteers 8	- TMC114: single 1-hour intravenous infusion of 150 mg - TMC114: single oral dose of 600 mg - TMC114: single 1-hour [redacted] of 150 mg on Day 3 + RTV 100 mg b.i.d., oral, Days 1-6 - TMC114: single oral dose of 600 mg on Day 3 + RTV 100 mg b.i.d., oral, Days 1-6
I	TMC114-C118 (Belgium)	Open-label, randomized, 4-way crossover Relative bioavailability for 2 formulations of TMC114 with a low dose of RTV, and the effect of food	Healthy volunteers 16	- TMC114: single dose, 400 mg, oral solution on Day 3+ RTV 100 mg b.i.d., oral, on Days 1-4 - Fasted - Fed - TMC114: single dose, 400 mg, oral tablet on Day 3 + RTV 100 mg b.i.d., oral, Days 1-4 - Fasted - Fed

RTV = ritonavir

5.3.1 Biopharmaceutic Studies Comparative Bioavailability and Bioequivalence Study Reports				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C103 (Belgium)	Open-label, randomized, 3-way crossover Effect of food on systemic exposure of TMC114	Healthy volunteers 27	- Treatment A: TMC114 (TF019): single dose, 800 mg, [redacted] fasted - Treatment B (fasted) and C (fed): - TMC114 (TF036): single dose, 800 mg, oral tablet - TMC114 (TF041): single dose, 800 mg, [redacted] - TMC114 (TF038): single dose, 800 mg, [redacted]
I	TMC114-C116 (France)	Open-label, 2 panel, randomized, 2-way crossover Bioequivalence between the clinical trial formulation (F001, F002) and commercial formulation (F016) of TMC114 with a low dose of RTV	Healthy volunteers 48	Panel 1: - TMC114 (F002): single oral 600-mg dose - TMC114 (F016): single oral 600-mg dose Panel 2: - TMC114 (F001): single oral 1200-mg dose - TMC114 (F016): single oral 1200-mg dose In each treatment period: RTV 100 mg b.i.d., oral, on Days 1-5, TMC114 is administered on Day 3 in fasted state

5.3.1 Biopharmaceutic Studies Comparative Bioavailability and Bioequivalence Study Reports				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C148 (Belgium)	Open-label, randomized, 4-way crossover Relative bioavailablity for 4 formulations of TMC114 with a low dose of RTV	Healthy volunteers 16	- TMC114: single dose, 400 mg, oral tablet on Day 3 + RTV 100 mg b.i.d., oral, on Days 1-5. Formulations: TF036A, TF036B, TF036C, TF036
I	TMC114-C154 (Belgium)	Open-label, randomized, 3-way crossover Effect of different particle size distributions of drug substance on relative bioavailablity of TMC114 in the presence of a low dose of RTV	Healthy volunteers 24	- TMC114: single dose, 400 mg, oral tablet on Day 3 + RTV 100 mg b.i.d., oral, on Days 1-5. Formulations: F002 (Batch X), F002 (Batch Y), F002 (Batch Z)
I	TMC114-C156 (Belgium)	Open-label, randomized, 2-way crossover Relative bioavailablity of TMC114 formulated as tablets using 2 different batches of drug substance	Healthy volunteers 16	- TMC114: single dose, 400 mg, oral tablet on Day 3 + RTV 100 mg b.i.d., oral, on Days 1-5. Formulations: F002, F009

5.3.1 Biopharmaceutic Studies
Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title
TMC114-ABL1982-AVR	Validation of the determination of TMC114 in human plasma using LC-MS/MS
TMC114-ABL1983-AVR	Validation of the determination of TMC114 in human urine using LC-MS/MS
TMC114-ABL3021-AVR	Validation of the combined determination of TMC114 and Ritonavir in human plasma using LC-MS/MS
TMC114-ABL5150-AVR	The cross-validation of the determination of TMC114 and Ritonavir in human plasma using [redacted] LC-MS/MS system
TMC114-ABL6044-AVR	The Cross-validation of the Determination of TMC114 and Ritonavir in Human Heparin Plasma by LC-MS/MS Using D4-TMC114 and D6-Ritonavir as Internal Standard.
TMC114-PBR040553-AVR	Validation of a method for the determination of TMC114 and ritonavir in human heparin plasma samples (PBRL-RD-642/PBR-040553/BA213/NC239)
TMC114-ABL3173-AVR	The validation of the free TMC114 in human plasma by centrifugal filtration with a 10.000 MW filter
NPR-ABL99804-AVR	Validation of the determination of Ritonavir in human plasma using LC-MS/MS
NPR-ABL2104-AVR	Validation of the combined determination of Rifabutin and its metabolite 25-O-Desacetylrifabutin in human plasma using LC-MS/MS
NPR-ABL99806-AVR	Validation of the determination of Saquinavir in human plasma using LC-MS/MS
NPR-ABL2241-AVR	Validation of the determination of Efavirenz in human plasma using LC-MS/MS

5.3.1 Biopharmaceutic Studies
Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title
NPR-ABL3230-AVR	Validation of the determination of nevirapine in human plasma using LC-MS/MS
NPR-ABL3026-AVR	Validation of the determination of pravastatin in human plasma using LC-MS/MS
NPR-ABL5242-AVR	The validation of the determination of paroxetine in human plasma by LC-MS-MS
NPR-ABL5243-AVR	The validation of the determination of sertraline in human plasma by LC-MS/MS
NPR-ABL3076-AVR	Validation of the determination of PMPA in human plasma using HPLC with fluorescence detection
NPR-ABL3188-AVR	Validation of the determination of PMPA in human urine using HPLC with fluorescence detection
NPR-ABL2184-AVR	Validation of the determination of lopinavir in human plasma using LC-MS/MS
NPR-ABL4247-AVR	The validation of sildenafil and desmethyl-sildenafil in human plasma over the range 2.00 - 2000 ng/mL, using [redacted] LC-MS/MS system
NPR-ABL4180-AVR	The validation of ketoconazole in human plasma using LC-MS/MS
NPR-ABL5173-AVP	The cross-validation of the determination of ketoconazole in human plasma using [redacted] LC-MS/MS system
NPR-ABL3161-AVR	The validation of atorvastatin and metabolites in human serum using LC-MS/MS
NPR-ABL3151-AVR	Partial validation of the determination of saquinavir in human plasma using LC-MS/MS

5.3.3 Human Pharmacokinetic Studies Healthy Subject Pharmacokinetics				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C103 (Belgium)	Randomized, double blind, placebo-controlled, dose escalation trial To assess the pharmacokinetics of single doses of TMC114 (oral solution)	Healthy volunteers 27	- TMC114: single dose, oral solution, of 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, 1600 mg, 2400 mg, 3200 mg, fasted
I	TMC114-C104 (Belgium)	Randomized, double blind, placebo-controlled, multiple dose escalation trial To assess the pharmacokinetics after repeated 2 or 3 times daily doses of TMC114 [redacted]	Healthy volunteers 36	- TMC114: oral 400 mg b.i.d. for 13 days, single dose on Day 14 - TMC114: oral 800 mg b.i.d. for 13 days, single dose on Day 14 - TMC114: oral 800 mg t.i.d. for 13 days, single dose on Day 14 - TMC114: oral 1200 mg t.i.d. for 13 days, single dose on Day 14
I	TMC114-C109 (Belgium)	Open label, randomized Mass balance trial with C-14 radiolabelled TMC114 with and without RTV to characterize excretion and metabolic profile	Healthy volunteers 8	- ^{14}C-TMC114: oral solution, single dose, 400 mg - ^{14}C-TMC114: oral solution, single dose, 400 mg on Day 1 – RTV, 100 mg b.i.d., oral, on Days -2 to 7

5.3.3 Human Pharmacokinetic Studies Healthy Subject Pharmacokinetics				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C117 (Belgium)	Open-label, parallel group, dose-ranging trial To assess the pharmacokinetics of various multiple dose regimens of TMC114 with a low dose of RTV	Healthy volunteers 40	- TMC114/RTV: oral 400/100 mg q.d. for 7 days - TMC114/RTV: oral 800/100 mg q.d. for 7 days - TMC114/RTV: oral 1200/100 mg q.d. for 7 days - TMC114/RTV: oral 400/100 mg b.i.d. for 6 days, single dose on Day 7 - TMC114/RTV: oral 800/100 mg b.i.d. for 6 days, single dose on Day 7 For all regimens, RTV 100 mg (q.d. and b.i.d. as for TMC114), oral, was taken on Days 1-11

5.3.3 Human Pharmacokinetic Studies Drug-Drug Interaction Studies				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
I	TMC114-C119 (UK)	Open label, randomized, 1-sequence, crossover trial Interaction between repeated dosing of TMC114 in combination with low-dose RTV and nevirapine	HIV-1 infected subjects 19	- subjects continued their current HIV therapy consisting of nevirapine and at least 2 NRTIs - TMC114/RTV, oral solution, 300/100 mg b.i.d. on Days 1-13 + a single dose on Day 14 on top of current HIV therapy (NRTIs + 200 mg nevirapine b.i.d.) - TMC114/RTV, oral tablet, 400/100 mg b.i.d. on Days 1-13 + a single dose on Day 14 on top of current HIV therapy (NRTIs + 200 mg nevirapine b.i.d.)
I	TMC114-C120 (Belgium)	Open label, randomized, one-sequence, crossover trial Pharmacokinetic interaction between TMC114 in combination with a low dose of RTV and a single dose of pravastatin	Healthy volunteers 14	- Pravastatin, oral, single dose, 40 mg - TMC114/RTV, oral, b.i.d., 600 mg/100 mg, 7 days + pravastatin, oral, single dose, 40 mg on Day 7

5.3.3 Human Pharmacokinetic Studies Drug-Drug Interaction Studies				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
I	TMC114-C121 (US)	Open-label, randomized, crossover Pharmacokinetic interaction between TMC114/RTV and paroxetine or sertraline	Healthy volunteers 36	Panel 1: - TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - paroxetine, oral, 20 mg q.d. for 7 days - paroxetine, oral, 20 mg q.d. and TMC114/RTV, oral, 400/100 mg b.i.d. for 7 days Panel 2: - TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - sertraline, oral, 50 mg q.d. for 7 days - sertraline, oral, 50 mg q.d. and TMC114/RTV, oral, 400/100 mg b.i.d. for 7 days
I	TMC114-C122 (US)	Open-label, randomized, 3-way crossover Pharmacokinetic interaction between TMC114/RTV with ranitidine and omeprazole	Healthy volunteers 17	- TMC114/RTV, oral, 400/100 mg b.i.d. for 4 days and single dose on Day 5 - ranitidine, oral, 150 mg b.i.d. and TMC114/RTV, oral, 400/100 mg b.i.d. for 4 days and single dose on Day 5 - omeprazole, oral, 20 mg q.d. and TMC114/RTV, oral, 400/100 mg b.i.d. for 4 days and single dose on Day 5

5.3.3 Human Pharmacokinetic Studies Drug-Drug Interaction Studies				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
I	TMC114-C124 (Belgium)	Open label, one-sequence, crossover trial Pharmacokinetic interaction between TMC114 boosted with a low dose of RTV and tenofovir	Healthy volunteers 13	- TMC114/RTV, oral, 300/100 mg b.i.d., 6 days and single dose on Day 7 - TMC114/RTV, oral, 300/100 mg, b.i.d., on Days 1-7 or Days 8-14 and 300 mg tenofovir, oral, q.d. for 14 days
I	TMC114-C125 (Belgium)	Open label, randomized, 4-way crossover trial Pharmacokinetic interaction between TMC114 and lopinavir both in combination with a low dose of RTV	Healthy volunteers 16	- LPV/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - TMC114/RTV, oral, 300/100 mg b.i.d. for 6 days and single dose on Day 7 - TMC114/RTV, oral, 300/100 mg b.i.d. for 6 days and single dose on Day 7 + LPV/RTV 400/100 mg, oral, b.i.d. for 6 days and single dose on Day 7 - TMC114, oral, 300 mg b.i.d. for 6 days and single dose on Day 7 + LPV/RTV, oral 400/100 mg b.i.d. for 6 days and single dose on Day 7
I	TMC114-C128 (USA)	Open label, randomized, 2-way crossover trial Pharmacokinetic interaction between TMC114 coadministered with a low dose of RTV and sildenafil	Healthy volunteers 16	- Sildenafil, oral, single dose, 100 mg - TMC114/RTV, oral, 400/100 mg b.i.d., 8 days + sildenafil, oral, 25 mg q.d. on Day 7

5.3.3 Human Pharmacokinetic Studies Drug-Drug Interaction Studies				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
I	TMC114-C129 (Belgium)	Open-label, controlled, randomized, crossover Pharmacokinetic interaction between TMC114 with and without low-dose RTV and ketoconazole	Healthy volunteers 26	- TMC114, oral, 400 mg b.i.d. for 6 days and single dose on Day 7 - TMC114, oral, 400 mg + ketoconazole, oral, 200 mg b.i.d. for 6 days and single dose on Day 7 - TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - ketoconazole, oral, 200 mg b.i.d. for 6 days and a single dose on Day 7 - TMC114/RTV, oral, 400/100 mg + ketoconazole, oral, 200 mg b.i.d. for 6 days and single dose on Day 7
I	TMC114-C133 (USA)	Open, randomized, 1-way crossover Effect of TMC114 with low-dose RTV on the PK of atorvastatin and its metabolites atorvastatin lactone and 2-and 4-hydroxy-atorvastatin	Healthy volunteers 16	- atorvastatin, oral, 40 mg q.d. for 4 days - TMC114/RTV, oral, 300/100 mg b.i.d. for 9 days + atorvastatin, oral, 10 mg q.d. on Days 4-7

5.3.3 Human Pharmacokinetic Studies
Drug-Drug Interaction Studies

Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C138 (Belgium)	Open-label, randomized, crossover Pharmacokinetic interaction between TMC114 and saquinavir with a low dose of RTV	Healthy volunteers 32	Session 1: - Panel 1: TMC114/RTV, oral, 400/100mg b.i.d. on Days 1-13 and single dose on Day 14 - Panel 2: saquinavir/RTV, oral, 1000/100 mg b.i.d. on Days 1-13 and single dose on Day 14 Session 2 (Panel 1 and 2): - TMC114/RTV/saquinavir, oral, 400/100/1000 mg b.i.d. on Days 1-13 and single dose on Day 14
I	TMC114-C141 (US)	Open-label, randomized, 3-way crossover Interaction between repeated dosing of TMC114 and indinavir both in combination with low-dose RTV	Healthy volunteers 17	- TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - indinavir/RTV, oral, 800/100 mg b.i.d. for for 6 days and single dose on Day 7 - indinavir/TMC114/RTV, oral, 800/400/100 mg b.i.d. for 7 days and single dose on Day 7
I	TMC114-C142 (Belgium)	Open-label, randomized, 3-way crossover Pharmacokinetic interaction between TMC114/RTV and clarithromycin	Healthy volunteers 18	- TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - clarithromycin, oral, 500 mg b.i.d. for 6 days and single dose on Day 7 - clarithromycin, oral, 500 mg b.i.d. for 6 days and single dose on Day 7 + TMC114/RTV, oral, 400/100 mg b.i.d. for 7 days

5.3.3 Human Pharmacokinetic Studies
Drug-Drug Interaction Studies

Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I	TMC114-C149 (USA)	Open-label, randomized, 3-way crossover Interaction between repeated dosing of TMC114 and atazanavir both in combination with low-dose RTV	Healthy volunteers 23	- TMC114/RTV, oral, 400/100 mg b.i.d. for 6 days and single dose on Day 7 - atazanavir/RTV, oral, 300/100 mg q.d. for 7 days - atazanavir, oral, 300 mg q.d. + TMC114/RTV, oral, 400/100 mg b.i.d. for 7 days
I	TMC114-C151 (Multinational)	Open-label, randomized, 3-way crossover Interaction between TMC114 and LPV/RTV in combination with 2 NRTIs with or without enfuvirtide	HIV-1 infected subjects 32	Panel 1: Treatments A, B, D; Panel 2: Treatments A, C, D. - Treatment A: current HIV therapy including LPV/RTV 400/100 mg b.i.d. for 14 days - Treatment B: current HIV therapy including LPV/RTV 400/100 mg b.i.d. + TMC114/RTV 1200/100 mg b.i.d. for 14 days - Treatment C: current HIV therapy including LPV/RTV 400/100 mg b.i.d. + TMC114 1200 mg b.i.d. + additional LPV/RTV 133.3/33.3 mg b.i.d. for 14 days - Treatment D: current HIV therapy without LPV/RTV + TMC114/RTV 1200/600 mg b.i.d. for 14 days

5.3.4 Human Pharmacokinetic Studies
Drug-Drug Interaction Studies

Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
[redacted]				

5.3.3 Human Pharmacokinetic Studies
Population Pharmacokinetics

Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
I - II	TMC114-C925 (Multinational)	Population PK - Empirical Bayes' estimation of pharmacokinetic parameters	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects 108 – 468	See individual trials TMC114-C129, TMC114-C137, TMC114-C138, TMC114-C154, TMC114-C156, – TMC114-C202, TMC114-C213.
I-II	TMC114-C927a	Population pharmacokinetic and covariate analysis of TMC114	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects 111 – 468	See individual trials TMC114-C129, TMC114-C137, TMC114-C138, TMC114-C154, TMC114-C156, – TMC114-C202, TMC114-C213.
I-II	TMC114-C927b	Emperical Bayesian feedback for trials TMC114-C202, TMC114-C213, and TMC114-C215	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects 702	See individual trials TMC114-C202, TMC114-C213, TMC114-C215.

5.3.4 Human Pharmacodynamic Studies				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
I	TMC114-C153 (France)	Open label, randomized, active controlled, placebo-controlled, 4-way crossover To evaluate ECG intervals in healthy volunteers receiving TMC114/RTV	Healthy volunteers 40	- TMC114/RTV, oral, 1600/100 mg q.d. for 7 days - TMC114/RTV, oral, 800/100 mg b.i.d. for 7 days - Moxifloxacine, oral, 400 mg q.d. for 7 days (control) - Placebo, oral, q.d. for 7 days
I - II	TMC114-C926 (Multinational)	Patient PK/PD study report	3-class-experienced, HIV-1 infected subjects 468	- Control: optimized background regimen, oral, 96 weeks - TMC114 /RTV: oral, 400/100 mg q.d., or , 800/100 mg q.d., or 400/100 mg b.i.d. or 600/100 mg b.i.d., for 96 weeks

5.3.5 Reports of Clinical Efficacy and Safety Studies Controlled Studies (Phase II)				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
IIa	TMC114-C201 (Austria, Germany, Great Britain, Italy, Poland, Russia, Switzerland)	Randomized, open-label, controlled, dose-finding trial To investigate the antiviral activity of TMC114 formulated as an oral solution in patients with multiple PI resistant strains (Proof-of-principle)	HIV-1 infected, PI-experienced subjects 34	- Control: remain on failing therapy - TMC114: oral, 400 mg b.i.d., or 800 mg b.i.d., or 800 mg t.i.d, or 1200 mg t.i.d., for 13 days followed by a single intake on Day 14
IIa	TMC114-C207 (Germany, Belgium, Italy, Poland, Great Britain, Austria, Switzerland)	Randomized, open-label, controlled, dose-finding trial To investigate the antiviral activity of TMC114 formulated as an oral solution co-administrated with a low dose of RTV in patients with multiple PI resistant strains (Proof-of-principle)	HIV-1 infected, PI-experienced subjects 50	- Control: remain on failing therapy - TMC114/RTV: oral, 300/100 mg b.i.d., or 600/100 mg b.i.d., or 900/100 mg q.d., for 13 days followed by a single intake on Day 14

5.3.5 Reports of Clinical Efficacy and Safety Studies Controlled Studies (Phase II)				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
IIb	TMC114-C202 (US, Argentina)	Two-part hybrid: randomized, controlled, partially-blinded Dose-finding study in 3-class experienced patients	3-class-experienced, HIV-1 infected subjects 278	- Control: optimized background regimen, oral, 96 weeks - TMC114 /RTV: oral, 400/100 mg q.d., or 800/100 mg q.d., or 400/100 mg b.i.d. or 600/100 mg b.i.d., for 96 weeks
IIb		Open label, controlled Long term efficacy and safety	319	- Control: optimized background regimen, oral, 96 weeks - TMC114 /RTV: oral, 600/100 mg b.i.d., for at least 96 weeks
IIb	TMC114-C213 (Australia, UK, Austria, Belgium, Brazil, Canada, France, Germany, Italy, Hungary, Switzerland, Spain, Portugal)	Randomized, controlled, partially-blinded Dose-finding study in 3-class experienced patients	3-class-experienced, HIV-1 infected subjects 318	- Control: optimized background regimen, oral, 96 weeks - TMC114 /RTV: oral, 400/100 mg q.d., or 800/100 mg q.d., or 400/100 mg b.i.d. or 600/100 mg b.i.d., for 96 weeks
IIb		Open label, controlled Long term efficacy and safety	318	- Control: optimized background regimen, oral, 96 weeks - TMC114 /RTV: oral, 600/100 mg b.i.d., for at least 96 weeks

5.3.5 Reports of Clinical Efficacy and Safety Studies Controlled Studies (Phase III)				
Study Phase	**Study (Country)**	**Design Study Objectives**	**Subjects N**	**Dosage Regimen Route of Administration Duration of Treatment**
III	TMC114-C211 (International, multicenter)	Randomized, controlled (LPV/RTV), open-label Primary objective: demonstrate non-inferiority with TMC114/RTV vs LPV/RTV in confirmed plasma viral load < 50 copies/mL	Treatment-naive HIV-1 infected subjects 660	- TMC114/RTV, oral, 800/100 mg q.d., for 96 weeks - LPV/RTV, oral, 800/200 mg q.d. or 400/100 mg b.i.d. (depending on approval of once-daily use of LPV/RTV), for 96 weeks + Fixed background of tenofovir/emtricitabin, oral, 300/200 mg q.d. for 96 weeks
III	TMC114-C214 (International, multicenter)	Randomized, controlled (LPV/RTV), open-label The primary objective: demonstrate non-inferiority with TMC114/RTV vs LPV/RTV in virologic response, defined as a confirmed plasma viral load < 400 copies/mL, at 48 weeks	Treatment-experienced (i.e., have been on a HAART regimen for at least 12 weeks) HIV-1 infected subjects 500	- TMC114/RTV, oral, 600/100 mg b.i.d. , for 96 weeks - LPV/RTV, oral, 400/100 mg b.i.d. (or 533/133 mg b.i.d. in case NNRTI is included in OBR), for 96 weeks + Optimized background regimen of at least 2 ARVs (NRTIs with or without NNRTIs)

5.3.5 Reports of Clinical Efficacy and Safety Studies Uncontrolled Studies (Phase II)				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
IIb	TMC114-C208 (International, multicenter)	Open-label trial For subjects who were randomized to TMC114-C201 or TMC114-C207 or from sponsor-selected Phase I trials and who may derive benefit from TMC114 therapy to assess long-term safety and tolerability	HIV-1 infected, PI-experienced subjects 29	- TMC114/RTV 400/100 mg b.i.d., oral, for 96 weeks After approval of the amendment to switch to the recommended dose, subjects will receive TMC114/RTV, oral, 600/100 mg b.i.d. + Optimized background regimen of at least 2 ARVs (NRTIs/NtRTIs, NNRTIs and/or enfuvirtide)
IIb	TMC114-C215 (Australia, UK, Austria, Belgium, Brazil, Canada, France, Germany, Italy, Hungary, Switzerland, Spain, Portugal, US, Argentina)	An open label 96-week trial of TMC114/RTV in HIV-1 infected subjects who failed trial treatment in the TMC114-C202 or TMC114-C213 trial and who may derive benefit from TMC114/RTV treatment, as judged by the investigator. In addition, to further evaluate the safety and efficacy of the recommended dose of TMC114/RTV, a total of 200 subjects who have not participated in the TMC114-C202 or TMC114-C213 trials were recruited.	3-class-experienced, HIV-1 infected subjects 431	- TMC114/RTV, oral, 400/100mg b.i.d., for 96 weeks After approval of amendment to switch to the recommended dose, subjects will receive TMC114/RTV, oral, 600/100 mg b.i.d. + Optimized background regimen of at least 2 ARVs (NRTIs with/without enfuvirtide)

5.3.5 Reports of Clinical Efficacy and Safety Studies Uncontrolled Studies (Phase III or Other)				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
III	TMC114-C209 (International, multicenter)	Open-label safety study to provide early access to TMC114 for highly ARV-experienced HIV-1 infected patients who have failed and exhausted treatment options based on commercially available ARVs.	Highly ARV-experienced HIV-1 infected subjects who have failed and exhausted treatment options based on commercially available ARVs = 250	- TMC114/RTV 600/100 mg b.i.d., oral Treatment will be continued until treatment limiting toxicity, lost to follow-up, withdrawal, pregnancy, discontinuation of TMC114 development or when TMC114 is commercially available to the patient.
NA	TMC114-C226 (International, multicenter)	Expanded Access Program To assess safety and tolerability of TMC114 in combination with low-dose RTV and other ARVs	TBD	- TMC114/RTV 600/100 mg b.i.d., oral Treatment will be continued until treatment limiting toxicity, lost to follow-up, withdrawal, pregnancy, discontinuation of TMC114 development or when TMC114 is commercially available to the patient.

5.3.5 Reports of Clinical Efficacy and Safety Studies Analyses of Data From More Than one Study				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
	TMC114-C908 (International, multicenter)	Pooled Week-16 interim analysis of all efficacy and safety information of TMC114-C202 and TMC114-C213: up to 26 July 2004 + Pooled Week-24 interim analysis of all efficacy and safety information of TMC114-C202 and TMC114-C213: up to 18 September 2004	3-class-experienced, HIV-1 infected subjects 353 (+ 89 control) + 397 (+ 100 control)	- Control: optimized background regimen, oral investigator selected PI, long term; - TMC114 /RTV: optimized background regimen, oral TMC114/RTV 400/100 mg q.d., or 800/100 mg q.d., or 400/100 mg b.i.d., or 600/100 mg b.i.d. until the subjects switched to 600/100 mg b.i.d.

5.3.5 Reports of Clinical Efficacy and Safety Studies Analyses of Data From More Than one Study				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
	TMC114-C910 (International, multicenter)	Safety pooling TMC114 Phase I trials + Pooled safety analysis of all safety information of TMC114-C202 and TMC114-C213 up to the actual dose switch to TMC114/RTV 600/100 mg b.i.d. + Pooled safety data of TMC114/RTV 600/100 mg b.i.d. of TMC114-C202 – TMC114-C213 + TMC114-C215 – TMC114-C208 + Pooled safety data of any dose of TMC114/RTV of TMC114-C202 + TMC114-C213 + TMC114-C215 + TMC114-C208 at any dose.	Healthy volunteers 566 + 3-class-experienced, HIV-1 infected subjects 637 + 810 (– 124 control) + 924 (– 124 control)	- Phase I: Various - Phase IIb controlled (TMC114-C202 + TMC114-C213): - Control: optimized background regimen, oral investigator selected PI, long term - TMC114 /RTV: optimized background regimen, oral TMC114/RTV 400/100 mg q.d., or 800/100 mg q.d., or 400/100 mg b.i.d., or 600/100 mg b.i.d. until the subjects switched to 600/100 mg b.i.d.; After 1 February 2005, subjects switched to 600/100 mg b.i.d. in the open-label part of the trials, long term. - Phase II open-label (TMC114-C202 – TMC114-C213: after switching to the recommended dose of 600/100 mg b.i.d. + TMC114-C215 – TMC114-C208): - Control (TMC114-C202 – TMC114-C213 only): optimized background regimen, oral investigator selected PI, long term - TMC114 /RTV (TMC114-C202 + TMC114-C213 + TMC114-C215 + TMC114-C208): optimized background regimen, oral TMC114/RTV 600/100 mg b.i.d., long term (Note: in trials TMC114-C215 + TMC114-C208 could have started on TMC114/RTV 400/100 mg b.i.d. before they received 600/100 mg b.i.d.)

5.3.5 Reports of Clinical Efficacy and Safety Studies Analyses of Data From More Than one Study				
Study Phase	Study (Country)	Design Study Objectives	Subjects N	Dosage Regimen Route of Administration Duration of Treatment
IIb	TMC114-C911 (International, multicenter)	Pooled efficacy analysis, of all efficacy information gathered up to 1 February, 2005 of both TMC114-C202 and TMC114-C213 trials + Long-term efficacy pooling of TMC114-C202 and TMC114-C213 (up to 72 weeks of treatment) + Efficacy pooling of TMC114-C202 + TMC114-C213 + TMC114-C215 + TMC114-C208 for virology and certain subgroup analyses	3-class-experienced, HIV-1 infected subjects 596 – 637 – 924 (+ 124 control)	- Phase IIb controlled (TMC114-C202 + TMC114-C213): - Control: optimized background regimen, oral investigator selected PI, long term - TMC114 /RTV: optimized background regimen, oral TMC114/RTV 400/100 mg q.d., or 800/100 mg q.d., or 400/100 mg b.i.d., or 600/100 mg b.i.d. until 1 February 2005; After 1 February 2005, subjects switched to 600/100 mg b.i.d. in the open-label part of the trials, long term - Phase II open-label (TMC114-C202 – TMC114-C213: after switching to the recommended dose of 600/100 mg b.i.d. + TMC114-C215 – TMC114-C208): - Control (TMC114-C202 – TMC114-C213 only): optimized background regimen, oral investigator selected PI, long term - TMC114 /RTV (TMC114-C202 – TMC114-C213 – TMC114-C215 + TMC114-C208): optimized background regimen, oral TMC114/RTV 600/100 mg b.i.d., long term (Note: in trials TMC114-C215 + TMC114-C208 could have started on TMC114/RTV 400/100 mg b.i.d. before they received 600/100 mg b.i.d.)

5.3.5 Reports of Clinical Efficacy and Safety Studies Other Study Reports	
Study	**Study Title**
TMC114-20040003	Exploratory analyses of genotypic changes observed in trial TMC114-C207
TMC114-20040004	Exploratory analyses of genotypic changes observed in trial TMC114-C201
TMC114-20050002	Antiviral activity of TMC114 against a panel of protease inhibitors and multidrug resistant HIV-1 primary isolates in human peripheral blood mononuclear cells
TMC114-20050003	Inhibition of the activity of human proteases by TMC114: part 1
TMC114-20050004	Inhibition of the activity of human proteases by TMC114: part 2
TMC114-20050005	Drug susceptibility profile of TMC114 against a large panel of HIV-1 quasispecies observed in clinical isolates
TMC114-20050006	Antiviral activity of TMC114 in combination with currently approved HIV-1 inhibitors
TMC114-20050007	Characterization of the interaction between TMC114 and wild type HIV-1 protease: Determination of association and dissociation constants

5.3.5 Reports of Clinical Efficacy and Safety Studies Other Study Reports	
Study	**Study Title**
TMC114-20050008	Antiviral activity of TMC114 at different multiplicities of infection
TMC114-20050009	Influence of the time of addition on the activity of TMC114 and determination of TMC114 HIV-1 protease inhibitory constant (K_i)
TMC114-20050010	Anti-HIV-1 activity of TMC114 in the presence of human serum proteins
TMC114-20050011	Antiviral activity of TMC114 against HIV-1 primary isolates from group M and O in human PBMCs
TMC114-20050012	In vitro selection of resistant HIV-1 starting from wildtype HIV-1 isolates, in the presence of TMC114, currently approved protease inhibitors, and tipranavir
TMC114-20050013	In vitro selection of resistant HIV-1 starting from HIV-1 isolates containing mutations associated with resistance to protease inhibitors in the presence of TMC114
TMC114-20050014	Antiviral activity of TMC114 against wild type HIV-1 and HIV-2, and SIV in T cell lines, peripheral blood mononuclear cells and monocytes/macrophages
TMC114-20050016	In vitro cytotoxicity of TMC114 in different cells of human origin

5.3.5 Reports of Clinical Efficacy and Safety Studies Other Study Reports	
Study	**Study Title**
TMC114-20050017	Antiviral activity of TMC114 against a screening panel of HIV-1 recombinant clinical isolates with various degrees of resistance to protease inhibitors
TMC114-20050019	Antiviral Activity of TMC114 on HIV-1/HXB2 harboring site directed mutations in the protease gene as of May 2005
TMC114-20050020	Exploratory analyses of genotypic changes in virologic failures observed in clinical trial TMC114-C202
TMC114-20050021	Exploratory analyses of genotypic changes in virologic failures observed in clinical trial TMC114-C213

4.3 Review Strategy

The Lead Clinical Reviewer, Neville A Gibbs MD, MPH was responsible for the overall clinical review process, for writing an overview of the review, the executive summary, the review of the pivotal/ registrational trials, plus the review of the integrated review of efficacy and the integrated review of safety. This clinical reviewer was supported by Anitra Denson M.D. who reviewed the Phase I supportive trials in healthy volunteers, the single and multiple dose bioavailability and other pharmacokinetic studies, the drug interaction studies, and the pharmacodynamic studies.

This efficacy and safety review was primarily based on the analysis of 24 week efficacy data and all available safety data up to the date of data lock from the two pivotal/ registrational studies, TMC114-C202 and TMC114-C213, and its associated roll-over trials TMC114-C215 and TMC114-C208. Given that the proof of darunavir efficacy was derived from 2 trials where the numbers of subjects exposed to the proposed dose was limited, the Division suggested that the sponsor enroll an additional 300 subjects in order to expand the safety database.

Additionally, SAE reports from the Phase III Trials TMC114-C214 in treatment-experienced subjects, and TMC114-C211 in treatment-naïve subjects also contributed to the safety review.

A joint review was carried out by various reviewers in other disciplines, including Statistics review (Dr Thomas Hammerstrom), who performed most of the efficacy review, Clinical Pharmacology, (Dr Vikram Arya), Dr Christine Barnett (Pharmacometrics), Dr Lisa Naeger (Microbiology), Dr James Farrelly (Pharmacology), and Dr K Rao (Chemistry).

The efficacy and safety conclusions presented in this review are based on all of the applicable data compiled from the different reviewers and studies.

4.4 Data Quality and Integrity

DAVP consulted the Division of Scientific Investigations (DSI) to inspect a sample of four U.S. sites. Selection of the USA-based study sites for inspection were selected based on the study sites with the largest number of study trial participants. The inspection of the sites of Drs Berger, Wilkin, Pierone and Steinhart did not identify any significant observations that would compromise the integrity of the data. The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. Overall the data appeared acceptable in support of the pending application.

4.5 Compliance with Good Clinical Practices

The darunavir trials were designed, conducted, performed, monitored, and analyzed according to Good Clinical Practice (GCP) and Accepted Ethical Standards. Informed Consent forms were adequate and accurately conveyed what is known about the product to the study participants and investigators. Protocol violations were few, and occurred in less than <2% of cases.
The trials were conducted in accordance with acceptable ethical standards

4.6 Financial Disclosures

In accordance with 21 CFR 54.2 (a), (b), (c), and (f), a large majority of the Clinical Investigators did not hold any disclosable financial arrangements with Johnson & Johnson, the parent company of the Sponsor Tibotec Inc.
Analysis of the financial disclosures of the investigators or the co-investigators did not cast any doubt on the integrity of the data or the inferential findings of the Trials.

5 CLINICAL PHARMACOLOGY

Please refer to Dr. Vikram Arya's Clinical Pharmacology and Biopharmaceutics review for a detailed analysis of the pharmacokinetics (PK), pharmacodynamics (PD) and exposure-response relationship of DRV/rtv. A summary of the important PK, PD and exposure-response issues raised in Dr. Arya's review are presented below.

5.1 Pharmacokinetics

The pharmacokinetics (PK) of darunavir co-administered with low-dose rtv has been evaluated in healthy adult volunteers and in HIV-1 infected subjects. DRV is primarily metabolised by CYP3A. RTV inhibits CYP3A, thereby increasing the plasma concentration of DRV.
Low-dose RTV increases DRV exposure; Food enhances bioavailability of the tablet formulation of DRV co-administered with rtv by approximately 30%. DRV co-administered with 100 mg rtv bid was absorbed following oral administration with a T_{max} of approximately 2.5-4 hours. DRV co-administered with rtv should always be taken with food.
DRV is approximately 95% bound to plasma proteins, and binds primarily to plasma alpha 1-acid glycoprotein (AAG). The elimination half-life of DRV was approximately 15 hours when combined with rtv. A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg rtv, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively.

The mass balance of ^{14}C-DRV/rtv showed that approximately 7.7% of the administered dose of DRV was excreted in the urine as unchanged drug. There are no PK data available in HIV-1 infected patients with severe renal impairment or end stage renal disease.

PK is dose proportional for daily dosing and less than dose-proportional for bid regimens.
Interaction profile appears to be similar to other RTV-boosted PI's.
The primary 24-week analysis of the data from Study TMC114-C213 in 31 HIV-1 infected patients indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

5.2 Pharmacodynamics

Significant relationship was observed between higher exposure and greater response to DRV. Fold change (FC) at baseline was a stronger prognostic factor than exposure. IQ was the strongest predictor of response. There was no apparent relationship between exposure and safety/tolerability.

5.3 Exposure-Response Relationships

A full exposure-response analysis as it relates to efficacy and safety was performed by Pharmacometrician Dr Christine Garnett. Please refer to Pharmacometric report for full details.

The exposure-response analysis of the combined phase 2b trials TMC114-C202 and TMC114-C213, demonstrated that the probability of having a response to darunavir treatment (measured either by 1 log reduction in viral load or HIV-1 RNA <50 copies/ml) by week 24 is related to the patient's darunavir inhibitory quotient. The inhibitory quotient (IQ) is the ratio between steady-state trough concentration and the baseline IC50 value. Larger IQ values are correlated with a higher response rates using logistic regression analysis.

FIGURE 5.3 A: SHOWING LOG REDUCTION IN VL , WITH INHIBITORY QUOTIENT (IQ) PLOTTED AGAINST THE PROBABILITY OF BEING A RESPONDER

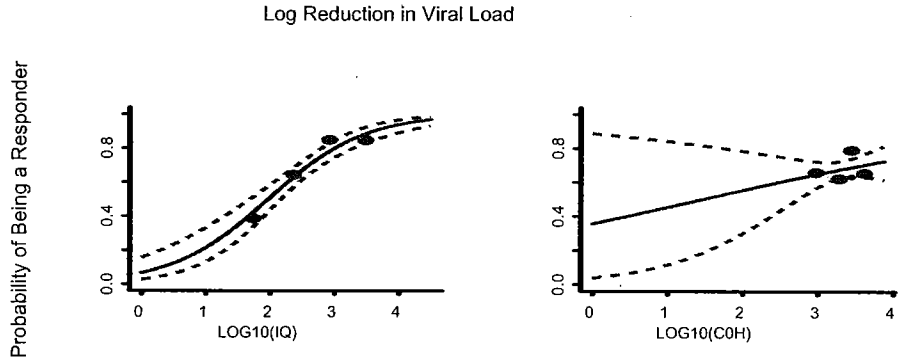
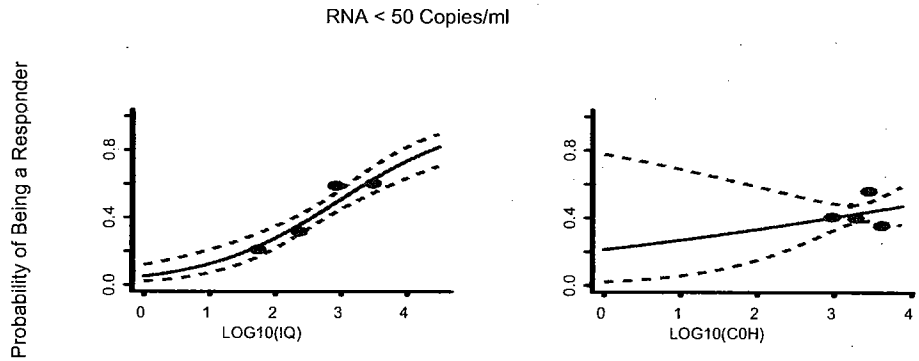
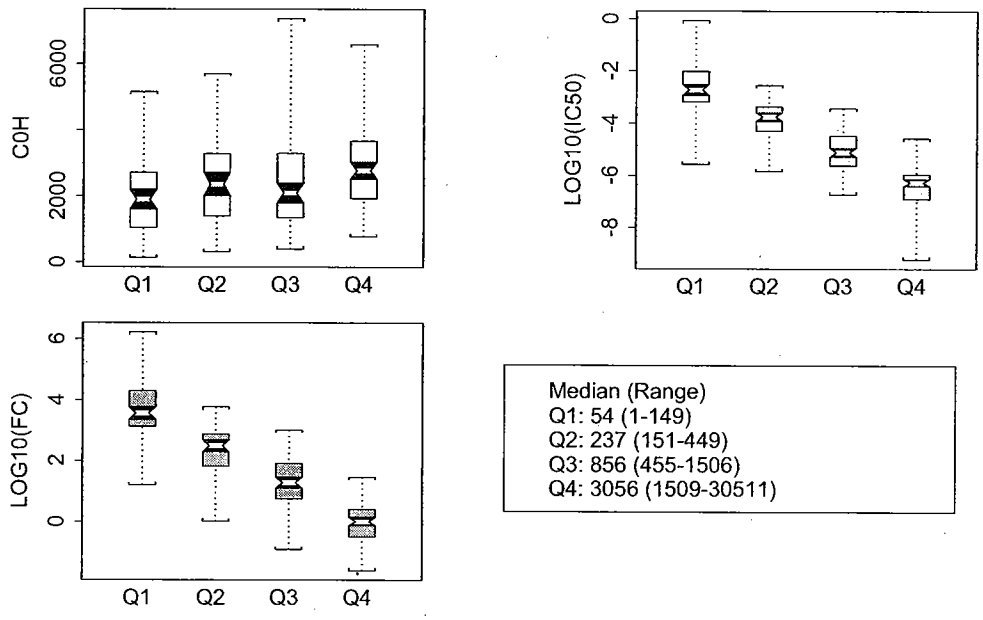


FIGURE 5.3 B: SHOWING HIV-RNA LEVELS(measured as subjects with undetectable VL below 50 copies /ml) PLOTTED AGAINST WITH INHIBITORY QUOTIENT (IQ)



Source: Courtesy of FDA's Pharmacometrician- Dr Christine Garnett

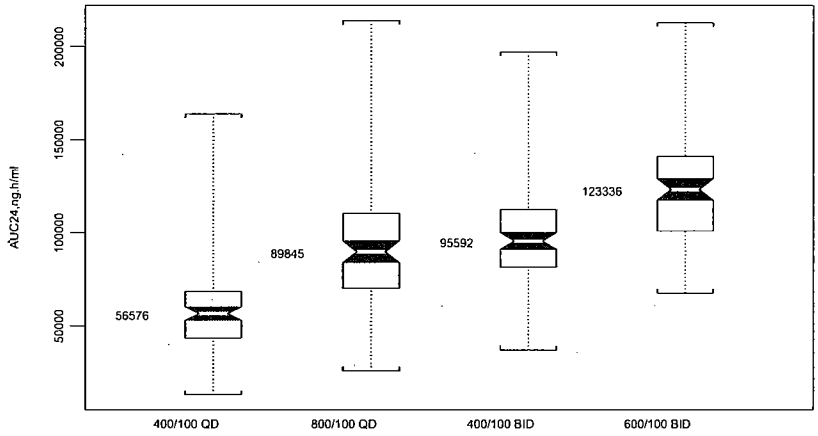
The figure below summarizes darunavir exposure, IC50, and fold-change values by darunavir IQ quartile. As illustrated, patients with the lowest IQ values in Q1 (and lowest response rate) have the highest IC50 values (increase in resistance). Fold-change (FC) is a measure of the fold-increase in the IC50 value relative to a standard IC50 value for a wild-type HIV-1 virus with no mutations. Patients with the lowest response rate have the highest darunavir FC at baseline.



Source: Courtesy of Christine Garnett, PhD

Exposure to darunavir does not increase proportionally to increasing doses of darunavir/rtv, as demonstrated by AUC 24 hours with increasing doses of DRV/rtv, and the non-proportional increase in 24 hour AUC exposure with 400/100 mg bid and 600/100 mg bid dose of darunavir/rtv. .

FIGURE 5.3.C SHOWING AUC 24 HOURS PLOTTED AGAINST DOSE COHORT OF DRV/rtv

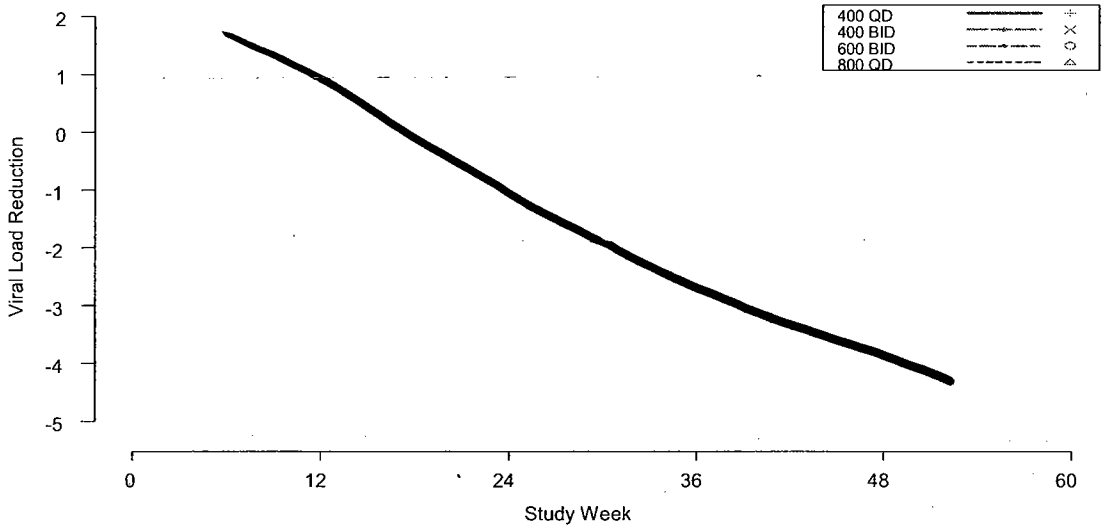


Courtesy of Christine Garnett, PhD - (Pharmacometrics Reviewer)

The recommended oral dose of darunavir/rtv 600/100 mg bid dose is consistent with the known exposure-response and exposure-toxicity relationships. The highest IQ values were observed in the 600/100 mg dose group and there are no additional toxicities observed with higher exposure to darunavir.

FIGURE 5.3.D (shown below) demonstrates dose-dependent reduction in viral load (VL) . Points are observed for individual subject . The figure shows that the 600/100 mg bid dose reduces the VL more than the other dose regimens.

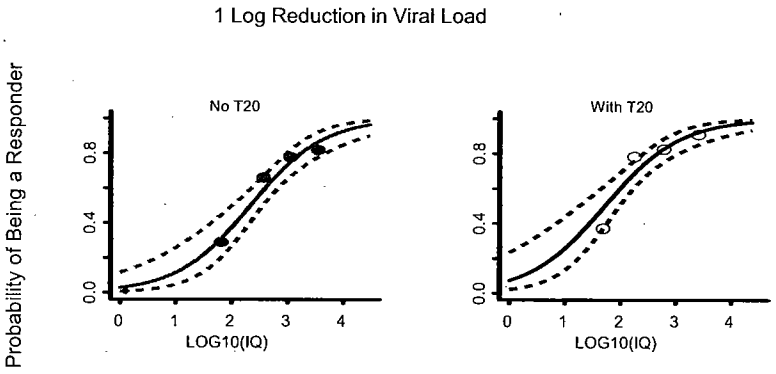
FIGURE 5.3.D: SHOWING VIRAL LOAD REDUCTION BY DOSE GROUP OVER TIME



Source : Courtesy of Pharmacometrics Reviewer- Dr Christine Garnett.

FIGURE 5.3.E : SHOWING THE VIRAL RESPONSE AT WEEK 24 VERSUS IQ, STRATIFIED BY CONCOMITANT USE OF ENFUVIRTIDE (T20)

The curve on the left shows viral response at Week 24 and the probability of being a responder (as measured by a 1 log reduction in VL) when enfurvitide is ***not*** used as part of the OBR. The curve on the right shows the viral response (or the likelihood of being a responder) when enfurvitide is used as part of the OBR. Please note that the curve on the right(with T20) is steeper than that on the left (without T20). This means that the probability of being a responder is greater when DRV/rtv is used in combination enfurvitide. Source



Source : Courtesy of Pharmacometrics Reviewer- Dr Christine Garnett

Appears This Way On Original

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Approval for the following indication is being sought by the sponsor:
"Darunavir (DRV/TMC114), in combination with 100 mg ritonavir (rtv) and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients in combination with 100 mg ritonavir (RTV) and with other antiretroviral agents".

This indication is based on Week 24 analyses of plasma HIV RNA levels and CD4+ cell counts from 2 controlled trials comparing DRV/rtv with a protease inhibitor regimen of choice, each given in combination with other antiretroviral drugs. Additional data is available from open label studies.

6.1.1 Methods

Week 24 interim efficacy data for the two Phase IIb pivotal trials, TMC114-C202 (POWER 1) and TMC114-C213 (POWER 2) were reviewed in support of the proposed indication that darunavir, in combination with 100 mg rtv bid is effective in the treatment of HIV-1 infection in treatment-experienced subjects.

6.1.2 General Discussion of Endpoints

Primary Efficacy endpoint
Viral load and CD4+ cell count are accepted as surrogate markers for efficacy in trials with ARV agents. In heavily treatment-experienced subjects with significant class cross-resistance, the scarcity of available therapeutic options makes it difficult to achieve a goal of complete and sustained suppression of viral replication. Therefore, a less stringent goal, and one more clinically relevant and feasible, has previously been used for such a population. Thus, the amended primary endpoint selected for trials TMC114-C202 and TMC114-C213 was confirmed virologic response at Week 24, defined as a decrease in viral load of ≥ 1.0 $\log_{10}$ copies/mL versus baseline, without (1) introduction of any ARV not originally foreseen in the trial regimen, or (2) discontinuation from the trial. [According to the TLOVR algorithm given in the Food & Drug Administration (FDA) guidance for industry].

Secondary Efficacy endpoints were also measured and included the following:

1) Full suppression defined as viral load < 50 copies/mL, and < 400 copies/mL respectively
2) Change in $\log_{10}$ viral load, and
3) Effects on CD4+ cell count

6.1.3 Study Design

TMC114-C202 and TMC114-C213 were randomized, controlled, Phase 2b trials consisting of 2 phases: an initial partially-blinded, dose-finding phase and a second long-term phase in which all patients randomized to darunavir/rtv received the recommended dose of 600/100 mg bid. The initial dose-finding part was a five-arm, parallel track, multi-center trial, conducted in North America, Argentina, and Europe. Subjects were randomly assigned in a 1:1:1:1:1 ratio to control of DRV/rtv at 400/100 mg qd, 800/100 mg qd, 400/100 mg bid, or 600/100 mg bid. Investigators selected a control PI and an OBR (with or without enfuvirtide) prior to randomization. The control PI or one of the four DRV/r doses was then chosen by the randomization. Both trials were partially blinded: subjects knew whether they were receiving control, one of the two DRV qd arms, or one of the two DRV bid arms.

Both trials treated the DRV arms differently from the control arm for the first two weeks. In the four DRV arms, patients had a two-week functional monotherapy in which they changed PI to DRV/r, added enfuvirtide if that was part of the new OBR, and kept their NRTI's the same. After 2 weeks, the NRTI's from the new OBR were begun. In the control arm, both the PI and the NRTI's of the new OBR were started immediately after randomization. If this difference in procedure had any effect on the final response, it should make the DRV arms perform worse by increasing the risk of early resistance mutations.

Because of their prior ART experience, not all subjects had a PI to which their virus was susceptible. Therefore, subjects were declared early failures if they failed to show at least a 0.5 log decrease in HIV-1 RNA by Week 12. Early failures were allowed to roll over to a non-randomized TMC114 trial. Failure was defined as a confirmed $\leq$0.5 log drop in VL measured first at 12 weeks, with virological confirmation at Week 16.

***MO COMMENT**: A similar definition of virological failure was used in the enfurvitide trials, a submission which also enrolled a population with advanced disease for whom the open-label control for some subjects might be expected in advance to be ineffective.*

Dynamic allocation was used to improve balance among the five arms on baseline HIV-RNA level, use of enfuvirtide or not, and number of primary PI mutations.

There were protocol specified interim analyses in each trial when 150 patients had reached their week 16 endpoint and a second analysis scheduled for when 200 patients in trial TMC114-C202 and 300 patients in trial TMC114-C213 had reached their endpoint. After discussions with the FDA, the protocol was amended so that results from the interim analyses were kept secret from the patients until Feb. 1, 2005, at which point all TMC114 randomized subjects were switched to the best performing DRV dose while controls continued on their assigned regimens. Both arms were followed until at least Week 48.

The approach to the analyses of efficacy was as follows:

1) Efficacy population #1 TMC114-C202 and TMC114-C213- Controlled data @ 24 weeks: Individual and pooled results across trials of the controlled long-term trials TMC114-C202 and TMC114-C213 are presented. Since the TMC114-C202 and TMC114-C213 trials are still ongoing, data presented in this section was derived from the primary Week 24 efficacy analyses, performed with a cut-off date of February 1st 2005. To avoid the inclusion of subjects with limited exposure in these analyses, only subjects with a minimum of 1 month of treatment; i.e. only subjects who started their treatment before 01 January 2005, were included. This part focuses on the results up to Week 24.

2) Efficacy population #2 – (Additional Data at the recommended dose)
The additional data at the recommended dose of DRV/RTV 600/100 mg bid are presented: TMC114-C202 and TMC114-C213 trials after the switch to the recommended dose (including the period between 01 February 2005 and the actual moment of the switch) until the cut-off date of 24 September 2005, showing data up to Week 48 and data for some subjects up to Week 72 from the individual studies and pooled, and TMC114-C215 and TMC114-C208 trials up to 24 September 2005. These data were pooled due to the small number of subjects in the TMC114-C208 trial and the similar study designs of the 2 studies.

Description of Clinical Studies

HIV-1 infected patients who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L/S/T, I84A/C/V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide. This analysis included 318 patients in TMC114-C202 and 319 patients in TMC114-C213 who had completed 24 weeks of treatment or discontinued earlier.

At 24 weeks, the virologic response rate was evaluated in patients receiving darunavir/rtv plus an optimized background regimen (OBR) versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Based on resistance testing and prior medical history, selected PI's in the control arm included: lopinavir/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 23% of the control patients used dual-boosted PIs. Approximately 47% of all patients used enfuvirtide, and 35% of the use was in patients who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline.

Additional data on the efficacy of darunavir/rtv 600/100 mg bid have been obtained in treatment-experienced patients participating in the non-randomized trials TMC114-C215 and TMC114-C208. The 246 patients from these trials included in the 24 week POWER 3 efficacy analysis initiated therapy with darunavir/rtv with the recommended dose of 600/100 mg bid. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for POWER 3 were the same as those for POWER 1 and POWER 2.

In the pooled analysis for POWER 1 and POWER 2, demographics and baseline characteristics were balanced between the darunavir/rtv arm and the comparator PI arm. The 131 patients in the darunavir/rtv 600/100 mg bid arm had a median age of 43.0 years (range 27-73), 89% were male, 81% White, 10% Black, and 7% Hispanic. The median baseline plasma HIV-1 RNA was 4.52 $\log_{10}$ copies/mL (range: 3.0 to 6.4 $\log_{10}$ copies/mL), and the median

baseline CD4+ cell count was 153 x 10^6 cells/L (range: 3 x 10^6 to 776 x 10^6 cells/L). 24.4% of patients had a baseline viral load > 100,000 copies/mL and 67% of patients had a baseline CD4+ cell count < 200 x10^6 cells/L. The median darunavir FC was 4.3.

Trial TMC114-C215/C208's baseline characteristics of patients included in the POWER 3 analysis were comparable to those of patients in TMC114-C202 and TMC114-C213. The median baseline plasma HIV-1 RNA was 4.60 $\log_{10}$ copies/mL (range: 1.69 to 6.43 $\log_{10}$ copies/mL), and the median CD4+ cell count was 115 x 10^6 cells/L (range: 0 x 10^6 to 831 x 10^6 cells/L). The median darunavir FC was 3.2.

Baseline characteristics are based on the total of 327 patients included in TMC114-C215 and TMC114-C208, whereas efficacy data are based on the available interim data from 246 patients who had reached 24 weeks of treatment or discontinued earlier than the 24-week cut-off of the POWER 3 analysis.

The two major differences between the trials were that TMC114-C202 was conducted in the United States and Argentina, while TMC114-C213 was conducted in Europe, Brazil, Canada and Australia. Additionally, TMC114-C213 and TMC114-C215/C208 enrolled subjects who were co-infected with hepatitis B and C , while TMC114-C202 did not enroll subjects with Hepatitis B and C.

MO COMMENT: PARTIAL BLINDING; "ESCAPE CLAUSE" for VIROLOGICAL FAILURE; 24 WEEK DURATION FOR ACCELERATED APPROVAL; EXTERNAL VALIDITY OF STUDY FINDINGS AND POOLING.

The randomized controlled trial design has the greatest probability of reducing bias. This partially blinded design, was the best design that the sponsor was able to provide, as it was impossible for the sponsor to blind the subject to the use of ritonavir capsules . The randomization feature in the design, the appointment of an endpoint committee, the prospective identification of an acceptable primary endpoint, the multiple secondary endpoints and the prospective statistical analysis plan helped to preserve the inferential integrity of the study, and helped in the minimization of the bias.

Both trials were partially blinded, in that subjects knew whether they were receiving control, one of the two darunavir qd arms, or one of the two darunavir bid arms. Because the control subjects knew that they were assigned to a likely inferior arm, they would have had incentives to quit early. The applicant attempted to minimize this problem by allowing for early exit of control subjects. If they reached 12 weeks without at least a one half log drop in HIV RNA, they were allowed to switch to DRV in a non-randomized roll-over study.

Similar criteria for early identification of treatment failures has been used in previous NDAs. (Fuzeon NDA 21481)

Subjects who were failing their ARV regimen and who were in need of a switch of therapy, essentially constituted the standard of care and the comparator arm. This design feature that provided a "bail-out" feature or an "escape clause", where subjects who were experiencing confirmed virologic failure and who were assigned to the control arm, were allowed to leave the study and have the opportunity to receive the study drug made this study ethically acceptable.

This active control design reduced the ethical concern that arises from failure to use drugs with documented health benefit.

The 24 week duration of observation for efficacy is considered adequate, and is standard in this Regulatory Division of the Agency for the accelerated approval of ARV drugs that are used for the treatment of HIV-1 infections in HIV-1 infected individuals.

The baseline characteristics of the study population in the POWER trials were similar to those in most trials in highly treatment- experienced HIV-1 infected population and are largely representative of the persons with the disease, except for the large proportion of white male subjects , and the relative under-representation of black males and females with the disease in the external (non-clinical trial) environment. Undoubtedly, however, despite the partially blinded design feature, the efficacy conclusions remain valid in that darunavir/rtv was superior compared to control.

The pooling of trials TMC114-C202 and TMC114-C213 was considered valid because all subjects were treatment- experienced HIV-1-infected subjects with limited or no treatment options of likely clinical benefit; All subjects received the same dose of DRV/RTV(recommended dose) from initial randomization; trials were performed at the same centers; all trials had a similar design in terms of inclusion/exclusion criteria(except that Trial TMC114-C202 was not allowed to enroll subjects who were co-infected with Hepatitis B and Hepatitis C ; baseline characteristics were grossly similar in all trials; and efficacy was similar in both trials.

6.1.4 Efficacy Findings

The evidence of efficacy of darunavir/rtv is based on the analyses of 24-week data from 2 ongoing, randomized, controlled trials in ARV treatment-experienced HIV-1 infected adult patients TMC114-C202 and TMC114-C213. These efficacy results were supported by the 24-week pooled analysis of the open-label non-randomized trials TMC114-C215 and TMC114-C208 analysis of patients who were initiated at the recommended 600/100 mg dose of DRV/rtv.

TABLE 6.1.4.1.A : SHOWING THE BASELINE CHARACTERISTICS OF STUDY SUBJECTS IN TMC114-C202 and TMC114-C213

Characteristics	**TMC114-C202**	**TMC114-C213**
% male	91%	86%
Mean age	45 years	44 years
Race		
Hispanic	*14%*	*4%*
White	*64%*	*81%*
Black	*19%*	*11%*
Median CD4 count	106 cells	179 cells
Mean HIV RNA	4.66 logs	4.48 logs
Duration of HIV	13 years	12 years
Prior ARV Experience		
Duration	114 months	112 months

>/= 2 PI's	98%	96%
>/= 4 NRTI's	95%	96%
>/= 1 NNRTI	97%	95%
ENF	14%	8%

TABLE 6.1.4.1.B: SHOWING THE OPTIMIZED BACKGROUND REGIMEN IN SUBJECTS IN TMC114-C202 and TMC114-C213

	TMC114-C202	**TMC114-C213**
Susceptible to		
>/= 1NRTI	66%	79%
>/= PI	8%	28%
ENF use		
Naïve	*38%*	*35%*
Continuing	*14%*	*8%*
Non user	48%	57%

MO COMMENTS: BASELINE CHARACTERISTICS*- The baseline variables and characteristics were in balance, although the subjects in TMC114-C213 were less advanced than the trial subjects in TMC114-C202, as demonstrated by the higher mean CD4 counts, the lower mean HIV RNA, and the minimally shorter duration of exposure to ARV agents.*

RESULTS OF PRIMARY EFFICACY END-POINT ANALYSIS

TABLE 6.1.4.1.C and TABLE 6.1.4.1.D noted below shows the results of the primary efficacy end-point analysis in Trials C202 and C213. The results show that the 600/100 mg bid dose achieved a 62% 1 log drop in VL compared to baseline versus 14 % in control in TMC114-C202 while TMC114-C213 achieved 82% versus 14 % drop in VL from baseline.

MO COMMENT: *The difference in the primary end point analysis between the two studies is likely a function of the baseline differences between the two studies with subjects in Trial TMC114-C213 being less advanced than the study population of TMC114-C202.*

TABLE 6.1.4.1.C SHOWING PERCENT OF SUBJECTS WITH PERCENT 1 LOG DROP IN VIRAL LOAD (VL) BELOW BASELINE AT WEEK 24 IN ALL DOSE ARMS OF TRIAL **TMC114-C202**

DRV/RTV ARM	% SUCCESSFUL	FITTED	95% INTERVAL	P-VALUE TO CONTROL
400/100 QD	17/40= 43%	45%	29-61%	<0.001
800/100 QD	19/41 =46%	48%	32-64%	<0.001
400/100 BID	20/39 = 51%	53%	36-69%	<0.001
600/100 BID	24/39 =62%	62%	45-76%	<0.001
CONTROL	6/42 = 14%	13%	6-28%	

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

TABLE 6.1.4.1.D SHOWING PERCENT OF SUBJECTS WITH PERCENT 1 LOG DROP BELOW BASELINE AT WEEK 24 IN ALL DOSE ARMS IN TRIAL **TMC114-C213**

DRV/RTV ARM	% SUCCESSFUL	FITTED	95% INTERVAL	P-VALUE TO CONTROL
400/100 QD	41/60= 68%	76%	63-85%	<0.001
800/100 QD	40/60 = 67%	78%	65-87 %	<0.001
400/100 BID	41/61 = 67%	73%	59-83 %	<0.001
600/100 BID	45/60 =75%	82%	71-90 %	<0.001
CONTROL	15/60 = 25%	24%	15-38%	

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

MO COMMENTS- DESIGN AND CONDUCT OF TRIALS

Additionally, the inferences from the multiple secondary endpoints analysis were in-line with each other and also in-line with the primary efficacy endpoint; In fact, in the dose-finding portion of TMC114-C202 and TMC114-C213, all doses of DRV/rtv were efficacious, even the doses of study drug that were below the proposed dose.

The FDA Statistical reviewer performed sensitivity analyses to explore potential of open label biases by reclassifying failures on the control arm as successes if they met either of two criteria: Firstly, they left the trial prior to their 12 weeks visit and thus did not meet the early exit criterion. Secondly, they left the trial between their 12 and 24 week visits, and that they had achieved at a one half log drop by week 12, and did not have a confirmed rebound from below baseline. One can see that only 7 control subjects in trial TMC114-C202 were changed in this revised analysis and that even with Bonferroni and O'Brien-Fleming adjustments for multiple arms and interim analyses, the conclusion of darunavir efficacy were confirmed.

The handling of drop-outs were appropriate. All drop outs were treated as failures.

No unplanned subset post hoc analyses were performed.

RESULTS OF ANALYSIS OF **SECONDARY EFFICACY END POINTS**

Tables 6.1.4 .1 E and F show results with percent of subjects with HIV RNA sustained below 400 or 50 copies/ml for all four DRV arms compared to control in both arms. Again, all dose arms of DRV/rtv were shown to be consistently statistically significantly more effective than control. The finding of DRV efficacy is not dependent on choosing a less commonly used endpoint.

TABLES 6.1.4.1 E SHOWING THE PERCENT OF TRIAL SUBJECTS **<400 copies/mL** @ WEEK 24

Covariate	**Mean Diff**	**Lower 95% Limit**	**Upper 95% Limit**	**DRV/rtv**	**Control**	**P-value**
TRIAL TMC114-C202						
400/100 qd	27.0%	12.7%	41.3%	25/65=38%	7/61=11%	0.0001
800/100 qd	29.1%	14.7%	43.6%	26/64=41%	7/61=11%	<0.0001
400/100 bid	40.9%	26.2%	55.6%	33/63=52%	7/61=11%	<0.0001
600/100 bid	44.6%	30.2%	59.0%	37/66=56%	7/61=11%	<0.0001 *
TRIAL TMC114-C213						
400/100 qd	38.7%	22.8%	54.5%	40/64=63%	15/63=24%	<0.0001
800/100 qd	38.1%	22.1%	54.0%	39/63=62%	15/63=24%	<0.0001
400/100 bid	44.4%	28.9%	60.0%	43/63=68%	15/63=24%	<0.0001
600/100 bid	45.4%	30.0%	60.8%	45/65=69%	15/63=24%	<0.0001 *

* TMC/114/RTV 600/100 mg bid - to be marketed dose

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

TABLE 6.1.4 .1 F SHOWING THE PERCENT OF SUBJECTS **<50 COPIES/mL** @ WEEK 24 IN TRIALS TMC114-C202 and TMC114-C213

Covariate	Mean Diff	Lower 95% limits	Upper 95% limits	DRV/rtv	Control	p-value
TRIAL TMC114-C202						
400/100 qd	18.1%	5.9%	30.2%	16/65=25%	4/61=7%	0.0008
800/100 qd	18.4%	6.1%	30.7%	16/64=25%	4/61=7%	0.0092
400/100 bid	30.0%	16.5%	43.4%	23/63=37%	4/61=7%	<0.0001
600/100 bid	29.8%	16.6%	43.0%	24/66=36%	4/61=7%	<0.0001 *
TRIAL TMC114-C213						
400/100 qd	26.3%	11.2%	41.4%	27/64=42%	10/63=16%	0.0008
800/100 qd	33.3%	18.0%	48.6%	31/63=49%	10/63=16%	<0.0001
400/100 bid	38.1%	22.8%	53.4%	34/63=54%	10/63=16%	<0.0001
600/100 bid	41.1%	26.0%	56.1%	37/65=57%	10/63=16%	<0.0001 *

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

Table 6.1.4.1 G (below) displays the difference between DRV/rtv at 600/100 mg bid and control in change from baseline in CD4 count at week 24, using both the LOCF (last observation carried forward) and observed case (OC) methods.

TABLE 6.1.4.1.G: SHOWING CHANGE IN CD4 COUNT FROM BASELINE TO WEEK 24 USING THE TO BE MARKETED DOSE OF **DRV/RTV 600/100 MG BID** COMPARED TO CONTROL IN TMC114-C202 and TMC114-C213

	Mean Diff	95% Lower Limits	95% Upper limit	Mean CD4 DRV/r	Mean CD4 Control	DRV/r N	Control N	p-value
Trial TMC114-C202								
LOCF	-55.8	-94.8	-16.8	69	13	54	60	<0.0051
OC	-57.6	-96.1	-19.1	73	15	30	54	<0.0034
Trial TMC114-C213								
LOCF	-102.9	-144.7	-61.1	117	14	55	64	<0.0001
OC	-98.9	-150.8	-46.9	121	22	30	61	<0.0002

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

In general there was a consistent pattern of increasing efficacy as one moves from a dose of DRV/RTV 400/100 mg qd to the to-be-marketed dose of 600/100 mg bid, in both the primary and secondary efficacy endpoints. (See Table 6.1.4.1.H).
Exceptions to the pattern are marked with asterixes *.

TABLE 6.1.4.1 H: SHOWING THE PATTERN OF INCREASING EFFICACY WITH INCREASING DOSE OF DRV FOR THREE ENDPOINTS: PERCENT OF SUBJECTS WITH HIV RNA < BASELINE - 1 LOG, HIV RNA <400 AND <50 COPIES/ML.

	<1 log drop in HIV RNA	**VL<400 copies/mL**	**VL<50 copies/mL**
Trial TMC114-C202			
400/100 qd	31/65=48%	25/65=38%	16/65=25%
800/100 qd	33/64=52%	26/64=41%	16/64=25%
400/100 bid	38/63=60%	33/63=52%	23/63=37%
600/100 bid	42/66=64%	37/66=56%	24/66=36% *
Trial TMC114-C213			
400/100 qd	45/64=70%	40/64=63%	27/64=42%
800/100 qd	45/63=71%	39/63=62% *	31/63=49%
400/100 bid	45/63=71%	43/63=68%	34/63=54%
600/100 bid	49/65=75%	45/65=69%	37/65=57%

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom
* = to be marketed dose

The FDA Statistical Reviewer verified the statistical significance of the observed dose response relationship by fitting logistic regressions to the three efficacy percentages, using two predictors: an indicator variable = 1 for any DRV dose and = 0 for control and an ordinal dose variable = 1,2,3,4 for 400 mg qd, 800 mg qd, 400 mg bid, 600 mg bid respectively. The p-values for dose were 0 .058, 0 .12, and 0 .018 for 1 log drop, <400, and <50 respectively. The 600 mg bid dose may be considered to be convincingly more effective than the lower doses although the magnitude of the effect is only 7-16% relative to 400 mg qd and 0-8% relative to 400 mg bid, compared to 23-33% superiority of the lowest DRV dose (400 mg qd) relative to control.

The FDA Statistical Reviewer also performed sensitivity analysis to explore potential open label biases by reclassifying failures on the control arm as successes if they met either of two criteria. First, they left the trial prior to their 12 weeks visit and thus did not meet the early exit criterion. Second, they left the trial between their 12 and 24 week visits, they had achieved at a one half log drop by week 12, and did not have a confirmed rebound from below baseline - 0.5 logs to above baseline -0 .5 logs. Table 6.1.4.1.I gives the comparison of the control arms in each of the two trials to all four DRV arms.

One can see that only 7 control subjects in trial 202 and 2 control subjects in trial 213 are changed in this analysis and that even with Bonferroni and O'Brien-Fleming adjustments for multiple arms and interim analyses, the conclusion of darunavir efficacy is confirmed.

TABLE 6.1.4.1.I: SENSITIVITY ANALYSES: WITH POTENTIAL EARLY EXITS COUNTING AS CONTROL SUCCESSES

DRV dose	Mean Diff	95% Lower	95% Upper	DRV/r	Control	P-value
Trial TMC114-C202						
600/100 bid	39.0%	23.2%	54.9%	42/66=64%	15/61=25%	<.0001 *
400/100 bid	35.7%	19.5%	51.9%	38/63=60%	15/61=25%	<.0001
800/100 qd	27.0%	10.6%	43.3%	33/64=52%	15/61=25%	.0012
400/100 qd	23.1%	6.8%	39.4%	31/65=48%	15/61=25%	.0053
Trial TMC114-C213						
600/100 bid	43.6%	28.1%	59.2%	49/65=75%	20/63=32%	<0.0001 *
400/100 bid	39.7%	23.7%	55.7%	45/63=71%	20/63=32%	<0.0001
800/100 qd	39.7%	23.7%	55.7%	45/63=71%	20/63=32%	<0.0001
400/100 qd	38.6%	22.5%	54.6%	45/64=70%	20/63=32%	<0.0001

* = to be marketed dose.

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom

Darunavir appeared to be clinically meaningfully superior to control for both sexes, all races with a reasonable number of subjects, all ages groups. Its superiority to control was also found at all levels of all baseline covariates examined, including baseline HIV RNA level and CD4 count, prior duration of ART, number of primary mutations at baseline, and presence or absence of enfuvirtide in the background regimen.

6.1.5 Clinical Microbiology

Please refer to Dr. Lisa Naeger's report for a more detailed analysis of the the clinical microbiology issues.
Darunavir is an inhibitor of the HIV-1 protease that selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

Using the three efficacy response parameters (at least 1 $\log_{10}$ decrease in viral load, viral load below 50 copies/mL, and change in viral load at Week 24) to assess the influence of individual protease mutations at baseline on the virologic outcome at Week 24 mutations **V11I, V32I, I15V, K20 R, F53L, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, and L89V** were identified to be associated with a decreased virologic outcome. Among those, **V11I, V32I, I47V, and I54L or M,** were identified by all 3 parameters of response. (See Table 6.1.5.A)

The presence of the mutations **V11I, V32I, L33F, I47V, I54L or M, I84V or L89V**, identified as associated with a decreased *in vitro* susceptibility to darunavir and with a decreased virologic response to darunavir when present at baseline, was typically associated with the presence of a

higher number of PI resistance-associated mutations as compared to patients who did not harbor those respective mutations at baseline.

Using the same 3 response parameters, a diminished virologic response was observed in patients with ≥ 7 primary PI mutations (any change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline. Nevertheless, the response rate in all subgroups (by type and number of mutations at baseline) was generally higher in the DRV/rtv groups compared to the response rate in the control group.

TABLE 6.1.5A: SHOWING SUMMARY OF MUTATIONS DEVELOPING ON DRV/rtv 600/100mg

Mutations Developing	**Studies C202, C213, and C215 N=164**
L10F/I/V	15 (9%)
I15V	22 (13%)
K20R/V/T/I	13 (8%)
V32I	58 (35%)
L33F/M	22 (13%)
I47V	19 (12%)
F53L	13 (8%)
I54L/M/V	40 (24%)
G73S/D/N/T/A/C/I	21 (13%)
L89V/I/M/F	28 (17%)

Source: FDA's Microbiologist – Dr L. Naeger

BASELINE PHENOTYPE AND VIROLOGIC OUTCOME ANALYSES

An analysis of response by 5-fold increments of baseline darunavir phenotype (fold change from reference) showed that response rates <50 copies/mL at week 24 decreased when baseline phenotype was ≥20-fold (Table 6.1.5 B). Baseline DRV phenotype (shift in susceptibility relative to reference) was shown to be a good predictive factor of virologic outcome. Response rates were 54%, 43% and 14% when baseline darunavir phenotype was <10, >10-20, and >20, respectively (Tablexyz). In Studies TMC114-C202 and TMC114-C213, the median baseline phenotype of responders was 2.1 (n=85) and the median baseline phenotype of virologic failures was 17 (n=40).

TABLE 6.1.5 B SHOWING: PROPORTION OF RESPONDERS IN STUDIES TMC114-C202 AND TMC114-C213 BY BASELINE PHENOTYPE

Baseline Phenotype n=123	**N**	**1 log decrease at Week 24**	**<50 copies/ml at Week 25**	**DAVG**
0-5	62	82%	58%	-2.28
>5-10	19	79%	42%	-2.06

>10-15	3	67%	0%	-2.68
>15-20	11	55%	55%	-2.34
>20-25	7	29%	14%	-0.64
>25-30	4	50%	25%	-1.81
>30-35	2	50%	50%	-2.35
>35-40	5	40%	20%	-1.77
>40	10	20%	0%	-0.796

Source: FDA's Microbiologist – Dr L. Naeger

Baseline darunavir FC was shown to be the most predictive factor of virologic outcome; activity of the OBR also contributed to the efficacy of the DRV/rtv containing regimen. Response (HIV RNA < 50 copies/mL at Week 24) of the DRV/rtv containing regimen with ≥ 1 susceptible NRTIs in OBR was 48% and without susceptible NRTIs was 30%; in patients who used enfuvirtide (ENF) for the first time 50%; in those who did not use ENF 44%.

Similarly, adding the phenotypic data from POWER 1, 2 and 3 (n=340 patients) determined that phenotypic subgroups of 0-5, 5-10 and >10 described responses rates in three tiers of 85%, 67% and 41% with a 1 $\log_{10}$ decrease from baseline, respectively, and 56%, 37%, and 19% with <50 copies/mL, respectively (Table). Patients who had darunavir phenotypes >10 at baseline had a median DAVG of 1.06 at week 24. (See Table 6.1.5.C)

Table 6.1.5.C . Response to 600/100 mg Darunavir/rtv by Baseline Darunavir Phenotype: Studies TMC114-C202, TMC114-C213 and TMC114-C215

Baseline Darunavir Phenotype n=340	**1 log decrease at Week 24**	**<50 copies/ml at Week 24**	**$DAVG_{24}$**
0 - 2	88% 119/136	60% 82/136	-2.28
>2 - 5	79% 50/63	48% 30/63	-2.24
0 - 5	85% 169/199	56% 112/199	-2.25
>5 - 10	67% 29/43	37% 16/43	-1.92
0-10	82% 198/242	53% 128/242	-2.18
>10	41% 40/98	19% 19/98	-1.06
0-3	87% 149/171	59% 101/171	-2.28
>3-6	71% 24/34	41% 14/34	-2.17
0-6	84%	56%	-2.25

	173/205	115/205	
>6-10	68% 25/37	35% 13/37	-1.871
0-7	82% 181/221	55% 122/221	-2.21
>7-15	68% 21/31	19% 6/31	-1.77
>15	41% 36/88	22% 19/88	-1.06
>7	48% 57/119	21% 25/119	-1.44

The efficacy of DRV/rtv containing regimens was greatest in patients who received more active antiretrovirals, it was in patients with higher FC that the magnitude of the difference in efficacy between those with and without an active OBR was most marked.

For patients with darunavir FC < 10 the percentage of patients with virologic response (decrease in viral load to < 50 copies/mL) with and without ENF were 53% and 52%, respectively. For patients with darunavir FC > 10 these percentages were 43% and 14%, respectively.

6.1.6 Efficacy Conclusions

The applicant has submitted results of TMC114-C202 and TMC114-C213 that have demonstrated statistically significant clinical benefit of the recommended dose of DRV/RTV (600/100 mg bid) in treatment-experienced HIV-1-infected subjects with no or limited treatment options, in combination with other antiretroviral agents. At the time of the protocol review for accelerated approval, the study design was considered adequate to demonstrate that the antiretroviral efficacy of DRV/rtv was superior when compared with the control group.

Independent FDA statistical analyses confirmed the applicant's analyses of the primary efficacy endpoint. The results for the *primary efficacy end point* analysis showed that 62% of subjects in trial TMC114-C202 on the 600/100 mg bid dose achieved decrease in VL by 1 $\log_{10}$ from baseline compared to 14% of controls, while in Trial TMC114-C213, 82% subjects on the 600/100 mg dose versus 24% of subjects on control achieved this goal. These results speak to the superiority of DRV/rtv.

Multiple *secondary efficacy end points* supported the conclusions of efficacy (VL < 50 copies/mL, VL <400 copies/mL and increases in CD4+ cell counts).

The responses were greater in all the TMC114 dose groups compared to control at all time points. The differences were statistically significant at the primary endpoint at Week 24. These

results were robust and consistent with various statistical sensitivity analyses. Analyses of available data also indicate that these differences were also statistically significant at Week 48.

The 24-week efficacy observed in the de novo subjects from TMC114-C215/C208 was similar to that seen in TMC114-C202 and TMC114-C213, thus supporting viral load reduction and CD4+ increase in the primary efficacy analysis of a larger sample size.

Three issues that might have had an impact on the outcome of the study and must be considered in interpreting the results of TMC114-C202 and TMC114-C213.

First, the applicant performed an interim analysis at Week 16 and this interim look on the efficacy data may have been the source of type I error. The FDA Statistical Reviewer performed O'Brien-Fleming boundary testing and the superiority of DRV/rtv remained intact.

The second source of type I error was resultant from the fact that the trials were originally phase II dose ranging studies, and presents issues on multiple inferences at the various dose levels of TMC114, allowing an ineffective drug to achieve statistical significance by chance. The FDA Statistical Reviewer fitted a number of statistical models to the observed data, and found that all the models gave p-values that were statistically significant after O-Brien-Fleming and Bonferroni adjustment and gave estimates of TMC efficacy relative to control of approximately the same magnitude, thus asserting that the statistical significance and the estimated treatment effect are not the artifacts of one particular model chosen by exploratory analysis.

The third issue concerns the potential bias from the partially blinded design, and that the control subjects were aware that they were likely assigned to an inferior arm, and had the incentive to quit the trial early. There were insufficient exits and insufficient excess unexplained drop outs in the control arm to make it plausible that the observed superiority could be attributed to the partially blinded study bias. Additionally, the FDA Statistical Reviewer performed a sensitivity analysis by reclassifying failures on the control arm as successes, if they left the trial prior to their Week 12 visit and did not meet the early exit criterion, or left the trial between 12 and 24 weeks. Even with this subject re-classification, the conclusion of DRV/rtv efficacy was confirmed.

The superiority of DRV/rtv was consistent across all subgroups including sex, race and age.

In summary, the submission for accelerated approval met its stated objective of demonstrating the superiority of DRV/rtv 600/100 mg bid over control PI-based regimen in the Week 24 efficacy analysis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for this NDA was provided in the form of electronic datasets containing tabulations of clinical adverse events and laboratory monitoring tests. Narrative summaries and case report forms were provided for all patients who died, developed serious adverse events (SAEs), or discontinued study drug because of an adverse event (AE). The Medical Officer compiled summaries of AEs, SAEs, deaths, study drug discontinuations, laboratory abnormalities using Review Statistical Software (Integrated Clinical Systems Inc.). All subjects who received at least one dose of assigned study medication were included in the safety analysis.

The evaluation of the safety and tolerability profile of darunavir/rtv was based primarily on the review of data from HIV-1 infected subjects from the following,

- Two ongoing Phase IIb, controlled, long-term, dose- finding trials in treatment-experienced subjects **(TMC114-C202** and **TMC114-C213)**, up to the date of the actual switch to the recommended dose and up to the cut-off date of 25th September 2005 for subjects randomized to control arm and to the 600/100 mg bid arm (*637 subjects).*

- Two ongoing Phase IIb, non-randomized, long-term, roll-over trials in treatment-experienced subjects **(TMC114-C215**, up to the cut-off date of 24 September 2005; and **TMC114-C208**, up to 1 September 2005) (*460 subjects*).

For each of the above studies, the final study reports, the case report forms, the summary of clinical safety were reviewed (SCS) and the data provided in the case report tabulations were analyzed in detail.

Other supportive safety data came from the following sources,

- Tirty-five completed trials in healthy volunteers (*748 subjects*) and Phase I data from 1 completed trial in HIV-1 infected subjects (*19 subjects*) the proof-of-principle data from 2 completed Phase IIa, controlled, short-term trials in PI-experienced subjects **(TMC114-C201 and TMC114-C207)** (84 subjects) were also included in the analysis of safety.

MO COMMENT: Throughout this Safety Review AE's are presented as straight proportions rather than by duration of exposure.

- Serious adverse event (SAE) data from all ongoing trials and submitted to the Division in the Safety Update Review on March 29th 2006.
    - **TMC114-C211** (Phase III treatment naïve study)
    - **TMC114-C214** (Phase III treatment-experienced study)
    - **TMC114-C209** (Open Label Safety Study)

- **TMC114-C226** (Expanded Access Program)

MO COMMENT: The data reviewed in the latter 4 studies will be described as further supportive evidence of what was observed in TMC114-C202, TMC114-C213, TMC114-C215, and TMC 114-C208 and are not included in pooled analyses.

7.1.1 Deaths

Deaths occurring on the DRV/rtv trials were evaluated in the following groupings:

A) Deaths occurring during the controlled portion of Studies TMC114-C202 and TMC114-C213 up to the September 25th 2005 database lock. (18 deaths)
B) Deaths occurring in the uncontrolled portion of the studies, before the September 25th 2005 database lock. (6 deaths)
C) Deaths reported in the safety update through the January 13th 2006 cutoff.(14 deaths)
D) Overall death rates for all three (3) DRV/rtv trials (TMC114-C202, TMC114-C213 and TMC114-C215) up to June 2006

7.1.1.A DEATHS OCCURRING DURING THE CONTROLLED PORTION OF TRIALS TMC114-C202 AND TMC114-C213.

There is an issue of concern with respect to safety and/or efficacy of DRV/rtv. Specifically, in the controlled portion of Studies TMC114-C202 and TMC114-C213, 17 deaths occurred on DRV arms, and 0 deaths occurred on control arms, when measured at the time of database lock on September 25th 2005.

When deaths were measured at the time point of deaths occurring up to Week 24 of study, the incidence of mortality was 1.2% (6/513) or 2.6 per 100 patient years in the DRV arm as compared to a rate of zero in the control arm.

Tables 7.1.1.A, Table 7.1.1.B , Table 7.1.1.C and Table 7.1.1.D summarizes the clinical features surrounding the deaths occurring in the Development program of DRV/rtv.

TABLE 7.1.1.A: SUMMARIZING DEATHS occurring during the controlled portion of the Pivotal Trials- TMC114-C202 + TMC114-C213 UP TO SEPTEMBER 25TH 2005

Age/Sex **ID #** **Treatment Group**	**Surrogate HIV marker** **▪CD4 &VL @ baseline**	**Concomitant AE's** **Duration of treatment in trial**	**Cause of death**
33y/o female **ID 202-1804** 800/100 mg qd	CD4=13x10^6 cells/L VL= 274,306 copies/mL	UTI Anemia (Severe) Thrombocytopenia GI Bleeding 122 days	Methicillin Resistant Staph Aureus (MRSA)
61y/o male **ID 202- 4907** 400/100 mg qd	CD4=2 x10^6 cells/L VL= 182,052	PCP Pancreatitis Thrush Shingles Oesophageal Candidiasis 87 days	AIDS related Lymphoma of Lung
46 y/o male **ID 202-5603** 400/100 bid	CD4=17 x10^6 cells/L VL= 187,990 copies/mL	Thrush Hypertriglyceridemia MAC 161 days	Adenocarcinoma of the Lung, with metastasis to: -pleura, -liver -bone
41 y/o female **ID 202-4905** 400/100 mg qd	CD4= 159 x10^6 cells/L VL= 1.7 million copies/mL	CMV Retinitis Cryptococcal Meningitis 264 days	Acute Myeloid Leukemia
40 y/o male **C202-0701** 400/100 mg bid	CD4= 315x 10^6 cells/L VL= 48,550 copies/mL	Respiratory failure, Clostridium difficile colitis, Disseminated Intravascular Coagulopathy 93 days	Multi Organ failure Septic Shock

Age/Sex **ID #** **Treatment Group**	**Surrogate HIV marker** **▪CD4 &VL @ baseline**	**Concomitant AE's** **Duration of treatment in trial**	**Cause of death**
42 y/o male **C202-1519** 600/100 mg bid	CD4= 148 x10^6 cells/L VL= 19,681 cp/mL	Wasting Syndrome Depression Anemia Vitamin deficiency Anal Carcinoma Rectal HSV 315 days	Illicit Methamphetamine Use / Overdose
49 y/o male **C202-1401** 600/100 mg bid	CD4= 3 x 10^6 cells/L VL= 405,882 cp/mL	-Chronic adrenocortical insufficiency -Renal insufficiency 549 days	Acute & Chronic Pulmonary Embolism Pneumomediastinum
50 y/o male **C202-2614** 400/100 mg qd → 600/100 mg bid	CD4= 72 x 10^6 cells/L VL = 26,962 cp/mL	-Asthenia -Depression -HIV Wasting Syndrome -Malnutrition -Chronic Renal Failure 515 days	Advanced HIV/AIDS Severe Metabolic Acidosis Pneumonia
71 y/o male **C202-3124** 600/100 mg bid	CD4= 4 x 10^6 cells/L VL= 65,559 cp/mL	Severe painful peripheral neuropathy 97 days	Death in Hospice, while treated for pain management
57 y/o male **C202-3503** 400/100 mg qd	CD4= 2 x10^6 cells/L VL= 489, 194 cp/mL	Diarrhea Hepatic enzyme increase- Grade 4 transaminitis/bili 137 days	® UL Pneumonia Elevated bilirubin LFT's abnormal End Stage HIV/AIDS

Age/Sex **ID #** **Treatment Group**	**Surrogate HIV marker** **▪CD4 &VL @ baseline**	**Concomitant AE's** **Duration of treatment in trial**	**Cause of death**
53 y/o old female **C202-5101** 800/100 mg qd →600/100 mg bid	CD4= $151x10^6$ cells/L VL= 489,194 cp/mL	Disseminated Intravascular Coagulation (DIC) 231 days	UTI Acute Renal Failure Rhabdomyolysis Septic Shock Streptococcal Sepsis
71 y/o male **ID 213-0668** TMC114 400/100 mg bid	CD4=170x 10^6 cells/L VL = 1,738,821 copies/mL	Vitamin deficiency Thrombocytopenia Pyrexia Anemia Hepatic Steatosis 20 days	Clostridium Colitis CMV Gastroenteritis Pneumonia
71 y/o male **ID 213-0120** TMC/RTV 400/100 qd	CD4= 16 x 10^6 cells/L VL = 73,556 copies/mL	Diarrhea Clostridial Infection Skin Carcinoma Pyrexia Oral Candadiasis Mycobacterial Infection 20 days	Multi-Organ Failure due to sepsis -Liver decompensation secondary to atypical mycobacteriosis - Pseudomembranous colitis
44 y/o male **ID 213-0139** TMC/RTV 400/100 bid	CD4= $95x10^6$ cells/L VL = 306,000 copies/mL	Ataxia Elevated blood triglycerides 302 days	Progressive Multifocal Leukoencephalopathy (PML)

Age/Sex **ID #** **Treatment Group**	**Surrogate HIV marker** **▪CD4 &VL @ baseline**	**Concomitant AE's** **Duration of treatment in trial**	**Cause of death**
43 y/o male **ID 213-0066** 600/100 mg bid	CD4= $391x10^6$ cells/L VL= 7,305 cp/mL	Anemia Rectal Hemorrhage Necrotizing fasciitis 543 days	Anal Carcinoma Necrotizing Fasciitis
53 y/o male **ID 213-0068** 400/100 mg bid to 600/100 mg bid	CD4= $266x10^6$ cells/L VL 1930 cp/mL	Cholelithiasis Diarrhea 183 days	CVA Pneumonia Refractory Septic Shock
38 y/o male **ID 213-0414** 600/100 mg bid	CD4 = $9 x10^6$ cells/L VL=41,419 cp/mL	Tuberculous Pericarditis Peripheral Neuropathy Asthenia Diarrhea 371 days	Sepsis
52 y/o male **ID 213-0677 to ID 215-0275** 600/100 mg po bid	CD4 = $6x10^6$ cells/L VL= 26,877 cp/mL	Depression Hypertriglyceridemia Kaposi's Sarcoma 261 days	Pancreatitis Multi-Organ Failure
44 y/o male **ID 202-0504 to ID 215-0045** control to 600/100 mg bid	CD4 = $2x10^6$ cells/L VL=26,105 cp/mL	Aspergilliosis Chronic Bronchitis Cardiomyopathy Diarrhea Skin Carcinoma 301 days	Aspergillus Pneumonia

TABLE 7.1.1. B DEATHS OCCURRING IN THE UNCONTROLLED PORTION OF THE TRIALS (TMC114-C215/C208), BEFORE THE SEPTEMBER 25TH 2005 DATABASE LOCK.

Age/Sex **ID #** **Treatment Group**	**Surrogate HIV marker** **▪CD4 &VL @ baseline**	**Concomitant AE's** **Duration of treatment in trial**	**Cause of death**
40 y/o male **ID 215-0086** 600/100 mg bid de novo	CD4 = $7x10^6$ cells/L VL= 20,388 cp/mL	- ↑Hepatic enzymes - Staphylococcal bacteremia - increased bilirubin - CMV chorioretinitis 110 days	- Pulmonary TB - Bacterial Endocarditis - Renal insufficiency - Increased Intracranial Pressure
31 y/o male **ID 215-0127** 600/100 mg bid de novo	CD4 = $2x10^6$ cells/L VL= 525,331 cp/mL	Renal Insufficiency 5 days	Acute Respiratory Failure Metabolic Acidosis
31 y/o male **ID 215-0212** 600/100 mg bid de novo	CD4 = (specimen hemolyzed) VL=57,638 cp/mL	Anemia Coagulopathy Convulsions Hyponatremia Pyrexia 170 days	Meningo Encephalitis
41 y/o male **ID 215-0216** 600/100 mg bid de novo	CD4 = $8x10^6$ cells/L VL= 35, 686 cp/mL	Nil reported 17 days	Septic Shock Multi Organ Failure
46 y/o male **ID 215-0374** 600/100 mg bid de novo	CD4 =$10x10^6$ cells/L VL= 18,172 cp/mL	CMV infection Anemia Thrombocytopenia Confusional State 84 days	-Cryptosporidial Gastroenteritis -Sepsis

48 y/o male **ID 215-0402** 600/100 mg bid de novo	CD4 =1x10^6 cells/L VL = 43,659 cp/mL	Sinus Tachycardia 21 days	-Cerebral Toxoplasmosis, with -Cerebral hemorrhage and Edema

C) DEATHS IN SAFETY UPDATE REPORT

After the database was closed on September 25th 2005, 14 additional deaths were reported in these uncontrolled trials:

- 6 additional subjects died in **TMC114-C209**
- 5 subjects died in **TMC114-C215**
- 2 subjects died in **TMC114-C226**
- 1 subject died in **TMC114-C208**.

(These deaths are summarized in Table 7.1.1.C noted below). All subjects were receiving TMC114. One subject who died while enrolled in TMC114-C215 was originally a control subject in Study TMC114-C202.

Ten of the fourteen deaths occurred in subjects with baseline CD4 < 20 cell/mm^3. One subject had a CD4 count of 37 cells/mm^3 and the other a CD4 count of 96 cells/mm^3. One patient who died of PCP and E.coli pneumonia had a CD4 count of 126 cells/mm^3.

Additional causes of death include 3 cases of lymphoma, MI, pneumonia, staph sepsis/renal failure, unspecified sepsis, pseudomonas, CMV encephalitis, hepatorenal syndrome, TB meningitis/Pulmonary Embolism, and CVA. (See Table 7.1.1 D noted below)

TABLE 7.1.1.C SHOWING DEATHS OCCURRING BETWEEN 25th SEPTEMBER 2005 to 13th JANUARY 2006 (SAFETY UPDATE REPORT)

Age/sex **Id #** Treatment group	**Cd4 &vl @ baseline**	**Cd4 & vl @ death**	**On rx by 24 wks @ death**	**Concomitant ae's** **Duration of treatment in trial**	**Cause of death**
53 y/o male **C215-0129** 600/100 mg bid	Cd4 = 12 Vl = 159,941	Cd4= 119 [redacted] Vl= 17,371 [redacted]	Unknown	Femur fracture Joint arthroplasty	Non-hodgkins lymphoma

Age/sex **Id #** Treatment group	**Cd4 &vl @ baseline**	**Cd4 & vl @ death**	**On rx by 24 wks @ death**	**Concomitant ae's** **Duration of treatment in trial**	**Cause of death**
41 y/o male **C215-0392** 600/100 mg bid	Cd4= 13 Vl= 598,181	Cd4=92 [redacted] Vl= 22,225 [redacted]	Yes	Cardiac failure 275 days	Myocardial infarction
41 y/o male **C215-0056** (formerly 202-1103)	Cd4=2 Vl= 14.226	Cd4= 3 [redacted] Vl= 38,460	yes	Weight loss > 577 days	Staphyloccal sepsis Renal failure
54 y/o male **C215-0335** 600/100 mg bid	Cd4= 3 Vl= 118,390	Cd4= 25 Vl= <50 [redacted]	Yes	Kaposi's sarcoma Fractured t11 vertebra Backache	Pseudomonas infection Multiorgan failure
54 y/o male **C215-0014 (formerly 202-1013)** Control/ 600/100 mg bid	Cd4= 12 Vl= 413,588	Cd4= 42 Vl=4,556 [redacted]	Yes	Cmv viremia Cmv encephalitis Pyrexia	Neurodegenerative disorder Cmv encephalitits
51 y/o male **Id 208-0003** 600/100 mg bid	Cd4=17 cells/mm^3 Vl= 2,210,000 Copies/ml	cd4=20 1,010,220 [redacted]	No (42 days)	Pneumonia Mai Myocardial infarction Hs keratitis Oropharyngeal candiadiasis 210 days	B- cell lymphoma Tmc started on 3/23/05 Dc/ed tmc 7/05 D of death= [redacted]
43 y/o male **Id 209-0073** 600/100 bid	Cd4= 96 cells/mm^3 Vl= 92,700 copies/ml	Not available	No – Rx dur= 52 days	52 days	- cva - coma

Age/sex **Id #** Treatment group	**Cd4 &vl @ baseline**	**Cd4 & vl @ death**	**On rx by 24 wks @ death**	**Concomitant ae's** **Duration of treatment in trial**	**Cause of death**
36y/o male **C209-0029** 600/100 mg bid	Cd4= ??? X 10^6 cells/l Vl= 507,000 Copies/ml	Cd4= 12 cells/l Vl=906,000 copies.	No Rx duration = 97 days	Pyrexia Perianal ulcers Sepsis Gluteal abscess 93 days	Sepsis
40 y/o male **C209-0001** 600/100 mg bid	Cd4= 7 cells/mm^3 Vl= 110,000 Cp/ml	Not available	No- Rx duration= 19 days	Metabolic acidosis 19 days	Death on [redacted]
45 y/o male **C209-0033** 600/100 mg bid	Cd4= 1 cell/mm^3 Vl= 47,200 cp/ml	Cd4=0 Vl= 433	No – Rx duration= 89 days	549 days	Non-hodgkins lymphoma with spread basal ganglia, cervical and thoracic
66 y/o male **C209-0061** 600/100 mg bid	Cd4= 37 cells/mm^3 Vl= 608,000 cp/ml	Not available	No- Rx duration= 17 days	Pyrexia Kaposi's sarcoma Cmv retinitis 4 days (started tmc [redacted]	Tb meningitis Pulmonary embolism Death on [redacted]
57 y/o male **C209-0038** 600/100 mg bid	Cd4= 9 cells/mm^3 Vl= 413,000 cp/ml			Hemorrhagic diarrhea Cryptococcal ge Pneumonia /pyrexia Anemia Pancytopenia 173 days	Pneumonia Death on [redacted]
40 y/o male **C226-0004** 600/100 mg bid	Cd4=10 x10^3 cells/l Vl= 210,000b	Not avail	No – Rx duration = 27 days	Dyspnea 27 days	Hepatorenal syndrome

Age/sex **Id #** Treatment group	**Cd4 &vl @ baseline**	**Cd4 & vl @ death**	**On rx by 24 wks @ death**	**Concomitant ae's** **Duration of treatment in trial**	**Cause of death**
44 y/o male **C226-0008** 600/100 mg bid	Cd4=126 x10^3 Vl=480,000	Not available	No – Rx duration = 21 days Died on [redacted] 5 months afer trial termination	Renal failure e.coli pneu	Pcp pneumonia

DISCUSSION OF DEATHS OCCURRING IN THE DARUNAVIR DRUG DEVELOPMENT PROGRAM

The development of DRV targeted HIV-1 infected subjects with limited available treatment options. Consequently, no restrictions on CD4+ cell counts were applied to clinical studies. As a result, approximately 30% of subjects with baseline CD4+ cells counts below 50 x 10^6 cells/L were enrolled, a well described predictive factor for mortality.

The mortality rate in the population of the Phase IIb trials for all subjects receiving DRV (N=924) was 3.3 subjects per 100 patient years exposure for darunavir-treated subjects. Eleven out of 458 subjects who initiated treatment with darunavir/ritonavir 600/100 mg bid died, resulting in a mortality rate of 3.6 subjects per 100 patient-years exposure.

No apparent dose-response relationship was observed for deaths occuring in the Phase IIb trials.

The apparent discordance in the death rates between control and DRV arm in the controlled trials were analysed as follows:
1) Analysis based on Clinical Cause of Death
2) Analysis based on comparative mortality in other HIV-1 treatment experienced trials
3) Analysis comparing deaths with survivors in drop-outs prior to receiving first dose of drug
4) Analysis comparing deaths with survivors on several baseline covariates- HIV-1 RNA viral load suppression sustained below baseline; the presence of neutropenia; baseline CD4 count
5) Analysis based on rate of SAE's, hospitalization and persistent disability rates

1) ANALYSIS BASED ON CLINICAL CAUSE OF DEATH

Most subjects died of complications or progression of HIV. Most of the AEs leading to death were of the System Organ Class "Infections and Infestations" (15 of 25 subjects) and included 4 cases of new AIDS-defining illnesses (i.e., cryptosporidiosis, tuberculosis, CMV colitis, and PML). Four deaths were from the SOC "Neoplasm Benign, Malignant and Unspecified", and

these were all isolated cases (anal cancer, lymphoma, acute myeloid leukemia, lung adenocarcinoma). Two deaths were from the SOC "Respiratory, Thoracic, and Mediastinal Disorder" (1 case of pulmonary embolism, and 1 case of acute respiratory failure). The remaining 4 deaths were all isolated individual cases from different SOCs.

The 4 subjects who died in the first 12 weeks of therapy had a median CD4+ cell count at baseline of 5 x 10^6 cells/L; the 8 subjects who died within 12 to 24 weeks after initiation of therapy had a median CD4+ cell count of 6 x 10^6 cells/L; the 4 subjects who died within 24 to 36 weeks after initiation of therapy had a median CD4+ cell count of 16 x 10^6 cells/L; and the 5 subjects who died within 36 to 48 weeks after initiation of therapy had a median CD4+ cell count of 71 x 10^6 cells/L at baseline. For those 4 subjects who died during the second year, the median CD4+ cell count at baseline was 169 x 10^6 cells/L. These data suggest that most fatal events occurred in subjects who were not on treatment long enough to benefit from therapy or who did not experience a substantial immunologic improvement over time.

AIDS-defining or AIDS progression events were captured in darunavir trials as adverse events only and were not specifically abstracted or adjudicated.

2) COMPARATIVE ANALYSIS OF MORTALITY IN other HIV-1 TREATMENT EXPERIENCED TRIAL SUBJECTS:

FDA reviewers previously conducted analyses of mortality rates in the NDA database of all "treatment-experienced" trials to support approval of antiretroviral drugs from the archives of DAVP, in order to place the mortality rate observed in the tipranavir trials into perspective (NDA 21814 and NDA 21418).

http://www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm.
http://www.fda.gov/cder/foi/nda/2005/021814 aptivus review.htm

Examination of subject baseline characteristics showed that the population enrolled in the T20 Phase 3 studies and the TPV Phase III studies closely approximated the population enrolled in the DRV studies.
The mortality rate from the DRV/rtv Phase IIb trials (2.6 events per patient year exposure) was in line with what is expected in a population of advanced HIV-1 infected subjects, and was comparable to the mortality rates at Week 24 in previously reported in trials performed in similar populations, specifically with enfuvirtide (3.3 events per 100 patient years), and the most recently approved PI tipranavir (4.5 events per 100 patient years).

Table 7.1.1.D COMPARISON OF MORTALITY PER 100 PATIENT-YEARS OF FOLLOW-UP IN MOST RECENT APPROVED HIV-1 "TREATMENT-EXPERIENCED" CONTROLLED REGISTRATIONAL TRIALS CLINICAL TRIALS.

The Deaths counted were deaths up to Week 24 of the Trial.

ENF Mortality at Wk 24 analysis of TORO trials		*TPV/RTV Mortality at Wk 24 analysis of RESIST trials*		*DRV/rtv Mortality at Wk 24 analysis of C202 and C213*	
ENF+/-OBR	*OBR*	*TPV/RTV+/- OBR*	*CPI/RTV +/- OBR*	*TMC/RTV+/- OBR*	*CPI/ RTV+/- OBR*
10/663 (1.5%)	*5/334 (1.5%)*	*12/582 (2.0%)*	*7/577 (1.2%)*	*6/513 (1.2%)*	*0/124 (0 %)*
Mortality rate = 3.3	*Mortality rate = 3.3*	*Mortality rate = 4.5*	*Mortality rate = 2.6*	*Mortality rate = 2.6*	*Mortality rate = 0.0*

Source: Data on ENF and TPV trials reprinted from Dr. Andrea James review of NDA 21-814

[Mortality rate per 100 years exposure = # of subjects with event x100/patient years of exposure]

As shown above, raw numbers of deaths or mortality rates between the test and control arms were similar for both the tipranavir (TPV) and enfurvitide (ENF) NDA's at 24 weeks. However, in the DRV studies, no subjects randomized to control arms died.

For all-cause mortality, the numbers of on-treatment deaths (17 DRV/rtv deaths versus 0 in the control arm appeared to be grossly different between the two arms or expressed in another way, the added virologic benefit (as measured by the surrogate of plasma HIVRNA) did not seem to translate into any reduction in mortality at the 24-week timepoint. However, these studies were not powered for mortality, and the September 2005 cut-off point may have been too premature to see any clinical endpoint differences, and the comparator arm's escape option at Week 12 (with confirmatory test at Week 16), may have salvaged subjects prior to prolonged virologic failure.

In addition, patients were randomized 4:1 to receive darunavir versus control in TMC114 dose-finding studies as compared to 2:1 randomization that occured in enfuvirtide studies and 1:1 in tipranavir studies. The randomization scheme and additional enrollment of darunavir-treated subjects in uncontrolled studies likely also contributed to the uneven distribution of deaths observed in this clinical trial database.

The relationship of plasma HIV RNA as surrogate endpoints to the actual clinical outcomes may be less well understood in studies of heavily pretreated populations with advanced disease.

3) ANALYSIS COMPARING DEATHS WITH SURVIVORS IN DROP-OUTS PRIOR TO RECEIVING STUDY DRUG

The reviewers noted that there were disproportionately more control subjects who withdrew from these open label trials between randomization and first drug dose. The control arm lost

13% (17/133) before starting drug, while the DRV arms lost 3.4% (17/495). This reviewer believes that it is not unreasonable to believe that these unblinded control subjects may have deliberately opted to go for a perceived potentially more efficacious drug option, prior to first dose of drug.

The FDA reviewer's also analysed the data to address the potential associations among low baseline CD4 count, decision not to participate after assignment to the control arm, and deaths. The number of control subjects withdrawing, continuing, and dying on each arm were stratified by baseline CD4 count for the pooled TMC114-C202 and TMC114-C213 trials. For each CD4 striatum, the percent of control subjects dropping out before starting drug was approximately the same as the percent of DRV subjects either dropping out prior to drug or dying on treatment.

4) ANALYSIS OF THE OVERALL DEATH RATES FOR ALL THREE (3) DRV/rtv TRIALS (TMC114-C202, TMC114-C213 and TMC114-C215) up to MAY 31st 2006

Recognizing that ill control subjects may have deliberately opted out of the controlled pivotal studies because of the perception of diminshed efficacy on the control arm, the reviewers requested the applicant provide the Division with any available data on the disposition of subjects who were randomized to either DRV or control arm who never received study medication and subjects who received DRV or control drug and did not rollover to TMC114-C215, and to indicate whether they were alive or dead, and if alive, whether they were enrolled in another clinical study. The results are shown in the Table 7.1.1E shown below.

The table gives the death rates on control and DRV arms, together with the point estimate and 95% confidence limits for control rate minus DRV rate (negative values correspond to higher death rates on DRV). In this analysis, because all subjects were followed up, as thoroughly as possible, until June 2006, differences in person years of exposure were approximately proportional to number of subjects and thus rates are computed per person rather than per person-year. If subjects tended to leave the control arm earlier to enter DRV rollover trials, the person-years would be relatively smaller for control and the rate per person-year would be relatively higher for control, relative to DRV. Thus, the analyses below are slightly biased against DRV.

TABLE 7.1.1.E – DEATH RATES IN TMC114-C202, TMC114-C213 AND TMC114-C15/-C-208

		Mean Diff	95% limits		Control	DRV/rtv
			Lower limits	Upper Limits		
Intent-to-treat analysis						
All subjects		0.8%	-2.9%	4.5%	7/144=4.9%	37/912=4.1%
Status	Treated	-0.6%	-3.9%	2.8%	4/124=3.2%	34/895=3.8%
	No_ drug	-2.6%	-26.6%	21.3%	3/20=15.0%	3/17=17.6%
As treated analyses						
All subjects		0.2%	-3.2%	3.6%	6/149=4.0%	38/992=3.8%
Status	Treated	-2.1%	-4.6%	0.5%	2/124=1.6%	36/980=3.7%
	No_drug	-0.7%	-26.2%	24.9%	4/25=16.0%	2/12=16.7%

SOURCE: ANALYSIS BY FDA'S STATISTICIAN- DR T. HAMMERSTROM

There are four analyses shown in **Table 7.1.1.E**, two of them being **ITT analyses** and two being **as-treated** analyses. One of each pair groups all subjects together, the other stratifies by whether the subjects took their initially assigned drug or did not take their assigned drug, either leaving Tibotec studies entirely or rolling over into another Tibotec trial. As was expected, a decision not to take the assigned drug appeared to be associated with an initial poor prognosis (15-17.6% death rate vs 3.2-3.8%).

The difference between the **ITT** analyses and the **as-treated** analyses is as follows. The ITT analyses count subjects randomized to control in either of trial -C202 or -C213 as control, even if they subsequently enroll in the drv arm in trial 215. The as-treated analyses reclassified subjects from their initially assigned arm as follows: a subject who was randomized to drv and starts drug is a drv subject. A subject who is randomized to drv but never starts drug and never rolls over into another Tibotec trial becomes a control subject. A subject who is randomized to control but never starts drug and rolls over into trial 215 or another tibotec trial becomes a drv subject. A subject who is randomized to control and starts drug is a control subject. Finally, if that subject subsequently discontinues control and rolls over into Trial -C215 or another Tibotec trial, that subject counts as a two subjects, one on Control from randomization to rollover and the other on DRV from rollover to last observation.

The FDA statistical reviewer considers the as-treated analyses as more appropriate for safety endpoints than the ITT analyses. If DRV actually increased the death rate, then counting deaths on DRV in a rollover trial as deaths on control would be misleading. None of the analyses showed a statistically significantly higher death rate for DRV. The stratum with subjects starting their assigned drug showed a somewhat elevated death rate for DRV (3.7% vs 1.6% in the as treated analysis).

The FDA reviewers also conducted a sensitivity analysis with respect to the requested long-term follow-up. In this analysis, subjects who were lost to follow-up as of July 1, 2005, were counted as deaths if they were on DRV, as alive if they were on control. The results are given in table 7.1.1.1 F. Even under this unfavorable assumption about DRV, one gets an **as treated** analysis with all subjects showing death rates of 5.4% for DRV and 4.0% for control with the DRV rate being between 4.9% higher and 2.0% lower (based on the 95% confidence limits).

TABLE 7.1.1 F: SENSITIVITY ANALYSES ON MISSING DATA IN FOLLOW-UP

	Mean Diff	95%_limits		Control	DRV/rtv
		Lower limit	Upper limit		
ITT	-1.6%	-5.5%	2.3%	7/144=4.9%	59/912=6.5%
As_treated	-1.4%	-4.9%	2.0%	6/149=4.0%	54/992=5.4%

SOURCE: FDA'S STATISTICIAN- DR. T HAMMERSTROM

It seems reasonable to conclude that the excess deaths in the DRV arms reflects mainly the preference for the most ill patients at baseline to discontinue if they failed to be randomized to the experimental drug and the longer follow-up on DRV arms and rollover studies in the initial submission.

5) ANALYSIS OF DEATH BASED ON SEVERAL BASELINE COVARIATES: HIV-1 RNA VIRAL LOAD; VIROLOGIC SUPPRESSION BELOW BASELINE AT 24 WEEKS; CD4+ CELL COUNT; AND NEUTROPHIL COUNT DURING TREATMENT

The FDA reviewers directly compared deaths with survivors on several baseline covariates, including CD4 count, serum HIV RNA level, virologic suppression response at 24 weeks, baseline phenotype, neutrophil count during treatment, duration of prior ARV therapy, and age. The only covariate that seemed to be a good predictor of death was CD4 count.

Review of the viral suppression data at baseline, and on the days surrounding death, showed that 10 of the 18 subjects (55.6 %) subjects on the study drug achieved sustained suppression of viral response to < 1 log drop below baseline at the time of death. Death was therefore not particularly associated with a sustained virological response in that the three highest CD4 counts were achieved in subjects with sustained suppression. The majority of deaths were in patients with baseline CD4 < 50. Therefore, low CD4 counts were associated with death.

FDA's Statistical reviewer compared the mean difference in neutrophil count between the for each DRV/rtv arm – control for each week of the two pivotal trials. The upper and lower 95% interval limits, and p-value are compared. Full details of this analysis is shown in Dr Hammerstrom's review. The p-value never achieved the significance level and the 95% upper limit was always above zero, and the lower limit was often above zero. Thus, there was no

significant decrease in neutrophil count on DRV/rtv compared to control. There did not seem to be any neutropenia associated with DRV/rtv.

6) ANALYSIS BASED ON RATE OF SAE's, HOSPITALIZATION and PERSISTENT DISABILITY RATES

Comparison of the rate of SAE's, hospitalizations and persistent disability rates between DRV and control arms revealed no differences. None of these endpoints showed a particular discrepancy in rates.

7.1.1 Overall Conclusions on the Mortality Rates in the Darnunavir Development Program Package for Traditional Approval

All of the deaths in trials TMC114-C202 and TMC114-C213 occurred on DRV arms. In the controlled pivotal trials, at Week 24 of study, the mortality rate on the DRV arm was 2.6 per 100 patient years as compared to a mortality rate of zero in the control arm.
The imbalance in mortality between darunavir and control subjects can be explained by the following:

1) There were disproportionately more control subjects who withdrew from these open label trials between randomization and first drug dose. The control arm lost 13% (17/133) before starting drug, while the DRV arms lost 3.4% (17/495). It is not unreasonable to to believe that these unblinded control subjects may have deliberately opted to go for a perceived potentially more efficacious drug option, prior to receiving the first dose of drug when they discovered that they were randomized to the control/comparator arm.

The Division asked the sponsor to ascertain the current status of all the control and study subjects who opted out of the trial prior to the first dose of drug. In order to pursue the possibility that extra deaths were occurring among the discontinuing controls, the FDA asked the applicant to determine the current status of all initially randomized subjects, regardless of when they discontinued the trial and regardless of what trials they subsequently enrolled in. Analysis of this long term follow up data showed that the incidence of death in **DRV- treated and/or randomized** subjects was **5.5%** (29/530), while the incidence of death in **control treated and/or randomized** subjects was **4.9 % (7/144).**

2) The high attrition rate due to virologic failure in the control group had an impact on exposure.
At 24 weeks, the virologic failure rate on the control arm was 65% versus a 12% rate in the DRV arm.
In addition, study subjects were randomized 4:1 to receive darunavir versus control in DRV dose-finding studies. As a result, darunavir subjects were on study approximately six (6) times longer for as compared to control subjects. The excesses of deaths on the darunavir arm may well be nothing but random variability.
4) The open-label design of the comparator arm, and the comparator arm's escape clause for lack of initial virologic response at 12-16 weeks made it difficult to discern treatment differences in some efficacy and safety parameters beyond 12 weeks of treatment.

The applicant is also conducting two planned Phase 3 trials comparing DRV/rtv to Kaletra in naive and moderately treatment-experienced populations. It is expected that the control arm will experience fewer

early discontinuations on those trials than in the pivotal trials -C202 and -C213. The issue of the apparent discordant deaths rate between the subjects randomized to DRV and subjects randomized to control will require further evaluation when the controlled data from the ongoing Phase III studies, *TMC114-C214 in treatment- experienced subjects* and *TMC114-C211 in Rx- naïve* subjects is available. The sponsor plans to submit the results of these studies as part of their traditional approval package. The issue of excess deaths on DRV/rtv will need to be re-visited once the data from these trials with more person-years of control exposure are available.

7.1.2 Other Serious Adverse Events

The SAE's reported during the trial were mainly in the gastrointestinal system, and the central nervous system. The proportion of SAE's in study arm vs the control arm were similar. (See Table 7.1.2.A noted below).
The overall rate of any grade 3 or 4 AE occurring in subjects on the proposed dose of DRV/rtv was 36.6 %, 30.8% in the total DRV subjects, and 31.5% in the control arm.
Most SAE's were reported in the Organ Class "Investigations", with 16.8 % subjects in the DRV/rtv proposed dose treatment arm and 11.5% total DRV reporting one or more SAE's; This proportion contrasts with a 9 % rate in the control subjects.
SAE's were reported next most commonly in the "Infections and infestations" Organ Class, with 9.2% of subjects in the DRV/rtv 600/100 mg arm reporting SAE's, 1.8 % subjects in the total DRV arm reporting SAE's, and 1.6 % controls reporting SAE's.

MO COMMENT: The apparent greater rate of SAE's in the DRV/rtv 600/100 mg arm as compared to control is probably a function of mean exposure. The mean exposure in the DRV/rtv 600/100mg arm was 62 weeks; 49 weeks in the total DRV arm, and 31.5 weeks in the control arm.
Again, we see that the shortened exposure in the control arm (related to high virologic failure rate, escape clause for early virologic failure, the longer follow-up on DRV arms, and the tendency for the most ill control subjects to withdraw early and roll-over into another Tibotec or non-Tibotec study, in order to receive an experimental drug that is perceived as more efficacious).

TABLE 7.1.2.1A : SHOWING DICTIONARY DERIVED SEVERE ADVERSE EVENT (SAE) TERMS IN TRIALS **TMC114-C202 and TMC114-C213** IN SUBJECTS RECEIVING DRV/rtv - ALL DRV AND PROPOSED DOSE DRV/rtv arm (600/100 MG) AT 48 WEEKS, CLASSIFIED BY BODY SYSTEM AND ORGAN CLASS, AND COMPARED TO CONTROL

System Organ Class, Preferred Term, n (%)	**DRV/ rtv (mg)**		**Control**
	600/100 bid N = 131	**Total Darunavir N = 513**	**N = 124**
Mean exposure (weeks)	62.29	49.03	31.54
Any grade 3 or 4 AE	***48 (36.6)***	***158 (30.8)***	***36 (29.0)***
Any grade 3 AE	***42 (32.1)***	***42 (32.1)***	***34 (27.2)***
Any grade 4 AE	***16 (12.2)***	***16 (12.2)***	***5(4.0)***
Investigations	**22 (16.8)**	**59 (11.5)**	**11 (8.9)**
Blood amylase increased	2 (1.5)	12 (2.3)	2 (1.6)
GGT increased	5 (3.8)	12 (2.3)	1 (0.8)
Lipase increased	3 (2.3)	10 (1.9)	2 (1.6)
AST increased	5 (3.8)	9 (1.8)	5 (4.0)
Blood triglycerides increased	4 (3.1)	8 (1.6)	2 (1.6)
Weight decreased	2 (1.5)	4 (0.8)	0
ALT increased	2 (1.5)	3 (0.6)	3 (2.4)
Blood ALP increased	1 (0.8)	2 (0.4)	0
Blood cholesterol increased	0	2 (0.4)	1 (0.8)
Neutrophil count decreased	0	2 (0.4)	1 (0.8)
AAG increased	1 (0.8)	1 (0.2)	0
Blood bilirubin increased	0	1 (0.2)	2 (1.6)
Blood creatinine increased	1 (0.8)	1 (0.2)	0
Blood CPK increased	0	1 (0.2)	0
Blood glucose increased	0	1 (0.2)	0
Blood uric acid increased	0	1 (0.2)	0
Heart rate irregular	0	1 (0.2)	0
Liver function test abnormal	0	1 (0.2)	0
Neutrophil count	0	1 (0.2)	0
Pancreatic enzymes increased	1 (0.8)	1 (0.2)	0
Platelet count decreased	0	1 (0.2)	0
Infections and infestations	**12 (9.2)**	**9 (1.8)**	**2 (1.6)**
Pneumonia	2 (1.5)	3 (0.6)	0
Meningitis cryptococcal	0	3 (0.6)	0
Oral candidiasis	1 (0.8)	2 (0.4)	0
Bronchopneumonia	1 (0.8)	2 (0.4)	0
Clostridium colitis	0	2 (0.4)	0
Progressive Multifocal-Leukoencephalopathy	0	2 (0.4)	0
Sepsis	1 (0.8)	1 (0.2)	0
Bronchiectasis	1 (0.8)	1 (0.2)	0
Catheter sepsis	0	1 (0.2)	0
Cellulitis staphylococcal	1 (0.8)	1 (0.2)	0
Cerebral acuminatum	0	1 (0.2)	0

SAE TABLE (contd from previous page)

System Organ Class, Preferred Term, n (%)	Darunavir/ RTV (mg)		Control
	600/100 bid N = 131	Total Darunavir N = 513	N = 124
Cytomegolovirus colitis	0	1 (0.2)	0
Disseminated cytomegoloviral infection	1 (0.8)	1 (0.2)	0
Encephalitis herpes	0	1 (0.2)	0
Fusarim infection	0	1 (0.2)	0
Gastroenteritis staphylococcal	0	1 (0.2)	0
Herpes zoster	0	1 (0.2)	2 (1.6)
Infection	1 (0.8)	1 (0.2)	0
Injection site abscess	0	1 (0.2)	0
Leishmaniasis	1 (0.8)	1 (0.2)	0
Mycobacterium avium complex infection	1 (0.8)	1 (0.2)	0
Necrotising fasciitis	1 (0.8)	1 (0.2)	0
Oesophageal candidiasis	0	1 (0.2)	0
Penile abscess	0	1 (0.2)	0
Perianal abscess	1 (0.8)	1 (0.2)	0
Pericarditis tuberculous	1 (0.8)	1 (0.2)	0
Septic shock	0	1 (0.2)	0
Upper respiratory tract infection	1 (0.8)	1 (0.2)	0
Bronchitis	0	0	1 (0.8)
Cellulitis	0	0	1 (0.8)
Molluscum contagiosum	0	0	1 (0.8)
Gastrointestinal disorders	**9 (6.9)**	**28 (5.5)**	**6 (4.8)**
Diarrhea	2 (1.5)	9 (1.8)	2 (1.6)
Abdominal pain	3 (2.3)	6 (1.2)	0
Vomiting	1 (0.8)	3 (0.6)	1 (0.8)
Nausea	0	2 (0.4)	0
Pancreatitis	0	2 (0.4)	0
Rectal hemorrhage	1 (0.8)	2 (0.4)	0
Diverticulitis	0	1 (0.2)	0
Dry mouth	1 (0.8)	1 (0.2)	0
Gastroesophageal reflux disease	1 (0.8)	1 (0.2)	0
Ileus	1 (0.8)	1 (0.2)	0
Mesenteric vein thrombosis	0	1 (0.2)	0
Rectal prolapse	0	1 (0.2)	0
Tooth disorder	0	1 (0.2)	0
Enteritis	0	0	1 (0.8)
Oesophasitis	0	0	1 (0.8)
Proctitis	0	0	1 (0.8)
Metabolism and nutrition disorders	**7 (5.3)**	**27 (5.3)**	**5 (4.0)**
Hypertriglyceridaemia	5 (3.8)	12 (2.3)	1 (0.8)
Dehydration	0	3 (0.6)	1 (0.8)

SAE Table (contd from previous page)

System Organ Class, Preferred Term, n (%)	Darunavir/ RTV (mg) 600/100 bid N = 131	Darunavir/ RTV (mg) Total Darunavir N = 513	Control N = 124
Hyperlipidemia	0	2 (0.4)	0
Decreased appetite	1 (0.8)	2 (0.4)	0
Diabetes mellitus non-insulin dependent	0	1 (0.2)	0
Hypercholesterolemia	1 (0.8)	2 (0.4)	1 (0.8)
Hyperglycemia	1 (0.8)	1 (0.2)	0
Hyperuricaemia	0	1 (0.2)	1 (0.8)
Hypercalcaemia	0	1 (0.2)	0
Hypoglycaemia	0	1 (0.2)	0
Hypovolemia	0	1 (0.2)	0
Lactic acidosis	0	1 (0.2)	0
Metabolic acidosis	0	1 (0.2)	0
Anorexia	0	0	1 (0.8)
Blood and lymphatic system disorders	**4 (3.1)**	**19 (3.7)**	**3 (2.4)**
Neutropenia	2 (1.5)	10 (1.9)	3 (2.4)
Thrombocytopenia	0	6 (1.2)	0
Anemia	2 (1.5)	3 (0.6)	0
General disorders and administration site conditions	**5 (3.8)**	**15 (2.9)**	**5 (4.0)**
Fatigue	1 (0.8)	3 (0.6)	2 (1.6)
Injection site reaction	2 (1.5)	3 (0.6)	1 (0.8)
Pyrexia	0	3 (0.6)	0
Asthenia	1 (0.8)	2 (0.4)	1 (0.8)
Death	1 (0.8)	1 (0.2)	0
Hyperthermia	0	1 (0.2)	0
Injection site inflammation	0	1 (0.2)	0
Malaise	0	1 (0.2)	0
Oedema peripheral	0	0	1 (0.8)
Surgical and medical procedures	**4 (3.1)**	**9 (1.8)**	**3 (2.4)**
Hip arthroplasty	2 (1.5)	2 (0.4)	0
Anal lesion excision	0	1 (0.2)	0
Drug implantation	0	1 (0.2)	0
Intestinal fistula repair	0	1 (0.2)	0
Pain management	1 (0.8)	1 (0.2)	0
Plastic surgery	1 (0.8)	1 (0.2)	0
Shoulder operation	0	1 (0.2)	0
Surgery	0	1 (0.2)	0
Hospitalisation	0	0	1 (0.8)
Rehabilitation therapy	0	0	1 (0.8)
Wrist surgery	0	0	1 (0.8)

SAE table (contd from previous page)

System Organ Class, Preferred Term, n (%)	Darunavir/ RTV (mg) 600/100 b.i.d. N = 131	Darunavir/ RTV (mg) Total Darunavir N = 513	Control N = 124
Musculoskeletal and connective tissue disorders	**5 (3.8)**	**11 (2.1)**	**2 (1.6)**
Aseptic necrosis bone	1 (0.8)	4 (0.8)	0
Pain in extremity	1 (0.8)	2 (0.4)	0
Back pain	0	1 (0.2)	1 (0.8)
Fistula	0	1 (0.2)	0
Intervertebral disc protrusion	1 (0.8)	1 (0.2)	0
Myalgia	1 (0.8)	1 (0.2)	0
Polymyalgia	1 (0.8)	1 (0.2)	0
Arthralgia	0	0	1 (0.8)
Nervous system disorders	**3 (2.3)**	**11 (2.1)**	**2 (1.6)**
Headache	1 (0.8)	5 (1.0)	1 (0.8)
Neuropathy peripheral	2 (1.5)	3 (0.6)	0
Dizziness	0	2 (0.4)	1 (0.8)
Cerebral disorder	0	1 (0.2)	0
Cerebrovascular accident	0	1 (0.2	0
Sleep apnoea syndrome	1 (0.8)	1 (0.2	0
Neoplasms- benign, malig and Unspec.	**3 (2.3)**	**10 (1.9)**	**2 (1.6)**
Papilloma	1 (0.8)	3 (0.6)	0
Acute myeloid leukaemia	0	1 (0.2)	0
Anal cancer	1 (0.8)	1 (0.2)	1 (0.8)
Basal cell carcinoma	1 (0.8)	1 (0.2)	0
Burkitt's lymphoma	0	1 (0.2)	0
Lung adenocarcinoma	0	1 (0.2)	0
Penis carcinoma	0	1 (0.2)	0
Respiratory papilloma	1 (0.8)	1 (0.2)	0
Skin carcinoma	0	1 (0.2)	0
Squamous cell carcinoma of skin	1 (0.8)	1 (0.2)	0
Tumour lysis syndrome	0	1 (0.2)	0
Kaposi's sarcoma	0	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	**2 (1.5)**	**6 (1.2)**	**0**
Dyspnoea	1 (0.8)	2 (0.4)	0
Cough	0	1 (0.2)	0
Hypoxia	0	1 (0.2)	0
Pulmonary embolism	1 (0.8)	1 (0.2)	0
Respiratory failure	0	1 (0.2)	0

System Organ Class, Preferred Term, n (%)	Darunavir/ RTV (mg) 600/100 b.i.d. N = 131	Darunavir/ RTV (mg) Total Darunavir N = 513	Control N = 124
Cardiac disorders	**0**	**6 (1.2)**	**0**
Myocardial infarction	0	2 (0.4)	0
Atrial flutter	0	1 (0.2)	0
Congestive cardiomyopathy	0	1 (0.2)	0
Myocarditis	0	1 (0.2)	0
Supraventricular tachycardia	0	1 (0.2)	0
Tachycardia	0	1 (0.2)	0
Renal and urinary disorders	**2 (1.5)**	**6 (1.2)**	**1 (0.8)**
Renal failure acute	2 (1.5)	3 (0.6)	1 (0.8)
Renal insufficiency	0	3 (0.6)	0
Urinary incontinence	0	1 (0.2)	0
Injury, poisoning and procedural complications	**2 (1.5)**	**5 (1.0)**	**0**
Collapse of lung	0	1 (0.2)	0
Drug exposure during pregnancy	1 (0.8)	1 (0.2)	0
Muscle strain	0	1 (0.2)	0
Overdose[b]	1 (0.8)	1 (0.2)	0
Vaccination complication	0	1 (0.2)	0
Immune system disorders	**1 (0.8)**	**4 (0.8)**	**1 (0.8)**
Cryoglobulinaemia	0	1 (0.2)	0
Hypersensitivity	1 (0.8)	1 (0.2)	0
Immune reconstitution syndrome	0	1 (0.2)	0
Type IV hypersensitivity reaction[a]	0	1 (0.2)	0
Drug hypersensitivity	0	0	1 (0.8)
Hepatobiliary disorders	**0**	**3 (0.6)**	**3 (2.4)**
Cholestasis	0	1 (0.2)	0
Cytolytic hepatitis	0	1 (0.2)	0
Hepatic steatosis	0	1 (0.2)	0
Hepatitis	0	1 (0.2)	0
Hyperbilirubinemia	0	1 (0.2)	3 (2.4)
Vascular disorders	**1 (0.8)**	**3 (0.6)**	**1 (0.8)**
Hypertension	1 (0.8)	2 (0.4)	0
Hypotension	0	1 (0.2)	0
Thrombosis	0	0	1 (0.8)
Eye disorders	**0**	**2 (0.4)**	**0**
Retinal detachment	0	1 (0.2)	0
Vision blurred	0	1 (0.2)	0

System Organ Class, Preferred Term, n (%)	Darunavir/ RTV (mg) 600/100 b.i.d. N = 131	Darunavir/ RTV (mg) Total Darunavir N = 513	Control N = 124
Reproductive system and breast disorders	**2 (1.5)**	**2 (0.4)**	**0**
Genital ulceration	1 (0.8)	1 (0.2)	0
Gynaecomastia	1 (0.8)	1 (0.2)	0
Skin and subcutaneous tissue disorders	**0**	**2 (0.4)**	**0**
Erythema multiforme	0	1 (0.2)	0
Lipohypertrophy	0	1 (0.2)	0
Endocrine disorders	**1 (0.8)**	**1 (0.2)**	**0**
Adrenocortical insufficiency chronic	1 (0.8)	1 (0.2)	0
Social circumstances	**1 (0.8)**	**1 (0.2)**	**0**
Drug abuser	1 (0.8)	1 (0.2)	0
Psychiatric disorders	**0**	**0**	**1 (0.8)**
Depression	0	0	1 (0.8)

7.1.3 Dropouts and Other Significant Adverse Events

During the combined Studies TMC114-C202 and TMC114-C213, 7.2 % or (37/513) DRV/rtv subjects discontinued because of virological failure, while 81/124 or (65.3%) of subjects on the control arm discontinued because of virological failure. (See Table 7.1.3A).
When these results are divided by DRV/rtv dose arm:

- 400/100 mg qd - 21/129 (16.3 %) discontinued because of virological failure
- 800/100 mg qd - 15/127 (11.8 %) discontinued because of virological failure
- 400/100 mg bid - 14/126 (11.1 %) discontinued because of virological failure
- 600/100 mg bid - 10/131 (7.6 %) discontinued because of virological failure

MO COMMENT: Sixty five percent (65%) of subjects in the control arm (81/124) versus (60/513) or 11.7 % of subjects in the DRV study arm, exhibited a suboptimal virologic response, and discontinued the trial because of virological failure. Additionally when this is analyzed by subgroup, there is a trend toward a smaller percentage of virological failures occurring in higher dose arm.(See above).

This high discontinuation rate of controls was because of virological failure , compared to study drug, and the trend toward decreasing proportion of virological failure with increased exposure to DRV/rtv is not unexpected considering the efficacy of darunavir/rtv.

TABLE 7.1.3.A : SHOWING DISPOSITION OF COMBINED TRIALS TMC114-C202 & TMC114-C213 at 24 weeks

PARAMETER	DRV/rtv 400/100 mg qd N= 129	DRV/rtv 800/100 mg qd N=127	DRV/rtv 400/100 mg bid N=126	DRV/rtv 600/100mg bid N=131	Total TMC/rtv N=513	CONTROL N=124
RANDOMIZED	131	130	133	136	530	144
TREATED	129	127	126	131	513	124
DISCONTINUED	38	29	31	23	121	98
- # AE (AE rate)	8 (6.2%)	8 (6.3%)	12 (9.5%)	9 (6.9%)	37 (7.2%)	6 (6.6%)
- LACK OF EFFICACY	21	15	14	10	60	81
- LOST TO FOLLOW UP	9	6	5	4	24	11

7.1.3.1 Overall profile of dropouts

The table shown below provides the disposition of study subjects in the control and the darunavir 600/100 mg bid study arm, of TMC114-C202, and TMC-C213, and classifies the reason for dropping out, by death, adverse event, loss to follow-up or virological failure.

TABLE 7.1.3.1A : SHOWING DISPOSITION OF PATIENTS ACCORDING TO TREATMENT RECEIVED – the recommended dose of DRV/rtv 600/100 mg bid versus control

DISPOSITION TERMINOLOGY	**TMC114-C202 (POWER 1) DRV/rtv 600/100 mg bid** (N= 66)	**COMPARATOR PI + OBR TMC114-C202** (N=61)	**TMC114-C213 (POWER 2) DRV/rtv 600/100 bid** (N=65)	**COMPARATOR PI +OBR TMC114-C213** (N=63)
Randomized	69	71	67	73
Treated	66	61	65	63
Did not complete 24 weeks of study	17	51	6	47
• *Adverse Event*	7	2	2	5
• *Suboptimal virologic response*	6	39	4	42
• *Patient lost to follow up*	4	10	0	1

7.1.3.2 Adverse events associated with dropouts

In theStudies TmC114-C202 and TMC114-C213, thirty five (35) subjects in the DRV/rtv study arms (7.1 %), versus six (5.0%) in the CPI/r group reported AEs leading to discontinuation of study medication.
(Deaths are discussed in greater detail in the Death Section- 7.1.1)

The adverse events associated with the drop outs were as follows:
Fourteen (14) subjects on the **study arms** of TMC114-C202 discontinued the trial because of AE's. Of these subjects, two subjects ***C202-6401*** and ***C202-6405*** discontinued the trial because of elevated GGT levels, while ***C202-4802*** discontinued because of elevated ALT and AST level and ***C202-2621*** discontinued because of increased blood amylase and lipase levels.
Two subjects ***C202-0202, C202-2913*** discontinued because of renal insufficiency; ***C202-0412*** because of diarrhea; ***C202-0503*** because of abdominal pain; ***C202-2503***-fever, abdominal pain and cramping; ***C202-5617*** because of dyspepsia.; ***C202-1016***- grade 3 erythema multiforme; ***C202-2601***- because of cerebrovascular accident & elevated lipase levels; ***C202-2612*** because of lethargy and weight loss, and Subject ***202-2706*** discontinued because of a pregnancy.

Subjects discontinuing from the TMC114-C202's **control arm** included: Subject ***C202-1524*** because of Kaposi's sarcoma and ***C202-2005*** because of an injection site reaction.

Fourteen (14) subjects in the **study arm** of Trial TMC114-C213, withdrew because of adverse events:

Subject ***C213-007*** withdrew from the trial because of aggravated diarrhea. ***C213-008*** withdrew because of pregnancy. **C213-0029** withdrew because of an injection site reaction; ***C213-0052*** withdrew because of cryoglobulinemia and myocarditis, while ***C213-0058*** withdrew because of asthenia and depression.
Subjects ***C213-0066*** developed anal carcinoma and was withdrawn, while subject ***C213-0068*** withdrew because of a cerebrovascular accident and pneumonia. ***C213-0106*** developed sepsis & Herpes Simplex infection, while subject ***C213-0112*** developed hot flashes, joint swelling and enophthalmos. Subject ***C213-0181*** discontinued the trial because of severe anorexia, while subject ***C213-0238*** developed cerebral toxoplasmosis
C213-0414 developed sepsis, and ***C213-0618*** developed eosinophillia, thrombocytopenia, methemoglobinemia and hepatic cytolysis.
C213-0681 was withdrawn from the trial because of Type IV hypersensitivity, and eosinophillia.

In Study TMC114-C213, five (5) subjects in the **control arm** were discontinued from the trial because of adverse event. Subject # ***C213-0104*** discontinued because of acute renal failure; Subject #***C213-0642*** discontinued because of increase in serum ALT, AST and GGT and Subject #***213-0664*** discontinued because of chronic adrenocortical insufficiency, cytomegalovirus chorioretinitis, and encephalitis. Subject # ***C213-0529*** developed vomiting, and was discontinued.

TABLE 7.1.3.2A: SHOWING ADVERSE EVENTS RESULTING IN DISCONTINUATION OF STUDY DRUG & CONTROL IN TMC114-C202 and TMC114-C213

MedDRA Preferred Term	**TMC114-C202 +C213 (N=513)**	**TMC114-C202 + C213 CONTROL ARM (N= 124)**
# of subjects who permanently discontinued treatment due to AE	**N = 35 (7.1%)**	**N = 6 (4.8%)**
SPECIFIC ADVERSE EVENTS RESULTING IN DISCONTINUATION		
Infections and infestations		
Pneumonia	*2*	
Cerebral toxoplasmosis	*1*	
Sepsis	*1*	
Investigations		
Elevated GGT	*2*	
Elevated ALT and AST	*1*	*1*
Elevated amylase and lipase	*1*	
Gastrointestinal disorders		
Abdominal pain	*1*	
Abdominal cramps	*1*	

Dyspepsia	*1*	
Diarrhea	*2*	
Fever, abdominal pain & Vomiting	*1*	
Vomiting		*1*
General disorders and Administration site conditions		
Injection site reaction	*1*	*1*
Respiratory, thoracic and Mediastinal disorders		
-Myocarditis	*1*	
Metabolism and nutrition disorders		
Weight loss	*1*	
Fever	*1*	
Lethargy	*1*	
Severe anorexia	*1*	
Renal and urinary disorders		
Renal failure & insufficiency	*2*	*1*
Nervous system disorders		
Cerebrovascular accident	*2*	
Neoplasms benign, malignant and unspecified		
Anal carcinoma	*1*	
Lymphoma		
Kaposi's sarcoma		*1*
Skin and subcutaneous tissue disorder		
Dermatitis medicamentosa	*1*	
Erythema multiforme	*1*	
Type IV hypersensitivity	*1*	
Psychiatric disorders		
Depression	*1*	
Blood and Lymphatic system		
-pancytopenia		
- eosinophillia, & thromboctyopenia	*1*	
Endocrine Disorders		
- adrenocortical insufficiency		*1*
Preganancy	*2*	

***MO COMMENT**: Although the proportion of subjects discontinuing for each Preferred Term is small, there is clearly an indication that gastrointestinal AE terms are DRV/rtv related. It is also important to note that although the proportion of subjects discontinuing because of adverse events were greater on study drug arm as compared to control arm, it should be remembered that study subjects spent a significantly shorter time on the control as compared to the DRV arm.*

7.1.3.3 Other significant adverse events

There were four safety signals identified throughout the darunavir development program: hepatotoxicity, rash, elevated pancreatic amylase and lipase, and hyperlipidemia. These are discussed in greater detail in Section 7.

These safety signals are as follows:

1) Hepatotoxicity
2) Rash
3) Elevated pancreatic amylase and lipase
4) Hyperlipidemia

7.1.3.3.1 Hepatic adverse events

The overall incidence of hepatic-related events reported as adverse events (AEs) was 9% in subjects who were treated with DRV/RTV 600/100 mg bid in all Phase IIb trials, as compared with an incidence of 12% noted in control subjects.

The incidence of liver-related events reported as adverse events in controlled studies C202 and C213 was 9.8 events per 100 patient years exposure in all TMC/RTV treatment groups combined and 20.0 events per 100 patient years exposure in the control group.

The most commonly reported liver-related AEs in subjects who initiated treatment with DRV/RTV 600/100 mg bid were related to laboratory investigations. Five percent of subjects in the TMC/RTV arm versus 7% of subjects in the control arm had a grade 3 or 4 liver-related AE. Abnormalities in liver enzyme tests were mainly observed for AST and ALT. Most graded individual liver abnormalities were grade 1 or 2 in severity. The incidence of grade 3 or 4 increases in ALT and AST was low (2%), and the mean values for AST and ALT decreased over time. These percentages did not appear to be significantly different than observed with the control group that consisted of subjects on approved protease inhibitors (PI's) The following table compares LFT abnormalities in all subjects who ever received DRV/rtv 600/100 bid to control subjects from Studies TMC114-C202 and TMC114-C213.

A) **Analysis based on Overall subjects exposed to DRV/RTV, and grade of ALT/ AST/ ALP/ bilirubin abnormality and compared with control**

TABLE 7.1.3.3.1A SHOWING ACTG GRADED LFT'S EMERGING AT RECOMMENDED DOSE IN THE TREATMENT PERIOD (TMC114-C202+ TMC114-C213 + TMC114-C215-C208 (WORST GRADE)

LABORATORY PARAMETER N (%)		TOTAL C202+C213+C215/208 (N=810)	C202 +C213 CONTROL (N= 124)
ALT	Grade 1	84 (10.5)	29 (22.6)
	Grade 2	26 (3.4)	9 (7.3)
	Grade 3	9 (1.1)	1 (0.8)
	Grade 4	4 (0.5)	2 (1.6)
AST	Grade 1	109 (13.6)	33 (26.8)
	Grade 2	26 (3.2)	11 (8.9)
	Grade 3	9 (1.1)	3 (2.4)
	Grade 4	3 (0.4)	2 (1.6)
ALP	Grade 1	33 (4.1)	11 (8.9)
	Grade 2	13 (1.6)	0
	Grade 3	3 (0.4)	0
Bilirubin	Grade 1	16 (2.0)	4 (3.3)
	Grade 2	4 (0.5)	15 (12.2)
	Grade 3	1(0.1)	4 (3.3)
	Grade 4	3 (0.4)	0

B) Analysis based on dose of DRV/rtv and compared with control in dose finding portion of TMC114-C202 and C213 Trials

There was no dose related response associated with development of elevation of serum ALT, AST, bilirubin elevation or alkaline phosphatase levels in the dose–related portion of the TMC114-C202 or the TMC114-C213 trials. There was no difference in the proportion of subjects who developed elevations of these serum enzymes and the control group.

C) Analysis based on liver injury and pattern of injury

Using the following definitions of liver injury [See NEJM 2006; 354:731-9]:

Definition #1- ALT of > 3 times the ULN and an ALP level of > 2 times the ULN. After searching the data bases submitted by the sponsor, this reviewer was able to find one subject who fit this definition of liver injury (CRF ID# C215-0052); please refer to Section D (below) for further clinical information on this subject.

OR

Definition #2 - Total bilirubin of > 2 times ULN, associated with an elevation of ALT or ALP level. This 2nd definition is said to suggest a cholestatic pattern of injury that is usually seen in sulfonamides drugs, such as darunavir. After examining the databases submitted by the Sponsor, none of the serum enzyme elevations were sustained; none resulted in reported AE's, or discontinuing study medications. Evaluation of controls, who exhibited this pattern of elevation, was confounded by the co-administration of atazanivir, which is known to cause an elevation of indirect bilirubin levels.

D) ANALYSIS BASED ON PERMANENT or TEMPORARY DISCONTINUATION OF STUDY DRUG

Three subjects (who were not reported as SAE's) discontinued any TMC/RTV trial due to liver-related AEs. Two subjects had elevated Grade 3/ 4 ALT's, one accompanied by a grade 2 ALP while the third subject had a Grade 3 ALT and Grade 2 AST.

The following three subjects (who were not reported as SAE's) had study drug permanently withdrawn from study because of hepatic AE's:

1) **C215-0052**- This 45 y/o male was a roll-over from the control arm of C202 (CRF ID 202-5507). The hepatic AE occurred after he was switched to TMC/RTV. His medications included DRV/RTV + Abacavir + TFV + 3TC. On Week 16 of study he developed Grade 3-4 ALT / AST / GGT elevations and Grade 2 alkaline phosphatase elevations. Concomitant (non-ARV) medications included: clarithromycin, dyazide, fluticasone, furosemide, "herbal preparations", medinite, ramipril, salbutamol, and valaciclovir hydrochloride. Concomitant medical conditions at time of enrollment were diarrhea, toxoplasmosis, neuropathy, herpes zoster, wasting syndrome, thrush, esophageal candidiasis, hypertension, and depression. Grade 3 ALT's were reported 114 days after starting treatment, with TMC/RTV. Five days later, ALT decreased to 205 U/L, without any adjustment in study medication. Three weeks after (March 23rd 2005,

AST/ALT/ GGT was reported as grade 4, and ALP grade 2 elevated. The study drug was permanently withdrawn after 145 days of treatment.

2) **C215-0408** – This 66 y/o male on DRV/RTV 600/100 mg + 3TC + ENF developed grade 3/4 ALT and AST levels and grade 1 ALP levels 29 days after starting treatment. Bilirubin levels were normal. (Serum hepatic enzyme levels were grade 1 at screening and baseline). Concomitant medications and conditions included aspirin for myocardial infarction, dronabinol for appetite enhancement, clarithromycin and ethambutol for MAC, trimethoprim/sulfamethoxazole for PCP and toxoplasmosis prophylaxis, and valganciclovir.

3) **C215-0500** – 37 y/o male with on DRV/RTV + DDI + TFV, who developed grade 3 ALT, grade 2 AST. Alkaline phosphatase levels were normal.

*4) **C202- 6401** - Patient receiving DRV/RTV 400/100 mg qd discontinued study medication permanently due to grade 4 increased GGT

*5) **C202- 6405** - DRV/RTV 600/100 mg bid permanently discontinued treatment due to grade 3 increase GGT

**MO COMMENT: Elevations of GGT causing permanent discontinuation of DRV/RTV during the trial is mentioned here merely for the sake of completeness. This reviewer is aware that the high sensitivity and low specificity of the serum GGT level measurements as an indicator of liver damage is of marginal value in detecting hepatotoxicity.*

The following subjects had study drug temporarily held:

C215-0032 – Subject was a 36 y/o male who started treatment at a dose of 400/100 mg bid as part of his ARV therapy, which included (DDI, emtricitabine, & TFV). Subject was also receiving gabapentin and cotylenol for a painful polyneuropathy. Twenty three (23) days after starting study drug temporarily withdrawn for 7 days, because of a Grade 4 AST. AST levels returned to Grade 1 level within 7 days. At the time of maximal AST elevation, ALT was Grade 2 elevated. There are no reports of bilirubin levels for this subject.

C215-0065 - This 44 y/o male started the study with a reactive HCV serology, and a history of HBV. Serum ALT / AST/ bilirubin levels were elevated (Grade 3) before he started on study medication; four weeks after starting on study medications another episode of Grade 3 ALT, AST and bilirubin elevation occurred. These enzyme elevations were attributed to Recurrent Hepatitis C Disease. Enzyme levels remained elevated at the time of database lock in September 2005. Study medication was stopped since 1/18/2005.

C215-0413 - This 35 y/o male was started on TMC/RTV 600/100 mg bid, with abacavir and DDI on 3/30/05. Eight weeks after starting therapy, patient developed Grade 4 ALT/ AST, Grade 1 ALP, with normal bilirubin levels. The study medication was temporarily stopped, with complete resolution of liver enzyme elevation. This subject was also receiving paracetamol.

C215- 0268 – This 33 y/o male was temporarily withdrawn from study medications TMC/RTV, abacavir, 3TC, ZDV) on Week 20 of study because of Grade 4 ALT and AST elevation, with normal direct bilirubin and alkaline phosphatase levels.

C215-0128- This 36 y/o female on TMC/RTV + d4T + TFV developed Grade 1 elevation of ALT, Grade 3 AST elevations 20 weeks after starting study medications. Alkaline phosphates levels remained normal. There is no report of concomitant bilirubin elevations. Dose of study medication was not changed, and enzyme elevation resolved.

C215-0016 - This 44 y/o male on TMC/RTV 400/100 mg bid + DDI + 3TC+ TFV + ENF developed grade 3 elevations of alkaline phosphatase levels, with normal AST/ ALT and bilirubin levels , 40 weeks after starting the study. Elevated enzyme levels resolved without changing dose of study medications.

C215- 0153- This 35 y/o male on TMC/RTV 400/100 mg bid + 3TC + TFV + d4T developed grade 3 ALT and Grade 2 AST between Week 16 – 20 of exposure to study meds. Alkaline phosphatase levels remained within normal limits. Study medication was temporarily held for 5 weeks. Enzyme levels resolved 26 days after elevation.

C202-6610- This 37 y/o male on TMC/RTV + DDI+ TFV developed meningitis and orchitis and required hospitalization. Narrative summary showed a grade 1 ALT, with normal bilirubin, AST and ALP levels. Study medication was temporarily stopped. (This subject is also reported in the SAE summary Section E noted below).

C202- 1501-This subject developed grade 3 ALT and grade 2 AST on trial day 595. ALT/AST recovered 64 days later. No concomitant elevation of serum bilirubin. Study medication temporarily stopped. At that time subject was diagnosed as having hepatitis C disease.

E) DISCUSSION OF INDIVIDUAL HEPATIC SAE'S NOTED THROUGHOUT DEVELOPMENT PROGRAM OF DRV/RTV

Eight hepatotoxic SAE's were observed in the Phase II trials of TMC/RTV.

Four of the eight subjects exhibited evidence of liver biopsy-proven hepatitis.

The 1st case of biopsy-proven drug induced hepatitis occurred very early in the clinical developmental process in subject CRF # 207-0019, a 36 y/o male in Trial TMC114-C207. Subject had grade 1 AST and GGT levels at baseline, and was treated with DRV/RTV 600/100 mg BID for 14 days; Grade 4 elevations of liver enzymes and clinical jaundice occurred 14 days after termination of the trial. A liver biopsy showed a histologic image compatible with an acute hepatitis of "medicamentous origin". The subject discontinued the trial during the follow-up period. The subject is said to have consumed 3 'units' of wine daily. CAT scan of the liver excluded obstructive biliary pathology. The subject recovered. Concomitant medications included IDV, SQV, d4T and DDI.

In a 2nd case, subject # C213-0688 the subject had normal bilirubin, ALT, AST, and GGT levels at baseline. Elevated ALT, AST, and GGT were noted 8 months after initiation of study medication. Concomitant medications included RTV, TFV, DDI, 3TC and pravastatin. Serum ALT was 57, AST- 57, GGT ranged from 138 to 224 and with a normal serum bilirubin. Hep A/B/C serologies were negative. The clinical picture was suggestive liver cirrhosis with ascites, and 4-5 litres of ascitic fluid was withdrawn from the abdomen. Culture of the ascitic fluid was negative for malignant cells, and cultures for acid fast bacilli are pending. An MRI of the liver was said to be suggestive of cirrhosis of the liver with portal hypertension. A transjugular approach liver biopsy was indicative of either an infection, or toxic liver damage secondary to medication. There was said to be no evidence of florid steatohepatitis. (This subject was also permanently withdrawn from study medication. He was not included in permanent withdrawal section of this analysis, as the SAE occurred after the September 2005 database lock).

In a 3rd case, subject CRF # C213-0077 exhibited an elevation of ALT's, AST's and bilirubin 15 months after initiating DRV/RTV 400/100 mg; Concomitant medications included TFV, and ENF. Liver biopsy showed evidence of alcoholic or non alcoholic steatohepatitis (NASH); This subject did not have a history of alcohol consumption. TMC/RTV was discontinued.

A 4th liver biopsy was performed in a 39 y/o female, (CRF ID#C-215-0333) with a history of HBV/ HCV at baseline. Biopsy was performed 8 weeks after initiating treatment with TMC/RTV 600/100 mg bid. Concomitant medications included diprosalic, abacavir, ENF, lamivudine, and TFV. Liver biopsy showed chronic hepatitis with minimal portal vein fibrosis. Serum ALT was elevated to grade 2 at Week 8 with normal alkaline phosphatase, normal AST levels, and normal bilirubin levels. This subject continued on TMC/RTV, without dose adjustment.

Of the remaining four cases, three of these occurred in association with other non-hepatic infectious illnesses (CRF ID #'s C202-3503, C213-0120 and C-202-6610), and the elevation of serum liver function tests that occurred were considered to be related to the associated infection.

One case (TMC114-PAA 2722) occurred in association with TPN, and the elevated alkaline phosphatase resolved when lipid free-TPN feedings were instituted.

SUMMARY TABLE 7.1.3.3.1.E OF SUBJECTS EXPOSED TO TMC/ RTV WHO EXHIBITED SAE'S

Subject # Age/Gender Trial #	BASELINE HBV/HCV/ LFT's/ liver biopsy	TMC114 Rx day of onset of ↑LFT	TMC114 Rx day of max. ↑LFT	Concomitant Medications	Intervention	Pattern of LFT elevation ALT	Post TMC biopsy Result	Investigations	Outcome
-JNJFOC-2005-1103596 20 y/o ♂ TMC114-PAA-2722	↑Alk Phos. baseline	Alk. Phos. 241@bl ATT-30Days	ALT=304 @ 30 Days. (Bili.= N)	Truvada, ENF, Nitazoxanide-(Cryptosp), Cyclizine-Nausea, TPN, Bactrim	Lipid Free TPN- w/o change in meds	↑ALK Phos.	None	Autoantibody screen- (N) Cholangiopancreatography- (N)	Improvement with lipid free TPN
-JNJFOC-2004-1206907 51 y/o ♂ TMC114-C213-0120	-Grade 1 AST/GGT. CD4=16 - Hepatic Steatosis (Biopsy 2001)			DDI/Emtric/ 3TC/ d4T/LPV/ Caspofungin/ Fentanyl/ Ethambutol/ Amphoterecin/ Moxifloxacin/ Rifanp/pentamid		(N) – bili;	None	Nil else	Death 2ry to -Porto-Cath sepsis -Hepatic failure – -Atypical Myco Bacter,
-JNJFOC-2005-100783 36 y/o ♂ C-207-0019	TMC 4/9/02→ 4/22/02 (14days) Suspicious of acute and chronic alcohol abuse; prior ↑ GGT		AST= 1784 & ALT= 1483 (5/7/02); GGT= 545 (5/6/02)	RTV(d/ced 4/25/02);IDV (d/ced 4/8/02); SQV (d/ced 4/23/02); d4T (d/ced 4/8/02); DDI (d/ced 4/23/02		Grade 4 ALT/ AST & Grade 4 Bilirubin	Drug-induced Hepatitis (5/10/02)	Drank 3 'units' of wine/day. CAT Scan excluded obstructive biliary pathology	Biopsy proven Drug-induced Hepatitis
-JNJFOC-2005-020401374 39 y/o ♀ C-215-0333	HBV/ HCV(+) at baseline; Biopsy-Chronic Hepatitis c w/ minimal portal vein fibrosis	Week 8- gr 2 ALT, & gr 1 AST. Alk Phos (N) Bili (N)		RTV/TFV/ 3TC/ ENF/ABC/ Acyclovir/bactrim/ diprosalic/meteospasmyl/valcyclovir		Gr 2 ALT; Gr 1 AST; (N)- bili	Pre-planned biopsy performed 8 days after starting TMC (see baseline)	Nil else	Continued on TMC/RTV. Dose not changed. Resolved

Subject # Age/Gender Trial #	BASELINE HBV/HCV/ LFT's/ liver biopsy	TMC114 Rx day of onset of ↑LFT	TMC114 Rx day of maximal ↑LFT	Concomitant Medications	Intervention	Pattern of LFT elevation ALT	Post TMC biopsy Result	Investigations	Outcome
[redacted] -JNJFOC-2005-0602618 57 y/o ♂ C202-3503				RTV, EMTRIC, TFV		ALT= 438, AST= 328, Bili= 8.9 Post-Pneumonia	None	No other liver related investigations performed in this terminal patient.	Death – Pneumonia End-Stage HIV
[redacted] -JNJFOC-2005-0605418 49 y/o ♂ C213-0077	(N) Bl. ALT/AST /GGT/Bili.		ALT-16mnths AST-19mths ALP-19mnths Bili.-14mnths	RTV/TFV /ENF			TMC 2/5/04 → 6/10/05 NASH biopsy ([redacted])	No Alcohol Consumption	Alcoholic or Non-Alcoholic Steato-hepatitis (NASH) TMC d/ced on [redacted]
[redacted] -JNJFOC-2005-0906839 38 y/o ♂ C202-6610	TMC started on 1/24/05			RTV/ TFV /DDI/ ZDV/ Alprazolam/, aspirin/cephalexin/dexamethasone	TMC temp d/ced on 9/25/05. Restarted on 10/11/05	Gr 1 ALT, (N) ALP (N) bili		Hep A/B/C Serologies (-) Hepatogram (N) Viral Meningitis- [redacted] Hepatitis - [redacted] Orchitis- [redacted]	Study medication temporarily withdrawn. Enzyme levels returned to (N).
[redacted] -JNJFOC-2005-1004584 46 y/o ♂ C213-0688	ALT/bili/ AST/GGT= (N) at baseline about 8/23	↑ALT 68 ↑AST 60 @ 1 mth ;	↑GGT, ALT, AST 8 months post TMC114	RTV/ TFV/ DDI/ 3TC/ Pravastatin	Transjugular Liver Biopsy; Liver MRI-Cirrhosis with portal hypertension	ALT=57 AST=57 GGT= 138→224 (N=10-61); bili-(N)	Drug Toxic liver damage [redacted]	Hep A/B/C Serologies (-) ↑ALT/AST/GGT, (N) Bili. Ascites culture- neg for malig cell & AFB cultures pending	TMC/RTV d/ced on [redacted] Δ=HIV or infectious obstructive bile duct disorder

F) CONCLUSIONS ON HEPATIC SAFETY ANALYSIS

The available data do not suggest a higher incidence of hepatic AE's with DRV/rtv relative to other available ARV's.

The results show that the AE's and laboratory biochemical abnormalities related to increases in ALT and AST seen in HIV-1 infected subjects receiving DRV/rtv were generally transient, in that most abnormalities either resolved with continued dosing or did not recur following reinitiation of treatment following temporary interruption, and only uncommonly lead to permanent treatment discontinuation, and that their frequency was lower than that observed in subjects receiving other PI's.

Inference(s) from the analysis of hepatic safety are limited by the following:

1) The very low sample size (n) in the control study arms, as ethically, the design of the trial needed to allow these very treatment-experienced study participants the opportunity to "bail out", should they experience confirmed virological failure. This relatively small comparator confounded the comparisons that could be made between control and study arm.
MO COMMENT: *Most ARV drugs are associated to some degree with hepatoxicity, although the mechanism is different for different classes of drugs, and sometimes different within a class. Examples include hepatoxicity secondary to mitochondrial toxicity for nucleoside reverse transcriptase inhibitors (NRTIs), nevaripine-associated hepatotoxicity that appears to be immune-mediated, and hepatotoxicity observed with other drugs in the class of protease inhibitors.*

2) The fact that the elevations of liver serum enzymes that denoted hepatic injury that occurred in control arm were not sustained, nor did they result in the discontinuation of study medications, and were further confounded by multiple pharmacopoeia, particularly the presence of the ARV agent, atazanavir, which is known to cause an elevation in the indirect bilirubin levels.
3) The presence of other concomitant medications confounded causative inferential assessment, included gabapentin, and or co-tylenol, which are used for treating painful polyneuropathy, or the use of "herbal medications" and/or ethanol.

7.1.3.3 Analysis of Rash

From the ***Phase I trials***, the rash associated with the use of TMC114 alone or in combination with RTV appeared to be mainly maculo-papular in nature, appearing about 9 days after exposure to the drug, and with a median duration of about 8-12 days. The rash occurred in 33% of subjects receiving TMC114 alone, and in 2% of subjects receiving DRV/rtv. There was no consistent pattern or syndrome for AE's occurring in association with the rash, except that 50% of cases were associated with pruritus. In the Phase I oral contraceptive study Trial TMC114-C131 treatment with DRV/rtv 600/100 mg bid in combination with Ortho-Novum 1/35 q.d. in 19 healthy female subjects resulted in a dropout rate due to cutaneous AEs of 26% (5/19 subjects).

A. PROOF OF PRINCIPLE PHASE IIa TRAILS

In the treatment-experienced Proof of Principle trials TMC114-C201, the incidence of rash was 24% or (7/29) of persons exposed to TMC114 alone, without RTV-boosting, compared to 0% of control subjects (See Table 7.1.2.2A); while in the TMC114-C207 trial, where subjects received TMC114 in combination with RTV, the incidence of rash was 18 % (7/38) versus 0 % rash in the control group; (See Table 7.1.2.2B).

Three (3) of 27 subjects in TMC114-C201 experienced treatment-emergent rash related AE's and included CRF# 201-0052 on TMC114 400 mg bid experienced grade 1 papular rash; Subject CRF #201-0046 on TMC114, 800 mg tid experienced grade 2 rash maculo-papular in nature, and Subject CRF# 201-0203, 800mg tid experienced grade 1 erythema.
None of the control subjects developed a rash, or discontinued drug due to an AE's.
There was no relationship between rash related AE's and dose of TMC/RTV.

TABLE 7.1.2.2A SHOWING AE'S OCCURRING IN MORE THAN 1 SUBJECT DURING THE TREATMENT PERIOD OF TRIAL TMC114-C201

Skin & Subcutaneous tissue	DRV 400 mg bid N= 8 (%)	DRV 800 mg bid N= 8 (%)	DRV 800 mg tid N= 7 (%)	DRV 1200 mg tid N= 6 (%)	Total DRV N= 29(%)	Control N= 5(%)
Any skin AE	2 (25)	0	3 (42.9)	2 (33)	7 (24)	0

TABLE 7.1.2.2B SHOWING AE'S OCCURRING IN MORE THAN 1 SUBJECT DURING THE TREATMENT PERIOD OF TRIAL DRV-C207

Skin & Subcutaneous tissue	DRV 300/100 mg bid N= 13 (%)	DRV 900/100 mg qd N= 13 (%)	DRV 600/100 mg bid N= 12 (%)	Total DRV N= 38 (%)	Control N= 12 (%)
Any skin AE	3 (23)	3 (23)	1 (8)	7 (18)	0

B. PHASE IIB REGISTRATIONAL TRIALS

TMC114-C202 and TMC114-C213

In Phase IIb registrational trials TMC114-C202 and TMC114-C213, the incidence of rash-related AEs was similar (both 8%) in the DRV/RTVgroups and in the control group. However, when the

incidence of rash-related AEs per 100 patient years of exposure was calculated, this newly calculated incidence was lower in the DRV/rtv groups than in the control group (DRV/RTV: 8.1 events per 100 patient years exposure; control: 13.3 events per 100 patient years exposure) . There was no relationship between the occurrence of rash-related AEs and DRV/rtv dose, as demonstrated in Table 7.1.2.2C noted below. The observed incidence and the incidence per 100 patient years exposure of rash-related AEs reported by more than 1 DRV/rtv-treated subject are presented in Table 7.1.2.2C below.

Table 7.1.2.2C: Showing commonly reported Rash-Related AE's : Observed Incidence and Incidence per 100 patient Years Exposure in Trials TMC114-C202 + TMC114-C213

	400/100 mg qd N=129	**800/100 mg qd N=127**	**400/100 mg bid N =126**	**600/100mg bid N=131**	**Total DRV N=513**	**Control N= 124**
Mean Exposure	**43.95**	**45.48**	**44.02**	**62.29**	**49.03**	**31.54**
Observed incidence, n (%)						
Any rash related AE	**13 (10.1)**	**10 (7.9)**	**9 (7.1)**	**8 (6.1)**	**40 (7.8)**	**10 (8.1)**
Erythema	2 (1.6)	6 (4.7)	0	1 (0.8)	9 (1.8)	1 (0.8)
Rash	4 (3.1)	0	3 (2.4)	2 (1.5)	9 (1.8)	0
Rash papular	4 (3.1)	1(0.8)	2 (1.6)	0	7 (1.4)	3 (2.4)
Rash maculo-papular	0	0	1 (0.8)	2 (1.5)	3 (0.6)	4 (3.2)
Exanthem	2 (1.6)	1 (0.8)	0	0	3 (0.6)	1 (1.8)
Dermatitis allergic	0	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.6)	0
Rash pruritic	1 (0.8)	1 (0.8)	1 (0.8)	0	3 (0.6)	0
Rash erythematous	0	1 (0.8)	0	1 (0.8)	2 (0.4)	0
Toxic skin eruption	0	0	1 (0.8)	1 (0.8)	2 (0.4)	0
Incidence per 100 patient years exposure						
Any rash related AE	**12.0**	**9.0**	**7.5**	**5.1**	**8.1**	**13.3**
Erythema	1.8	5.4	0	0.6	1.9	1.3
Rash	3.7	0	2.8	1.3	1.9	0
Rash papular	3.7	0.9	1.9	0	1.5	4.0
Rash maculo-papular	0	0	0.9	1.3	0.6	5.3
Exanthem	1.8	0.9	0	0	0.6	1.3
Dermatitis allergic	0	0.9	0.9	0.6	0.6	0
Rash pruritic	0.9	0.9	0.9	0	0.6	0
Rash	0	0.9	0	0.6	0.4	0

erythematous						
Toxic skin eruption	0	0	0.9	0.6	0.4	0

C. SUBJECTS PERMANENTLY DISCONTINUING DRV/RTV DUE TO SKIN RASH

Three subjects in the Phase IIb controlled trials permanently discontinued DRV/RTV due to skin rash; one subject because of type IV hypersensitivity; a second due to erythema multiforme, and a 3rd due to "dermatitis medicamentosa". A fourth case from the treatment-naive Phase III trial was permanently discontinued from study medication, based on a biopsy proven evidence of Stevens Johnson Syndrome.

1) CRF ID# C213-0681- This 20 y/o male started DRV/rtv 400/100 mg on August 19th 2004, as part of his ARV treatment that included abacavir, 3TC, ZDV and TFV. Concomitant medications included dapsone for PCP prophylaxis, (history of allergy to bactrim during childhood). Concomitant medical diagnoses included herpetic stomatitis, thrombocytopenia, splenectomy, growth retardation, and repeated bouts of pulmonary infection.
On [redacted], during screening period, the subject was hospitalized due to grade 3 diffuse cutaneous allergy. Two to three days after starting to take study drug, he developed **toxidermia (toxic skin eruption)** on the neck, legs, back and arms. The symptoms improved with symptomatic treatment, but 2 days later the eruption extended to the abdomen; The toxic skin eruption was reported as a type IV hypersensitivity reaction. TMC/RTV was started on August 19th, and discontinued on September 1st 2004, because of type IV hypersensitive reaction and hypereosinophilia. Dapsone was started prior to initiation of the trial, was discontinued on September 9th 2004.
Grade 3 elevation of AST noted on September 10th 2004; Eosinophilia was noted initially on August 26th 2004; Eosinophils decreased to normal levels on September 9th, eight days after the study drug was withdrawn.
On September 1st 2004, he was permanently withdrawn from the study drug and the trial.
On September 9th he was started on oral Prednisone 30 mg daily.

This event was a grade III SAE leading to treatment discontinuation was probably related to the study medication. The concomitant eosinophilia, and elevated AST suggest an allergic etiological origin to this constellation of signs and symptoms.

2) CRF ID# 202-1016- This 45 y/o male started treatment with DRV/rtv 800/100 mg qd from February 25th 2004 until July 2nd 2004, as part of ARV therapy that also included TFV, 3TC and DDI. Concomitant medical diagnoses included an abacavir rash, kaposi's sarcoma, shigellosis, genital HPV, dizziness, allergic dermatitis, eczema, diarrhea and depression. On July 1st 2004, subject developed **Grade 3 erythema multiforme,** and study medication was withdrawn. He was treated with Prednisone 20 mg po bid, hydroxizine embonate 50 mg im qd, and 50 mg po qid for the rash. During the trial subject suffered with multiple dermatological problems, namely: Grade 1 eosinophillic pustular folliculitis (March 2nd -18th 2004); Dry skin – Feb 24th – (ongoing)

3) CRF #215-0303- This 37 y/o woman started the trial with a dose of DRV/rtv 600/100 mg bid, on March 31st 2005. Other ARV medications included 3TC+ TFV+ ZDV. At the time of enrollment she had a history of jaundice due to atazanavir exposure.

On April 10th 2005, eleven days after starting treatment, she developed "dermatitis medicamentosa". She was treated with dexchlorpheniramine and hydroxyzine form April 9th to 16th 2005. The subject was said to recover from this rash 5 days later. Study medication was permanently stopped on April 11th 2005, because of this AE. Serum ALT and AST levels although normal at baseline were elevated to grade 2 and grade 1 levels on April 20th , until one week after discontinuing the medication.

No control subjects discontinued study drug because of skin AE's.

4) CRF # 211-0344 - A case of biopsy-proven Stevens Johnson Syndrome was submitted via Med Watch on May 11th 2006. This subject was also permanently discontinued from study medication.

This 28 y/o black male was enrolled in the treatment naive study TMC114-C211. He was randomized to receive DRV/rtv 800/100 mg qd on May 9th 2006, along with emtricabine and TFV. Concomitant medications included dapsone, (started 6 weeks prior to onset of rash) for prophylaxis of PCP pneumonia., loratidine for seasonal allergies, clavulanate for sore throat and Augmentin (started 8 days prior to rash onset) for pharyngeal pain. The patient had a past history of drug allergies when talking sulfonamides.

Two days after initiating DRV/rtv, he developed sore throat, fever and sweats, and on [redacted] after receiving first receiving DRV, he was moved to the ICU for closer monitoring , and was diagnosed with Stevens Johnson Syndrome. DRV/rtv was permanently discontinued. The rash had not cleared at the time of writing this report.

D. ANALYSIS BASED ON SUBJECTS WHO IDENTIFY AS HAVING A HISTORY OF SULFUR ALLERGY

The rate of rash was similar in control subjects who self identify (9.5%) as having a sulfonamide rash, as compared to controls who did not self identify as having a sulfonamide allergy (7.8%) are similar.

On the other hand, of all subjects who ever received DRV/RTV at the proposed dose and who self identified as having a sulfonamide rash, had twice the rate of rash (6.7%), as compared to those who do not self identify as having sulfonamide rash (3.3%), and who are exposed to DRV/RTV. (See Table 7.2.2.2D(i).

There does not appear to be a particular predilection to the occurrence of rash by gender, as demonstrated in Table 7.1.2.2D(ii)below. When the incidence of rash is analyzed by gender in de novo subjects, and in controls, the 95% confidence intervals for the odds ratios include one, suggesting no significant difference in the occurrence of rash between males and females.

TABLE 7.1.2.2D(i): SHOWING OVERVIEW OF RASH-RELATED AE's IN SUBJECTS WHO IDENTIFY or DO NOT IDENTIFY AS HAVING SULFONAMIDE ALLERGY

PREFERRED TERM	SUBJECTS SELF IDENTIFYING AS HAVING SULFONAMIDE ALLERGY		SUBJECTS WHO DO NOT SELF IDENTIFY AS HAVING A SULFONAMIDE ALLERGY	
	DRV/RTV 600/100 mg bid N=150	**Control N=21**	**DRV/RTV 600/100 mg bid N=660**	**Control N=103**
ACTUAL INCIDENCE ANY RASH RELATED AE	10 (6.7)	2 (9.5)	22 (3.3)	8 (7.8)
Dermatitis allergic	1 (0.7)	0	1 (0.2)	0
Dermatitis medicamentosa	0	0	1 (0.2)	1 (1.0)
Exanthema	1 (0.7)	1 (4.8)	0	0
Erythema	1 (0.7)	0	1 (0.2)	1 (1.0)
Rash	1 (0.7)	0	6 (0.9)	0
Rash Erythematous	3 (2)	0	1 (0.9)	0
Rash macular	1 (0.7)	0	2 (0.3)	0
Rash maculo-papular	1 (0.7)	1 (4.8)	3 (0.5)	3 (2.9)
Rash morbiliform	0	0	1 (0.2)	0
Rash papular	2 (1.3)	0	2.0 (0.3)	3 (2.9)
Rash pruritic	0	0	2.0 (0.3)	0
Toxic skin eruption	0	0	2.0 (0.3)	0

Table 7.1.2.2.D(ii): Showing Rash- Related Adverse Events by Gender - All Darunavir Data TMC114-C202 + TMC114-C213 + TMC114-C215/C208

Preferred Term	**600/100 mg bid de novo**		**Total Darunavir**		**Control**	
	Female	Male	Female	Male	Female	Male
	N= 56	N=402	N=109	N= 815	N= 15	N= 109
Any Rash related AE	**3 (5.4)**	**24 (6.0)**	**5 (4.6)**	**63 (7.7)**	**1 (6.7)**	**9 (8.3)**
	Odds ratio = 1.1 (95% CI = 0.33,3.9) p value = 0.86		Odds ratio = 1.7 (95% CI = 0.7,4.4) p value = 0.24		Odds ratio = 1.26 (95% CI = 0.15,10.7) p value = 0.83	

E. OVERALL CONCLUSION OF DRV/ rtvAND THE DEVELOPMENT OF RASH

The incidence of rash was about 8% and similar in both the study arm (DRV/rtv) and the control arm of the controlled Phase II trials. However, when the incidence of rash per 100 patient years of exposure was compared between was compared between both groups, the TMC/RTV arm was slightly less than the control arm (8 versus 13). There is no significant difference in the occurence of rash between males and females.

Rash SAEs occurred only in subjects receiving DRV/rtv arm. No control subjects discontinued study drug because of rash SAE's, while 2/513 (0.3%) subjects in trial TMC114-C202 and TMC114-C213 discontinued study drug because of SAE, and 1/327(0.3%) of subjects in trial C215/C208 discontinued study drug because of SAE's. Additionally, when SAE's occurred in association with DRV/RTV use, treatment with systemic prednisone and /or hospitalization was required.

From the Phase I trials, the rash appeared to be mainly maculo-papular in nature, appearing about 9 days after exposure to study drug, and with a median duration of about 8-12 days. Rash occurred with or without mucosal involvement. There was no consistent pattern or syndrome for concurrent AE's occurring in association with the rash, except that 50% cases were associated with pruritus.

The development of rash in subjects who were exposed to DRV/rtv at the proposed dose was twice as frequent in subjects who self-identified as having a sulfonamide allergy, as compared to subjects who did not identify as having a history of sulfur allergy. However, no difference was observed in the incidence of rash between subjects taking any dose of DRV/rtv who did and did not identify sulfonamide allergy in controlled clinical trials

MO COMMENT: *A warning in the label seems to be appropriate for a drug with a known sulfonamide chemical structure, which appears to predispose to the development of rash.*

The following description will be added to the WARNING SECTION of the label:

Skin Rash

Severe skin rash, including erythema muliforme and SJS have been reported. In some cases, fever and elevations of transminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of patients treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

Sulfa Allergy

Darunavir contains a sulfonamide moiety. PREZISTA (darunavir) should be used with caution in patients with a known sulfonamide allergy.

MO DISCUSSION OF RASH: *The incidence of Stevens-Johnson Syndrome/toxic epidermal necrolysis is 1 to 2 per million population per year. [Semin Cutan Med Surg 1996; 15 (4): 236–43]. The rate in this population is over 2000 times the background rate. At present time, there is no satisfactory way for determining greatest risk for developing drug-associated Stevens-Johnson Syndrome/toxic epidermal necrolysis and hence of preventing it, short of avoiding drugs altogether. There has been a single study suggesting that early withdrawal of the agent at the first sign of the illness may improve the outcome. [Garcia-Doval I, et al. Archives Dermatol 2000; 136 (3): 323-7]. Although this intuitively makes sense, this study needs to be replicated. Even if this is proven correct, its practical application is limited because it is very difficult to identify the very earliest lesion in a timely manner because of the rapid progressive nature of this illness and its non-specific prodromic features. Another challenge in the prevention of SJS/TEN is that very little is known about the underlying pathogenetic mechanisms. DRV/rtv is efficacious for the treatment of multiple drug-resistant HIV-1 infected subjects but it is important for physicians prescribing this drug to be aware of the association of the drug with eythema multiforme/SJS and to consider whether the risk is in proportion to the benefit.*

7.1.2.3 Abnormalities of Lipid metabolism

Table 7.1. 3.3 A: Showing any grade Grade 3 or 4 Lipid related Adverse Events- TMC114-C213

Lipid Lab parameter	TMC/RTV 400/100 mg qd N= 64 (%)	TMC/RTV 800 mg qd N= 63 (%)	TMC/RTV 400/100 mg bid N= 63 (%)	TMC/RTV 600/100 mg bid N= 6 5(%)	Total TMC/RTV N= 255(%)	Control N=63(%)
Any Grade 3 or 4 lipid metabolism AE	3(4.7)	5 (7.9)	2 (3.2)	5 (7.7)	15 (5.9	2(3.2)
Hypertrigly ceridemia	1 (1.5)	2 (3.2)	1 (1.6)	3 (4.6)	8 (3.1)	1 (1.6)
Blood TG increased	0 (1.6)	1 (1.6)	1 (1.6)	1 (1.5)	4 (1.6)	0
Blood cholesterol increased	0	2 (3.2)	0	0	2 (0.8)	0
Hyperchole sterolemia	0	1 (1.6)	0	1 (1.5)	2 (0.8)	1 (1.6)

Table 7.1.3.3 B: Showing any Grade 3 or 4 Lipid related Adverse Events – TMC114-C202

Lipid Lab parameter	TMC/RTV 400/100 mg qd N= 64 (%)	TMC/RTV 800 mg qd N= 63 (%)	TMC/RTV 400/100 mg bid N= 63 (%)	TMC/RTV 600/100 mg bid N= 6 5(%)	Total TMC/RTV N= 255(%)	Control N=63(%)
Any Grade 3 or 4 lipid metabolism AE	0	1 (1.6)	4 (6.3)	4 (6.0)	9(3.5)	2(3.3)
Hypertrigly ceridemia	0	1 (1.6)	1 (1.6)	2 (3.0)	4 (1.6)	0
Blood TG increased	0	0	2 (3.2)	0 (1.5)	2 (0.8)	0
Blood cholesterol increased	0	0	1 (1.6)	3 (4.5)	4 (1.6)	2 (3.3)
Hyperchole sterolemia	0	0	0	0	0 (0.8)	1 (1.6)

The incidence of lipid related AE's was 8.1% in subjects who initiated treatment with DRV/RTV 600 mg bid in the Phase II b Trials.

Lipid related AE's were mainly hypertriglyceridemia and increased (8.6%) and cholesterol (4.9%). The central tendency analysis showed an overall decrease in triglycerides for DRV treated subjects, however some subjects were observed to have graded increases in triglycerides. Graded increases in cholesterol levels however were observed, with the rate of grade 3 cholesterol levels being twice that of control.

Lipid-related AEs were most commonly increases in triglycerides (preferred terms hypertriglyceridemia and increased blood triglycerides). Four percent of subjects who initiated treatment with DRV/rtv 600/100 mg bid from the start had a grade 3 or 4 lipid related AE. No lipid-related AEs were considered serious, and none led to treatment discontinuation.

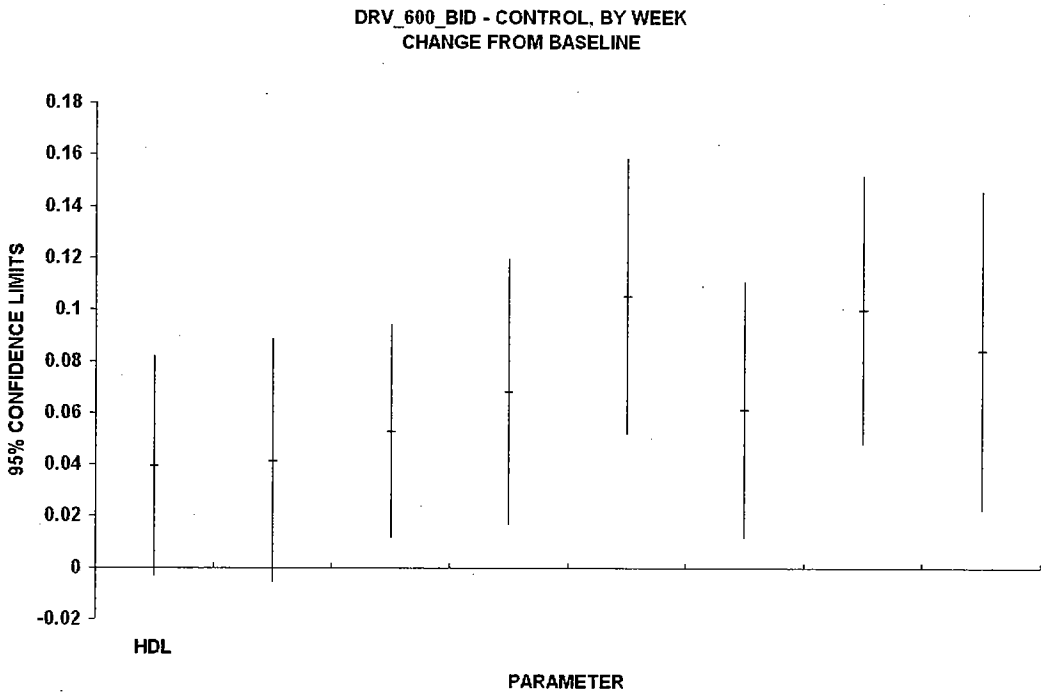
TABLE 7.1.2.3C: SHOWING ADAPTED ACTG GRADED LIPID ABNORMALITIES EMERGING IN THE TREATMENT PERIOD (WORST TOXICITY GRADES) TMC114-C202+ TMC114-C213+ TMC114-C215/208

Lipid Lab parameter	Worst Grade	DRV/RTV 600/100 mg bid C202+C213 (A) N= 131 (%)	C215/208 (B) N= 327 (%)	A+B N= 458	C202+213 Control N=124 (%)
Mean Exposure (weeks)		**63.5**	**23.9**	**35.2**	**31.5**
Blood TG increased	Grade 2	12 (9.2)	43 (13.3)	55 (12.1)	24 (19.5)
	Grade 3	15 (11.5)	13 (4.0)	28 (6.2)	5 (4.1)
	Grade 4	6 (4.6)	5 (1.5)	11 (2.4)	2 (1.6)
Hyperchole sterolemia	Grade 2	2 (2.3)	13 (4.0)	16 (3.5)	1 (0.8)
	Grade 3	9 (6.9)	11 (3.4)	20 (4.4)	2 (1.6)
	Grade 4	0	2 (0.6)	2 (0.4)	1 (0.8)

FDA's Statistical Reviewer performed a special analyses on four lipid parameters: cholesterol, fasting triglycerides, low density lipoprotein (figure 7.1.2.3 B) and high density lipoprotein (figure 3.2.2 A), by plotting the difference between DRV/r, 600 mg bid minus control PI in change from baseline of these four lipid parameters. The 95% confidence interval for the difference between 600 mg bid DRV/r and control for each of the three lipid parameters was plotted for Weeks 1, 2, 4, 8, 12, 16, 20, and 24.

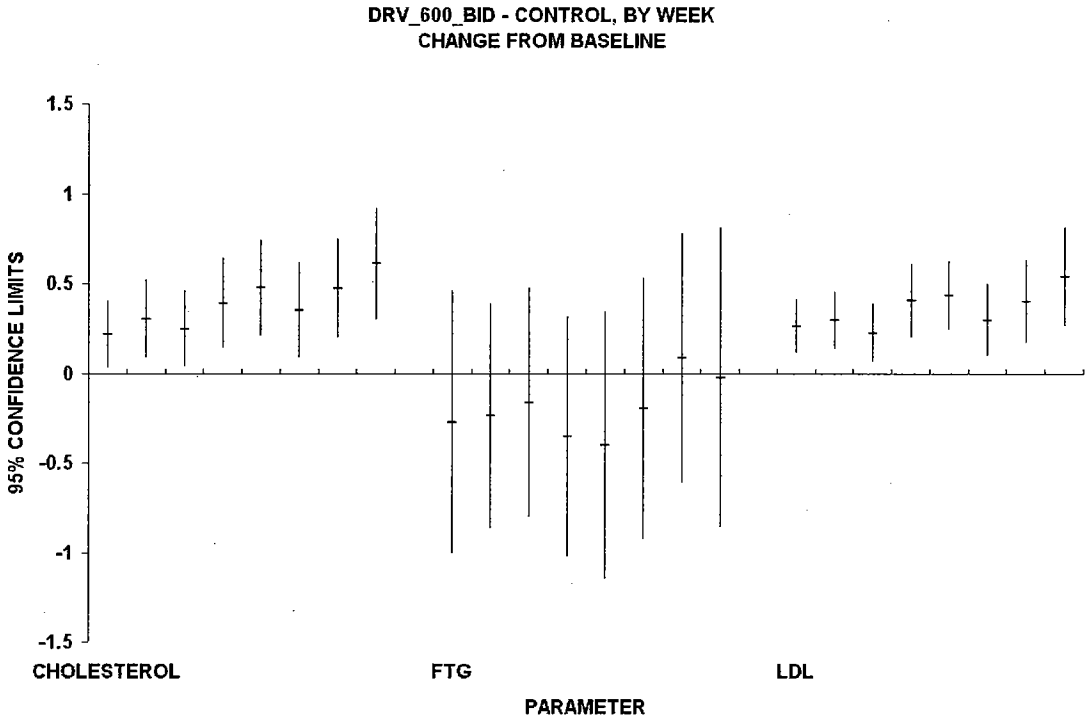
Significantly higher increases were observed in cholesterol and LDL, and somewhat lower increases in fasting triglycerides, while increases in HDL were significantly higher. (See Figure 7.1.2.3A & B noted below).

FIGURE 7.1.2.3 A: SHOWING A PLOT OF THE 95% CONFIDENCE INTERVAL OF THE DIFFERENCE BETWEEN MEASUREMENTS OF **HDL** IN DRV/rtv AND CONTROL SUBJECTS IN TRIAL TMC114-C202 AND TMC114-C213



SOURCE: Analysis by Dr T. Hammerstrom (FDA's Statistician)

FIGURE 7.1.2.3 B: SHOWING A PLOT OF THE 95% CONFIDENCE INTERVAL OF THE DIFFERENCE BETWEEN MEASUREMENTS OF ***CHOLESTEROL, FASTING TRIGLYCERIDES AND LDL*** IN DRV/rtv AND CONTROL SUBJECTS IN TRIAL TMC114-C202 AND TMC114-C213



SOURCE: Analysis by Dr T. Hammerstrom (FDA's Statistician)

CONCLUSIONS:

Use of DRV/rtv can be associated with increases in triglycerides and total cholesterol.

Analysis by FDA's Statistician showed that **cholesterol** and **LDL increases in DRV-treated subjects were higher relative to control**, while **fasting triglycerides improved relative to control**, and **HDL** increases were observed. However, interpretation is associated with the length of ARV history, the variable durations of exposure to study drug at the proposed dose, and variable exposure to varieties of lipid lowering agents. Overall, there is no pattern showing DRV/rtv to be either better or worse than the control PI's in this population of HIV subjects.

7.1.2.4 Abnormalities of Pancreatic amylase and lipase

The incidence of increased pancreatic enzyme-related adverse events in the controlled studies in the all darunavir/ritonavir treatment group was comparable to the control group. Mean changes in pancreatic enzyme levels over time were small and not considered clinically relevant.

Grade 3 or 4 abnormalities for amylase were observed in 6.6% of the subjects who initiated treatment with DRV/rtv 600/100 mg from the start. Grade 3 abnormalities for lipase were observed in 3.5% of the subjects; there were no grade 4 abnormalities for lipase.

TABLE 7.1.2.4 A) SHOWING ADAPTED (WORST) ACTG GRADED LABORATORY ABNORMALITIES EMERGING DURING THE TREATMENT PERIOD TMC114-C202 +TMC114-C213

Lab parameter	Worst grade	DRV/RTV					Control
		400/100 qd N=129	800/100 qd N=127	400/100 bid N=126	600/100 bid N=131	Total TMC/RTV N=513	N=124
Mean Exposure (weeks)		**43.95**	**45.48**	**44.02**	**62.29**	**49.03**	**31.54**
Pancreatic amylase	Grade 1	31(24)	21 (16.5)	23 (18.3)	27 (20.8)	102 (19.9)	22 (17.9)
	Grade 2	11(8.5)	11(8.7)	3(2.5)	12 (9.2)	37 (7.2)	5 (4.1)
	Grade 3	6 (4.7)	9 (7.1)	5 (4.0)	8 (6.2)	28 (5.5)	6 (4.9)
	Grade 4	0	0	0	1 (0.8)	1 (0.2)	0
Pancreatic lipase	Grade 1	9 (7.0)	6 (4.7)	8 (6.3)	10 (7.7)	33 (6.4)	6 (4.9)
	Grade 2	5 (3.9)	4 (3.1)	2 (1.6)	5 (3.8)	16 (3.1)	4 (3.3)
	Grade 3	2 (1.6)	6 (4.7)	3 (2.4)	6 (4.6)	17 (3.3)	1 (0.8)
	Grade 4	0	1 (0.8)	0	0	1 (.2)	0

B) FATAL AND SERIOUS CASES OF PANCREATITIS

There was one fatal case of clinical pancreatitis in a subjects treated with DRV/rtv.

CRF ID # 213-0067 (alternatively CRF ID # 215-0275) - This subject had very advanced HIV-disease and significant comorbidity factors (bacteremia due to E. Coli and multi-organ failure). This subject had a CD4+ cell count of 6 x 10^6 cells/L at baseline, and history of hypertriglyceridemia. The OBR of this subject included didanosine (ddI) and tenofovir (TDF). Hypertriglyceridemia and coadministration of ddI and TDF are recognized risk factors for pancreatitis.

One case of acute pancreatitis, which was accompanied by hypoglycemia, alcoholic hepatitis, amphetamine and opiate and benzodiazepine intoxication.

C) Analysis of the DOSE FINDING PART OF TMC114-C202 and TMC114-C213

The proportion of subjects with serum amylase and serum lipase elevations by grade of abnormality was compared between each dose arm of DRV/rtv and controls. The proportion of subjects with elevations of serum amylase and lipase were similar in all DRV/rtv treatment arms and in controls. The dose of DRV/rtv did not affect the toxicity grade. There was no evidence of dose responsiveness.

Two study subjects grade 4 serum amylase and lipase elevations were identified as the follows:

1) **CRF ID # C202-2621** and **CRF ID # C202-0202**, were taking DDI and TFV as part of their concomitant medications.
2) **CRF ID # C213-0078** was receiving TFV and DDI, and subject **C213-0097** was receiving TFV as part of the ARV regimen.

D) SUBJECTS PERMANENTLY AND TEMPORARILY DISCONTINUING STUDY DRUG BECAUSE OF DEVELOPMENT OF PANCREATITIS

Two (2) subjects **permanently discontinued** the study drug because of pancreatitis.
CRF ID # 202-2912- This 42year old male entered trial TMC114-C202 on a dose of DRV/RTV 800/100 mg qd in combination with 3TC; One month later 3TC replaced with emtricitabine, TFV, and ZDV. Subject's past medical history included hives as a reaction to Fortavase, surgery for anal condyloma, cryptosporidium diarrhea, and pancreatitis. Current concomitant medical conditions included hyperlipidemia, oral hairy leucoplakia, and psoriasis of hands, back, chest, groin, scalp and forehead.

At screening, amylase and lipase levels were mildly elevated (Grade 1), and gradually increased to grade 2 elevated level, four (4) weeks after. Sixty one (61) days after initiating study medication he developed a grade 3 elevation of pancreatic amylase and lipase.
Study medication was discontinued permanently, and the subject was permanently withdrawn from the study. The amylase and lipase levels returned to their baseline (grade 1) level within a few days of discontinuing study drug. No concomitant medications were administered for these AE's.

CRF ID # 202-6605- This 50 year old male started the study on a dose of DRV/RTV 800/100 mg, in combination with DDI and TFV. Two weeks later the background medication was optimized to 3TC + ZDV and ENF. Amylase and lipase levels were normal at screening.

Fifty seven days after initiating study drug, a grade 3 elevation of amylase and a grade 2 elevation of lipase was noted. The study medication was discontinued 5 days later and the subject was withdrawn from the study. Amylase and lipase level remained grade 3 elevated 2 months after study drug, DDI, TFV, ZDV and 3TC were discontinued.

DDI, TFV, ZDV, 3TC were discontinued, and two months later he was switched to SQV, amprenavir, low-dose RTV.

Additional medical diagnoses included: mild jaundice, molluscum contagiosum, mild peripheral neuropathy, sporadic diarrhea, and osteopenia.

b) Two additional subjects **temporarily discontinued** the study drug because of elevated pancreatic amylase and lipase.

CRF ID # 215-0031- This 46 y/o male started treatment at a dose of DRV/RTV 400/100 mg bid as part of an ARV regimen that included DDI +TFV+ ENF. This patient was a PI control from TMC114-C202 (CRF ID # 202-4701).

Concomitant medications included acyclovir, amitriptylline, cyanocobalamin, dapsone, doxycycline, esomeprazole sodium, fenofibrate, flufenazine deconate, fluticasone propionate, ramipril, tadalafil and testosterone.

On [redacted] after starting study drug he was diagnosed with pancreatitis, and was hospitalized with abdominal pain and grade 3 elevations of amylase and lipase. All ARV medications, including study medication were discontinued on August 20th 2004, and he was placed on a clear liquid diet, and treated with flagyl and clarithromycin. The pancreatitis resolved on September 1st 2004, and he was restarted on DRV/RTV 400/100 mg bid on September 13th 2004, and switched to open label DRV/RTV at the recommended dose of 600/100 mg bid on May 2nd 2005.

MO Comment: The acute pancreatitis that developed in this subject was probably related more to the DDI and TFV medications. When re-challenged with TMC/RTV, the subject tolerated the study medication well.

CRF ID# 202-2402- This 48 y/o male started treatment with DRV/RTV on July 7th 2004 as part of an antiviral regimen that included DDI + TFV + 3TC +ENF.

On April 10th 2005, forty weeks after starting the above combination of ARV drugs, he developed a grade 3 serum amylase elevation, and grade 2 lipase elevation. TMC/RTV, DDI, ENF and TFV were discontinued. After the episode of elevated serum pancreatic enzymes resolved, on May 24th 2005, he was restarted on 3TC, RTV, TFV and ENF.

CONCLUSION:

1) The incidence of treatment emergent elevation of serum amylase and lipase was comparable to that of the control group.
2) There was no suggestion of dose-related changes in amylase and lipase elevations in the dose finding portions of Trial TMC114-C202 and Trial TMC114-C213.
3) Individual subjects with grade 3 and 4 elevations of serum amylase and lipase were subjects who were on ARV regimens containing tenofovir (TFV) and diadosine (DDI). This combination regimen is a known risk factor in the development of pancreatitis.

7.1.3 Other Search Strategies

Additional searches were carried out by Tibotec, Inc and the FDA to evaluate safety signals observed in the preclinical studies. Neither the FDA nor Tibotec Inc noted any additional safety signal from any source.

7.1.4 Common Adverse Events

The common adverse event profile was as follows:
Injection site reactions (ISR's) occured in 27.5% of subjects on the 600/100 mg arm of the study drug versus 21.8% of control. Adverse events occurred most commonly in the gastrointestinal system, with diarrhea occurring 20% of the time in the 600/100 mg bid dose arm, versus 28% time in the control arm, nausea 18.3% time in the study arm versus 13% time in the control arm, and nasopharyngitis 13.7% cases of the study arm versus 10.5% of control cases . (See Table 7.1.5.A noted below).

TABLE 7.1.5.A: SHOWING THE INCIDENCE OF COMMON ADVERSE EVENTS IN THE DRV/rtv 600/100 MG STUDY ARM VERSUS CONTROL IN TMC114-C202 and TMC114-C213

ADVERSE EVENT	DRV/rtv 600/100 mg bid	CONTROL
ISR	27.5%	21.8%
DIARRHEA	19.8 %	28.2 %
NAUSEA	18.3 %	12.9 %
HEADACHE	15.3 %	20.2 %
NASOPHARYNGITIS	13.7 %	10.5 %

MO COMMENT: *The incidence of common adverse events needs to be viewed with respect to the duration of exposure. Mean duration of exposure of subjects on the 600/100 mg study arm was 63.5 weeks versus a mean exposure of 31.5 weeks for subjects on the control arm. This shortened duration of exposure of subjects on the control arm biases results in favor of the control arm.*

The ISR rate in both arms is attributed to the use of concomitant injectible medications such as enfurvitide, and is not related to the use of darunavir.

This reviewer also analysed the incidence of common adverse events by dose of DRV/rtv, and contrasted each dose arm with control. The proportion of adverse events by organ system is roughly equal to that of control in all dose groups. This suggests a lack of dose-relatedness of adverse events in subjects exposed to DRV/rtv.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events (AE's) were elicited at every visit using patient interviews, which consisted of both direct and indirect questions; the results of these interviews were reported from screening onwards until the last study-related activity. Visits were performed weekly for the first two weeks, then every 4 weeks until Week 24, then every 8 weeks until Week 48. Clinical events were scored for severity using the NIAID Common Toxicity Grading Scale. The investigator determined the relationship between the event and randomized study drug (not related, not likely related, possibly related, or probably related). Laboratory abnormalities was reported as AEs if, in the opinion of the investigator, the laboratory abnormality was clinically significant. There were no guidelines to ensure that investigators reported laboratory-related AEs uniformly.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Tibotec, Inc used the MedDRA dictionary of System Organ Class and Preferred Terms to organize the medical terms for the various AEs provided by the investigator; for Phase II studies, MedDRA version 6.1 was used, while MedDRA version 8.1 was used for the Phase III and more

recent studies. In general, Tibotec Inc grouped the individual investigator terms under MedDRA preferred terms appropriately. In cases where this reviewer identified MedDRA preferred terms that were inappropriate or more clinically meaningful when grouped a different way the terms were regrouped and those changes are reflected throughout the review.

7.1.5.3 Incidence of common adverse events

Incidence rates for common adverse events were estimated from the small portion of the overall database contained in the controlled trials TMC114-C202, and TMC114-C213. The common treatment-emergent, potentially drug-related adverse events were diarrhea, vomiting, abdominal pain, constipation and headache. The rates were similar in both control and study arms. (See Table 7.1. 5.4 A and B).

7.1.5.4 Common adverse event tables

The TABLE 7.1.5.4.A and TABLE 7.1.5.4.B show below demonstrate the incidence of occurrence of AE's of all grades occurring in the 600/100 mg to be marketed dose of of DRV/rtv and compared with control. The proportions are similar between study and control arms. The selection of the 1% cut-off rate was arbitrary. The most common adverse event occurring in the 600/100 mg dose of DRV/rtv in trial TMC114-C202 other than injection site reaction (25%) was nausea (22%) , diarrhoea (19 %), fatigue (19%), headache (16%), upper respiratory tract infection (16%), vomiting (10%), and abdominal pain (10%). In Trial TMC114-C213 other than injection site reaction (28%) was nausea (22%) , diarrhoea (25%), nasopharyngitis (21%), fatigue (19%), nausea (19%), and headache (13%).

TABLE 7.1.5.4.A SHOWING: ALL GRADE (1-4) ADVERSE EVENT BY MEDDRA PRFERRED TERMS OBSERVED IN > 5 % SUBJECTS IN EITHER TREATMENT GROUP AT WEEK 48 in **Trial TMC114-C202**

Dictionary-Derived Term	Control	DRV/rtv 600 BID
Diarrhea	**20 (30.77%)**	**13 (19.40%)**
Injection Site Reaction	**13 (20.00%)**	**17 (25.37%)**
Fatigue	**13 (20.00%)**	**13 (19.40%)**
Headache	**12 (18.46%)**	**11 (16.42%)**
Nausea	**5 (7.69%)**	**15 (22.39%)**
Upper Respiratory Tract Infection	**10 (15.38%)**	**11 (16.42%)**
Bronchitis	**5 (7.69%)**	**7 (10.45%)**
Pyrexia	**8 (12.31%)**	**4 (5.97%)**
Nasopharyngitis	**6 (9.23%)**	**5 (7.46%)**
Cough	**2 (3.08%)**	**5 (7.46%)**
Sinusitis	**6 (9.23%)**	**6 (8.96%)**
Vomiting	**6 (9.23%)**	**7 (10.45%)**
Abdominal Pain	**3 (4.62%)**	**7 (10.45%)**

Oral Candidias	**2 (3.08%)**	**4 (5.97%)**
Back Pain	**1 (1.54%)**	**6 (8.96%)**
Dizziness	**5 (7.69%)**	**5 (7.46%)**
Herpes Simplex	**2 (3.08%)**	**6 (8.96%)**
Depression	**6 (9.23%)**	**5 (7.46%)**
Aspartate Aminotransferase Increased	**3 (4.62%)**	**6 (8.96%)**
Constipation	**0 (0.00%)**	**4 (5.97%)**
Abdominal distension	**1 (1.54%)**	**5 (7.46%)**
Anaemia	**3 (4.62%)**	**3 (4.48%)**
Neuropathy peripheral	**2 (3.08%)**	**4 (5.97%)**
Myalgia	**5 (7.69%)**	**4 (5.97%)**
Folliculitis	**1 (1.54%)**	**6 (8.96%)**
Blood triglycerides increased	**3 (4.62%)**	**5 (7.46%)**
Influenza	**0 (0.00%)**	**4 (5.97%)**
Hypertension	**2 (3.08%)**	**4 (5.97%)**
Herpes zoster	**3 (4.62%)**	**4 (5.97%)**
Pruritus	**1 (1.54%)**	**4 (5.97%)**
Pharyngitis	**1 (1.54%)**	**6 (8.96%)**
Condyloma acuminatum	**2 (3.08%)**	**4 (5.97%)**
Gamma-glutamyltransferase increased	**1 (1.54%)**	**4 (5.97%)**
Anorexia	**2 (3.08%)**	**4 (5.97%)**

TABLE 7.1.5.4.B SHOWING: ALL GRADE (1-4) ADVERSE EVENT BY MEDDRA PRFERRED TERMS OBSERVED IN >5 % SUBJECTS IN EITHER TREATMENT GROUP AT WEEK 48 in **Trial TMC114-C213**

Dictionary-derived Term	**Control N= 67**	**DRV/RTV 600 /100 BID N= 68**
Injection site reaction	**14 (20.59%)**	**19 (28.36%)**
Diarrhoea	**23 (33.82%)**	**17 (25.37%)**
Headache	**16 (23.53%)**	**9 (13.43%)**
Nasopharyngitis	**10 (14.71%)**	**14 (20.90%)**
Nausea	**13 (19.12%)**	**13 (19.40%)**
Oral candidiasis	**11 (16.18%)**	**5 (7.46%)**
Pyrexia	**11 (16.18%)**	**7 (10.45%)**
Cough	**10 (14.71%)**	**7 (10.45%)**
Herpes simplex	**2 (2.94%)**	**11 (16.42%)**
Abdominal pain	**6 (8.82%)**	**8 (11.94%)**
Electrocardiogram	**3 (4.41%)**	**4 (5.97%)**

abnormal		
Asthenia	**12 (17.65%)**	**5 (7.46%)**
Insomnia	**6 (8.82%)**	**3 (4.48%)**
Influenza	**6 (8.82%)**	**7 (10.45%)**
Arthralgia	**6 (8.82%)**	**8 (11.94%)**
Vomiting	**8 (11.76%)**	**5 (7.46%)**
Fatigue	**8 (11.76%)**	**4 (5.97%)**
Bronchitis	**6 (8.82%)**	**6 (8.96%)**
Depression	**4 (5.88%)**	**6 (8.96%)**
Sinusitis	**5 (7.35%)**	**5 (7.46%)**
Pruritus	**4 (5.88%)**	**6 (8.96%)**
Hypertension	**4 (5.88%)**	**4 (5.97%)**
Upper respiratory tract infection	**0 (0.00%)**	**5 (7.46%)**
Dizziness	**3 (4.41%)**	**7 (10.45%)**
Gamma-glutamyltransferase increased	**5 (7.35%)**	**4 (5.97%)**
Condyloma acuminatum	**2 (2.94%)**	**6 (8.96%)**
Seborrhoeic dermatitis	**2 (2.94%)**	**5 (7.46%)**
Back pain	**2 (2.94%)**	**5 (7.46%)**
Myalgia	**4 (5.88%)**	**2 (2.99%)**
Weight decreased	**6 (8.82%)**	**2 (2.99%)**
Herpes zoster	**1 (1.47%)**	**4 (5.97%)**
Pain in extremity	**0 (0.00%)**	**5 (7.46%)**
Anorexia	**4 (5.88%)**	**3 (4.48%)**
Blood triglycerides increased	**2 (2.94%)**	**4 (5.97%)**
Influenza like illness	**1 (1.47%)**	**4 (5.97%)**

7.1.5.5 Identifying common and drug-related adverse events

These studies were not powered for the reliable detection of significant differences across dose arms. There are no consistent differences between the proportion of subjects with specific AE's between control and study arms, and there is no evidence of dose response.

7.1.5.6 Additional analyses and explorations

Exploration for demographic interactions based on gender, age, race did not reveal any specific predilection for the occurence of adverse event(s) in any of the demographic covariates.

Please refer to the Section 7.1.3.3 for explorations of specific adverse events of special interest –

namely- **hepatotoxicity, rash , hyperlipidemia, and elevations of pancreatic amylase and lipase.**

7.1.5 Less Common Adverse Events

It was not feasible to evaluate the occurrence of unusual or rare adverse events in this controlled safety review study with 512 controlled subjects on study drug and 124 subjects on control.

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

Clinical laboratory monitoring for safety included assessments of routine hematology studies, serum biochemical studies, and urinalysis at screening, baseline, and each study visit. Visits occurred every week for the first four weeks, every two weeks until Week 12, then every 4 weeks from Week 12 to Week 24, and then every 8 weeks from Week 24 to Week 48, and every 12 weeks thereafter.

7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This reviewer conducted analyses on the number and percentage of subjects who developed treatment-emergent grade 2-4 laboratory abnormalities at 48 weeks, in subjects who were exposed to DRV/rtv and control PI. The percentages were similar between the study drug arm versus the control arm in Trials TMC114-C202 and TMC114-C213. [See Table 7.1.7.2.(a) and Table 7.1.7.2.1(b)]. The greatest percentage change was observed in serum cholesterol and triglyceride levels; serum ALT, AST, GGT and bilirubin levels. The percentage of subjects exhibiting grade 2 to grade 4 change was similar in the study arm and control arm.

7.1.6.3 Standard analyses and explorations of laboratory data

7.1.6.3.1 Analyses focused on measures of central tendency

The changes in laboratory parameters were mild to moderate in severity. [See Table 7.1.6.3.1(a) Table 7.1.6.3.1(b)].

The tables below show the baseline, the Week 24 mean, the mean change from baseline of the main hematologic and biochemical laboratory tests for all DRV treatment arms combined; As can be seen from Tables 7.1.7.1 A and B, no significant change from baseline was identified. The mean change from baseline was similar for the study and the control arm.

Table 7.1.6.3.1 (A) showing baseline and mean changes from baseline in select **Hematologic abnormalities** in **Trials TMC114-C202** and **TMC114-C213**

MEAN HEMATOLOGIC PARAMETER	TMC114-C202 N=258			TMC114- C213 N= 269		
	MEAN BASELINE	MEAN @ WEEK 24	CHANGE FROM BASELINE TO WEEK 24	MEAN BASELINE	MEAN @ WEEK 24	CHANGE FROM BASELINE TO WEEK 24
Hemoglobin (g/dL)	13.6	14.2	+ 0.6	14.08	14.25	+ 0.17
Hematocrit (%)	40.4	42.2	+1.8	41.65	42.85	+ 1.2
Platelet count ($x10^3/mm^3$)	214	231	+ 17x 10^3	202.8	225.8	+ 23
WBC count ($x10^3/mm^3$)	4.77	5.39	+ 0.62	4.92	5.68	+ 0.76
Neutrophil Count ($x10^3/mm^3$)	2.74	3.03	+ 0.29 x 10^3	2.74	3.03	+ 0.29

Table 7.1.6.1 (B) showing baseline and mean changes from baseline in select **Chemistry abnormalities** in TMC114-C202, TMC114-C213

MEAN CHEMISTRY PARAMETER	TMC114-C202			TMC114- C213		
	MEAN BASELINE	MEAN @ WEEK 24	CHANGE FROM BASELINE TO WEEK 24	MEAN BASELINE	MEAN @ WEEK 24	CHANGE FROM BASELINE TO WEEK 24
Alkaline Phosphatase	116.5	103.2	- 13.3	100.3	98	- 2.3

(u/L)						
ALT (U/L)	42.6	33.7	- 8.9	39.3	34.8	- 4.5
AST (U/L)	42.0	34.5	- 7.5	38.6	32.1	- 6.5
Tot. bilirubin	11	9.28	- 1.72	10.3	8.7	- 1.6
Cholesterol (mg/dL	447	438	- 9	488	477	- 11
Triglyceride (mg/dL)	361	244	- 117	340	249	- 91
Amylase (u/L)	41.34	34.94	- 6.4	37.3	32.6	- 4.7
Lipase (u/L)	48.2	40.9	- 7.3	44.6	41.7	+ 2.9

Table 7.1.7.3.1(B) **TMC114-C213** Treatment –Emergent Grade 2 to 4 laboratory abnormalities, compared to control

LAB TEST	GRADE 2		GRADE 3		GRADE 4	
	DRV/rtv 600/100 mg bid	CONTROL	DRV/rtv 600/100 mg bid	CONTROL	DRV/rtv 600/100mg bid	CONTROL
Trig	**9 (1.29%)**	**20 (2.87%)**	**9 (1.29%)**	**6 (0.86%)**	**5 (0.72%)**	**5 (0.72%)**
CHOL	**17 (2.44%)**	**19 (2.73%)**	**5 (0.72%)**	**7 (1.00%)**	**0 (0.00%)**	**2 (0.29%)**
GGT	**8 (1.15%)**	**7 (1.00%)**	**7 (1.00%)**	**4 (0.57%)**	**1 (0.14%)**	**3 (0.43%)**
AST	**7 (1.00%)**	**11 (1.6%)**	**0 (0.00%)**	**2 (0.29%)**	**0 (0.00%)**	**1 (0.14%)**
ALT	**4 (0.57%)**	**11 (1.6%)**	**1 (0.14%)**	**2 (0.29%)**	**0 (0.00%)**	**1 (0.14%)**
Glc	**6 (0.86%)**	**11 (1.6%)**	**0 (0.00%)**	**1 (0.14%)**	**0 (0.00%)**	**0 (0.00%)**
Ptt	**4 (0.57%)**	**3 (0.43%)**	**1 (0.14%)**	**0 (0.00%)**	**6 (0.86%)**	**3 (0.43%)**
Tb	**3 (0.43%)**	**10 (1.4%)**	**1 (0.14%)**	**3 (0.43%)**	**0 (0.00%)**	**0 (0.00%)**
Amylase	**4 (0.57%)**	**6 (0.86%)**	**1 (0.14%)**	**3 (0.43%)**	**1 (0.14%)**	**0 (0.00%)**
Ua	**5 (0.72%)**	**7 (1.00%)**	**1 (0.14%)**	**2 (0.29%)**	**0 (0.00%)**	**0 (0.00%)**
Neutro count	**3 (0.43%)**	**4 (0.57%)**	**1 (0.14%)**	**2 (0.29%)**	**2 (0.29%)**	**1 (0.14%)**
Lipase	**3 (0.43%)**	**2 (0.29%)**	**2 (0.29%)**	**1 (0.14%)**	**0 (0.00%)**	**0 (0.00%)**
Pc	**3 (0.43%)**	**1 (0.14%)**	**0 (0.00%)**	**1 (0.14%)**	**0 (0.00%)**	**1 (0.14%)**
Pt	**2 (0.29%)**	**0 (0.00%)**	**1 (0.14%)**	**1 (0.14%)**	**1 (0.14%)**	**0 (0.00%)**
Na	**2 (0.29%)**	**0 (0.00%)**	**0 (0.00%)**	**1 (0.14%)**	**1 (0.14%)**	**0 (0.00%)**
Alp	**2 (0.29%)**	**1 (0.14%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**
Mg	**1 (0.14%)**	**1 (0.14%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**
Creat	**0 (0.00%)**	**1 (0.14%)**	**0 (0.00%)**	**1 (0.14%)**	**0 (0.00%)**	**0 (0.00%)**
Hgb	**0 (0.00%)**	**2 (0.29%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**
K	**0 (0.00%)**	**2 (0.29%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**	**0 (0.00%)**

Urea	0 (0.00%)	1 (0.14%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

7.1.6.3.2 Analyses focused on outliers or shifts from normal to abnormal

Most of the laboratory abnormalities noted above were at the Grade 2 level. The grade 3 and grade 4 abnormalities were few, and the proportions were similar between the control and study arm.

7.1.6.3.3 Marked outliers and dropouts for laboratory abnormalities

No striking differences were observed between DRV treatment arms and control with regard to the incidence of marked outliers in laboratory abnormalities.

However, four subjects in the study arm, and one subject in the control arm did permanently discontinue the trial because of laboratory abnormalities. Two study subjects discontinued because of elevated GGT levels, one study subject discontinued because of elevated amylase and lipase levels, and another study subject discontinued because of elevated ALT and AST levels. One subject in the control arm discontinued because of elevated laboratory abnormalities (elevated AST and ALT levels).

Laboratory abnormalities were also evaluated in terms of subjects remaining on assigned study drug who experienced markedly abnormal values, defined as Grade 3 or 4 according to the protocol grading system

(See Section 7.1.2 Other Serious Adverse Events under Adverse Events of Special Interest)

7.1.6.4 Additional analyses and explorations

The Clinical Reviewers were concerned about a possible hepatic signal identified during the clinical development program.

A Hepatology Consult was sought from Dr John Senior, Associate Director for Science, in the Office of Pharmacoepidemiology and Statistical Sciences.

Dr Senior did not find clear evidence of darunavir-induced liver toxicity in the data accrued up to the time of the September 25th 2005 data base lock. He believed that a few cases suggested possible contributing injury to pre-existing liver problems, but definite attribution of causality was difficult in patients with such prolonged and complex illness and exposure to so many drugs.

He also suggested that the biopsy slides for case C213-0688 (CH JNJFOC-20051004584) be forwarded to Dr. Zachary Goodman, hepatopathologist at the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, for his review and opinion. Dr Goodman's review of the slides was unremarkable, and he was unable to determine a cause for this subject's hepatomegaly, ascites and portal hypertension.

Dr Senior did not believe that there was an indication for special labeling of darunavir/rtv as causing clearcut liver injury.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

The following are the sponsor's **PARAMETER DEFINITIONS** for changes in **pulse, diastolic blood pressure (DBP) and systolic blood pressure (SBP):**

Pulse (bpm)
- abnormally low = change $\leq$ -15 and value of $\leq$ 50 bpm
- abnormally high = change $\geq$15 and value of $\geq$ 120 bpm

Diastolic BP (mmHg)
- abnormally low = change $\leq$ -15 and value $\leq$ 50 mmHg
- abnormally high = change $\geq$ 15 and value $\geq$ 120 mm Hg

Systolic BP (mmHg)
-abnormally low = change $\leq$ -20 and value of $\leq$90 mmHg
-abnormally high = change $\geq$ 20 and value of $\geq$ 180 mmHg

For **orthostatic hypotension** the following abnormailities are defined as:
- Decrease in diastolic BP (standing-supine) of at least 10 mmHg.
- Increase in Heart rate (standing-supine) of at least 15 beats/min.

MO COMMENT: The Sponsor's definitions of parameters for changes in blood pressure, pulse and orthostatic blood pressure are reasonable.

The following table summarizes vital sign abnormalities for all DRV treatment arms versus control in the controlled clinical trials.

TABLE 7.1.8.1 (A) SHOWING: TREATMENT-EMERGENT VITAL SIGN ABNORMALITIES (WORST ABNORMALITY) DURING THE TREATMENT PERIOD – TMC114-C202 + TMC114-C213

Vital sign parameter	Darunavir/RTV N=512	Control N= 124
Standing systolic blood pressure (mmHg)		
Abnormally high	9 (1.8)	0
Abnormally low	26 (5.1)	5 (4.0)
Supine systolic blood pressure (mmHg)		
Abnormally high	9 (1.8)	0
Abnormally low	29 (5.7)	7 (5.6)
Standing diastolic blood pressure (mmHg)		
Abnormally high	27 (5.3)	4 (3.2)
Abnormally low	14 (2.7)	2 (1.6)
Supine diastolic blood pressure (mmHg)		
Abnormally high	20 (3.9)	8 (6.5)
Abnormally low	15 (2.9)	2 (1.6)
Standing pulse (bpm)		
Abnormally high	23 (4.5)	4 (3.2)
Abnormally low	1 (0.2)	1 (0.8)
Supine pulse (bpm)		
Abnormally high	7 (1.4)	1 (0.8)
Abnormally low	2 (0.4)	0

Individual treatment-emergent abnormalities in pulse, systolic and diastolic blood pressure, and orthostatic hypotension were reported with similar incidence in the DRV/rtv group and in the control group. No trends or relationship to dose was observed. [See Table 7.1.8.1.(A)]. Overall, vital signs abnormalities were infrequent. There was no indication of treatment-related orthostatic blood pressure abnormalities.

7.1.8 Electrocardiograms (ECGs)

"Thorough QT/QTc Study"

Trial **TMC114-C153** was an open-label, randomized, placebo and active-controlled, 4-way crossover trial to assess the cardiac safety of DRV in the presence of low-dose rtv in healthy adults, with particular attention to the QT/QTcF interval duration and the influence of darunavir in combination with ritonavir on other ECG parameters, such as QRS and PR intervals. Moxifloxacin was included as positive control. The study population consisted of 40 healthy subjects. Each subject received treatment in 4 sessions:

1) Treatment A (supra-therapeutic dose) –DRV/rtv 1600/100 mg qd for 7 days
2) Treatment B (therapeutic dose) – DRV/rtv 800/100 mg bid for 7 days
3) Treatment C (active control) - moxifloxacin 400 mg qd for 7 days

4) Treatment D (placebo control) - for darunavir qd. for 7 days

In this trial, darunavir was formulated as the solid formulation F001 (400-mg tablet).

Maximum mean time-matched changes in QTcF versus placebo control observed across all active treatment groups were accentuated by within-group time-matched changes in the placebo control group. *Within-group time-matched changes* in QTcF versus Day -1 showed that during treatment with darunavir mainly decreases in QTc were observed, or increases no greater than 2.1 ms, while increases of approximately 7 to 8 ms were observed during treatment with moxifloxacin.

QTcF values decreased versus Day –1 at all but one time point after dosing in the placebo control group, by approximately 4 ms. This decrease in QTcF during treatment with placebo control contributed to a positive change when compared to placebo control for the darunavir arms, and to the substantial increase versus placebo control in the moxifloxacin arm of the trial. When evaluating the 2-sided 90% CIs of the time-matched mean changes versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary on both Day 1 and Day 7.

There were no pathologically prolonged QT/QTc values and no QT/QTc increases larger than 60 ms during the trial. Prolonged corrected QT interval was noted for one subject during both moxifloxacin at several time points and DRV/rtv 800/100 mg bid treatment at one time point, and for another subject during DRV/rtv 800/100 mg bid treatment at one time point only.

For ECG parameters other than QT/QTc (i.e., PR, QRS and HR), no relevant differences versus placebo were noted with a possible exception of slight increases in PR interval during DRV/RTV treatment. The incidence of individual abnormally long PR intervals was low in all treatment groups.

Conclusions: DRV is not associated with any clinically relevant changes of any ECG parameters, including the QT/QTC interval.

7.1.8.1 Overview of ECG testing in the development program, including brief review of preclinical results

The remainder of this Section ,7.1.8 will be submitted as an addendum.

7.1.9 Immunogenicity

DRV/rtv is from a class of drugs, protease inhibitors, that is not expected to be immunogenic. Evidence from repeat-dose studies in mice, rats and dogs did not suggest that DRV had immunostimulatory or immunosuppressive potential.

The following immunotoxicity studies were performed during the preclinical development program:

1) Local lymph node assay (TMC114-NC245)

A sample of darunavir was assessed for the potential to cause skin sensitization using the mouse Local Lymph Node Assay (LLNA). The assay determines the level of T- lymphocyte prol;iferation in the lymph nodes draining the site of chemical application by measuring the amount of radiolabelled thymidine incorporated into the dividing cells. The results showed that darunavir was not incorporated into the dividing cells. The conclusion was that under the conditions of the study, darunavir was found to be negative when tested in LLNA assays and was considered to be unlikely to have the potential to cause skin sensitization.

2) 4-Week immunotoxicity study with DRV/rtv by daily gavage in rats
Darunavir alone was not found to cause any immunological response at doses ranging from 20 to 500 mg/kg/day under conditions of the study. Similarly for rtv alone or in combination with darunavir, no immunotoxicological response was observed.

Please refer to Dr J. Farrelly's Pharmacology/Toxicology report for further details.

7.1.10 Human Carcinogenicity

The carcinogenicity studies in mice and rats are ongoing. The protocols for the two studies were approved by the Executive Carcinogenicity Assessment Committee (ExeCAC) and the studies will be finished as a Phase 4 commitment.

7.1.11 Special Safety Studies

Special safety Pharmacology Studies included the following:
i) Neurological effects- No neurological effects were noted in rats in a single dose up to 2000 mg/kg, without any overt changes in behavior or reflexes.
ii) Cardiovascular Effects - Darunavir showed no effect on in vitro and in vivo cardiac electrophysiology and on dog cardio-hemodynamic parameters.
iii) Pulmonary effects- No effects were noted in respiration in rats in doses of up to 2000 mg/kg.

iv) Gastrointestinal effects – no effects were noted in gastrointestinal transit time in rats.

No other special safety studies were submitted with this application.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Specific clinical trials or systematic analyses evaluating the potential withdrawal and rebound effects of DRV alone or co administered with low-dose RTV have not been conducted.

However, post hoc assessment of withdrawal emergent signs and symptoms of the adverse event profile and clinical laboratory abnormalities, vital signs and ECG abnormalities occurring during washout periods and during follow-up periods after last intake of study medication, showed that the overall safety/tolerability profile of DRV alone or co-administered with low-dose RTV was not negatively impacted by interruption or discontinuation of treatment.

These findings suggest that serious medical complications are unlikely to result from the interruption or discontinuation of DRV/rtv administration at the recommended dosages.

7.1.13 Human Reproduction and Pregnancy Data

No formal studies were carried out in humans on the effects of DRV/RTV on pregnancy and reproduction. There were however 4 inadvertent cases of exposure to the study drug during pregnancy. Two cases occurred in two Phase I studies (TMC114-C149 and TMC114-C153) and in two other cases in the ongoing Phase IIb trials (TMC114-C202 and TMC114–C213). According to the sponsor, in all 4 cases, study subjects consented to use effective double birth control methods for at least one month after the last dose of study medication, and in all pregnancies, the study medication was stopped immediately and the subjects were withdrawn from the trial.

The list of subjects who became pregnant while on study were as follows:

1) *CRF ID C153-0955*- an unremarkable voluntary abortion was induced.
2) *CRF ID C149-0091*- Sponsor was unable to obtain any information regarding the status of the pregnancy from the investigator.
3) *CRF ID 213-0008* - subject discontinued from the trial, but continued to take other antiretroviral agents; the subject aborted spontaneously 5 months later. The cause of fetal death was noted as intrauterine growth retardation and asphyxia.
4) *CRF ID 202-2706* – This subject's pregnancy was detected at Week 16 of pregnancy, at which time study drug was discontinued, and zidovudine was continued. A term infant was born on with mild retromicroagnathia.

No additional data on pregnancy or lactation are available from the clinical trials included in this submission.

Darunavir coadministered with low-dose RTV should not be used during pregnancy unless the potential benefit justifies the potential risk.

It is not known whether darunavir coadministered with low-dose RTV is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving darunavir co-administered with low-dose RTV.

In animal studies, darunavir had no effect on fertility and early embryonic development.

Teratogenicity studies in mice, rats and rabbits showed no teratogenic potential. However, exposure levels to darunavir in these species were below human exposures.

7.1.14 Assessment of Effect on Growth

No long term pediatric data exist for this product thus no assessment of darunavir/rtv's effect on growth can be made.

7.1.15 Overdose Experience

Cases of intentional or accidental acute overdose with darunavir alone or in combination with low-dose ritonavir were not reported during clinical trials. No systematic examination of overdose potential was performed in the clinical trials included in the submission.

Single doses up to 3200 mg of DRV alone and up to 1600 mg of DRV in combination with RTV have been administered to healthy subjects without untoward symptomatic effects.

Multiple doses of up to 1200 mg DRV tid alone for 14 days and TMC/RTV 800/100 mg bid for 7 days have been administered in healthy subjects and up to 1200 mg tid for 14 days of darunavir alone and 600/100 mg bid. For up to 72 weeks of DRV/RTVin HIV-1 infected subjects.
All these dose regimens of DRV alone or co administered with low-dose RTV were generally safe and well tolerated.
At the higher dose regimens in the earlier trials where darunavir was administered as a Vit E-TPGS/PEG400-based oral solution, there was a relatively high incidence of diarrhea, which was most likely related to the PEG400 component of the DRV oral solution formulation.

There is no known specific antidote for overdose of DRV. The sponsor recommends that treatment of overdose should consist of general supportive measures including monitoring of vital signs and clinical observations of the patient. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. DRV is highly protein bound; therefore dialysis is unlikely to be beneficial in significant removal of the active substance.
This section is not applicable since neither this reviewer nor the applicant has any knowledge of any subjects who deliberately or inadvertently overdosed on darunavir/rtv.

7.1.16 Postmarketing Experience

This section is not applicable since no postmarketing studies or assessments have been conducted on DRV/rtv.

7.2 Adequacy of Patient Exposure and Safety Assessments

All reasonably applicable tests were conducted to assess the safety of darunavir/rtv.

The doses and durations of exposure were appropriate. There was adequate experience with this drug in terms of patients. The demographic subset of patients was appropriate.

All appropriate pre-clinical tests were carried out.

The metabolic work up of DRV/rtv was adequate. All appropriate in vitro studies of drug-drug interaction were carried out according to the present guidelines. All potentially important findings were adequately explored.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety data sources included the controlled 48 week data from Trial TMC114-C202 and TMC114-C213. 513 subjects were exposed. (Please refer to Section 4 of this review).

This reviewer reviewed all death and SAE narratives, CRF's and CRT's in the evaluation of the safety of this drug.

7.2.1.1 Study type and design/patient enumeration

Please refer to Table 4.2:1 for a description of the 39 clinical trials submitted and reviewed for safety. Please refer to Section 7.1 for how these 39 clinical trials were ranked and divided for review. Briefly, the two pivotal Phase IIb studies TMC114-C202 and TMC114-C213 and TMC114-C215/208 were the primary sources of safety data.

7.2.1.2 Demographics

The demographic and baseline HIV characteristics of the treatment-experienced study populations of Studies TMC114-C202 and TMC114-C213 are summarized in Table 7.2.1.2A. As with many other HIV clinical trials of highly treatment-experienced subjects, the participants in this study were predominately white and male. The patients who enrolled in Study TMC114-C202 and TMC-114-C213 represented an advanced population of previously treated patients with a median duration of HIV of 12 -13 years, and with > 95% subjects having been exposed to 2 or more PI's, 4 or more NRTI's and one or more NNRTI.

TABLE 7.2.1.2 : SHOWING THE BASELINE CHARACTERISTICS OF SUBJECTS ENTERING TRIAL **TMC114-C202** and **TMC114-C213**

CHARACTERISTIC	**TRIAL TMC114-C202**	**TRIAL TMC114-C213**
% MALE	91%	86%
MEAN AGE	45 years	44 years
RACE		
WHITE	64 %	81%
BLACK	19%	11%
HISPANIC	14%	4%

MEDIAN CD4 count	106 cells	179 cells
MEDIAN HIV RNA	4.66 logs	4.48 logs
DURATION OF HIV	13 years	12 years
Prior ARV experience		
Duration		
>/= 2 PI's	98%	96%
>/= 4 NRTI's	95%	96%
>/= 1 NNRTI	97 %	95%
ENF	14%	8%
>/= 3 Primary PI's mutations	56%	57%
CDC CLASS		
A	34%	32 %
B	25%	23 %
C	41%	44 %

7.2.1.3 Extent of exposure (dose/duration)

A total of 637 subjects enrolled in TMC114-C202 and TMC114-C213 were included in this analysis of data up to the switch to the recommended dose. Of these subjects, 513 were randomized to one of the 4 DRV/rtv treatment groups, and 124 were randomized to the control group.

The mean duration of DRV/rtv treatment in the proposed dose of 600/100 mg bid group was 62.3 weeks, while the mean duration of exposure in the other 3 DRV/rtv groups, (which were to switch to the 600/100 mg bid (proposed dose) was approximately 45 weeks (See Table 7.2.1.3 A). The mean duration of exposure of the control group was considerably lower (31.5 weeks), as a result of the high discontinuation rate secondary to virologic failure, which allowed control subjects to rollover into a open label study, and receive study drug. The total patient years exposure to any DRV/rtv dose was 483.7 weeks and the control group was 75.1 weeks.

A high discontinuation rate was observed in the control group mainly due to virologic failure. Control subjects could rollover to TMC114-C215 in case of virologic failure, which was defined as a less than 0.5 $\log_{10}$ reduction in plasma HIV-1 RNA from baseline at Week 12 or beyond. One confirmatory viral load result was required, which could be obtained using a planned protocol visit as of Week 16, since this was the first visit after Week 12. After Week 24, fewer than 50% of the control subjects were still in the trials.

The lower exposure in the control arm could lead to a bias in favor of the control group.

***MO COMMENT**: In an effort to correct for the difference in exposure between the control and the study arm, throughout the submission the sponsor analyzed AE's based on the customary observed incidence, in addition to AE's per 100 patient years exposure.*

TABLE 7.2.1.3 A) SHOWING: THE DURATION OF INTAKE STUDY MEDICATIONS AND CONTROLS DURING THE TREATMENT PHASE –TMC114-C202 + TMC114-C213

Total duration (weeks)	DRV/rtv					Control (N=124)
	400/100 qd (N= 129)	800/100 qd (N=127)	400/100 bid (N=126)	600/100 bid (N=131)	Total DRV (N=513)	
Mean (SD)	44.0 (18.2)	45 (19.8)	44.0 (19.5)	62.3 (23.2)	49 (21.7)	31.5 (22.1)
Median (range)	45.9 (4; 74)	48.1 (4; 74)	47.8 (1; 77)	68.3 (1; 96)	48.9 (1; 96)	21.2 (1; 94)
Patient years exposure	109.0	111.1	106.6	156.9	483.7	75.1

Source: Display 56

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no secondary data sources for this NDA application. All studies were conducted under the IND. There is no post marketing data, as this drug is [redacted]

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Not applicable

7.2.2.3 Literature Review

The applicant provided a detailed REFERENCE Section related to the treatment of HIV-1 and in particular resistant HIV-1. In addition, this reviewer reviewed literature regarding HIV and Hepatitis B and C co-infection, and the incidence of rash in response to medication administration.

7.2.3 Adequacy of Overall Clinical Experience

The overall development program for darunavir has provided adequate clinical experience to assess the safety and efficacy of TDF in combination with other antiretroviral drugs in the treatment of HIV-1 infected persons.

Adequate numbers of subjects were exposed to the study drug for a sufficient duration of time. The doses and durations of exposure were adequate to assess safety for the intended use. The

amount of exposure surpasses the amount of exposure required by the current ICH guidance on extent and duration of exposure needed to assess safety.

The shorter duration of exposure of subjects on the control arm was unavoidable, as the RTV component of the ARV drug cocktail could not be blinded, and trial participants had to be offered an opportunity to receive study drug should they be experiencing virological failure.

MO COMMENT: In this highly treatment experienced, HIV-1 infected patient population treatment options are limited and trials need to be designed to give patients the best chance at treatment success. Designing trials such as the POWER trials where patients on the control arm and even on the DRV/rtv arm could end up with no or one active drug(s) is unacceptable when as clinicians we believe that two or more active ARVs are needed in any ARV regimen. Regulatory agencies and pharmaceutical companines need to work together to design better trials for HIV infected patients with limited options to ensure that the data resulting from these trials are robust, reproducible and adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

All appropriate special animal studies special animal studies and *in vitro* testing were performed by the sponsor and the results have been reviewed by Dr James Farrelly. The Carcinogenicity toxicology studies are ongoing and will be completed as a Phase IV Commitment.

Please refer to Section 3.2 and Dr Farrelly's review for details of the preclinical pharmaco-toxicological development program of DRV/rtv.

7.2.5 Adequacy of Routine Clinical Testing

The types of routine clinical and laboratory testing of subjects during the pivotal trials were adequate. The appropriate laboratory tests were performed on clinical subjects at an appropriate frequency throughout the clinical development program. The frequency of clinical tests were also adequate. The methods of eliciting adverse events was also adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequate in vitro and in vivo testing was carried out by the applicant. Please refer to Section 5 and to Dr Arya's review for details of the Clinical Pharmacology review for details of the metabolism, clearance and interaction workup of DRV/rtv.

Results of this testing can be summarized as follows:

1) Inhibitory quotient(IQ) is a stronger predictor of response than exposure.
2) Response is primarily driven by baseline FC and less by exposure.
3) Exposure to DRV increases less than proportionally with increasing doses of DRV; increases in DRV/rtv dose above the 600/100 mg bid dose is less than likely to result in increased response, due to the large variability in IC50 values , and the less than proportional increase in plasma concentration with dose.

4) *In vitro*, DRV is a substrate and inhibitor of CYP3A (I/Ki=25). DRV has a low inhibitory potential towards 2B6, 2C9, 2C19, 2D6 enzymes. DRV is also a "weak" inducer of CYP3A. DRV is extensively metabolized via hydroxylation, glucuronidation, and N-dealkylation. The resultant metabolites are 10-fold less active than study drug. *In vivo*, DRV/rtv acts as an inhibitor of CYP3A.
5) In Phase I studies, 3-5% of the dose of DRV is excreted unchanged through the renal route. Mass balance studies showed that most of administered ^{14}C-darunavir related radioactivity was excreted in the feces. In the presence of RTV, 48.8 % of the dose recovered unchanged (41.2 % in feces and 7.7 % in urine).
6) PK results from 14 drug-drug interaction studies were included in the label. Eight (8) studies were performed with HIV drugs (atazanavir, indinavir, kaletra, ritonavir, unboosted and boosted saquinavir, efavirenz, nevirapine and tenofovir). Six (6) studies were performed with non-HIV drugs -clarithromycin, ketoconazole, omeprazole, paroxetine, ranitidine and sertraline.

MO COMMENT ON DRUG INTERACTION STUDIES:
Although most of the drug interaction studies were conducted using the 400/100 mg dose of DRV/rtv and not the 600/100 mg(proposed dose), data extrapolation is acceptable because of:

1) *Significant overlap in exposures between the DRV/rtv 400/100 and 600/100 bid regimens*
2) *The relevant interactions and recommendations would have been the same for drugs with significant interactions.*
3) *Most of the drug interaction studies had no clinically significant impact on DRV exposures.*

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Although we use VL as a surrogate endpoint for clinical benefit we normally make an attempt at assessing clinical benefit by looking at the frequency of new AIDS defining events (ADEs). FDA guidance recommends that these ADE's be determined prospectively by a blinded adjudication committee. Tibotec Inc chose to collect these events as part of the routine AE data and retrospectively define these AEs as ADEs.

MO COMMENT: *This type of data collection and analysis is not a reliable assessment of ADEs for multiple reasons including but not limited to the data being analyzed retrospectively and not prospectively. Additionally, the trials were partially blinded, leaving significant potential for bias. ADEs are very complex diagnoses to make in real time, and post-hoc determinations of ADE's are even more difficult to make.*

7.2.8 Assessment of Quality and Completeness of Data

The applicant included adequate numbers of subjects who were exposed to study drug for adequate durations of time, which are in keeping with the ICH document on safety. The overall

quality and completeness of the data submitted for the safety review is adequate, with the following exceptions:

1) Tibotec Inc retrospectively re-assigned AEs as ADEs instead of having an independent, blinded adjudication committee prospectively determine ADEs.
2) Tibotec Inc allowed investigator discretion in follow-up of AEs, which lead to inconsistent follow-up of AEs.

7.2.9 Additional Submissions, Including Safety Update

The safety update required under 21 CFR 314.50(d)(5)(vi)(b)was submitted by the applicant on March 29th 2006. This submission was reviewed particularly with respect to serious adverse events and deaths. Results of this review is reported here and not integrated into the Safety review. No new safety signals were identified between the time of the original database lock and January 2006.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following issues were identified during the review:
- Rash (See Section 7.1.2)
- Imbalance in mortality rate between study and control arm – (See Section 7.1)
- Lipid abnormalities- (Summarized in Section 7.1.2)
- Small numbers of elderly subjects, women, hepatically impaired and renally impaired subjects were studied. The exposure in other subgroups although small, was adequate. These subjects will be studied post approval.
- Relatively low representative percentage of Blacks and females within the trials, as compared with the number of subjects with the disease in the external population. This issue will be addressed in the post approval process.

7.4 General Methodology

This section will be submitted as an addendum.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This submission contained data from two partially blinded, randomized and controlled pivotal studies TMC114-C202 and TMC114-C213. The data from these studies was pooled to a form a single, randomized, partially blinded study comparing 2 treatment regimens in highly treatment-experienced HIV-infected patients. Pooling of these similarly structured trials were appropriate, as these studies were similar in design, with similar inclusion and exclusion factors.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study TMC114-C201 evaluated the PK/PD relationships of DRV when administered (alone) as the oral solution. The analyses indicated that better PD responses were associated with higher exposure to DRV. Subjects who had a better antiviral response also had Cmin values above baseline EC_{50} values (corrected for protein binding) for DRV. No consistent relationship was observed between exposure to DRV and the occurrence of adverse events or laboratory abnormalities.
Study TMC114-C207 evaluated the PK/PD relationships of DRV when co administered with low-dose rtv. Median Cmin values were above the target EC_{50} value of 550 ng/mL against PI-resistant HIV-1 strains when corrected for protein binding for all 3 DRV/rtv dosing regimens (300/100 mg b.i.d., 900/100 mg q.d., 600/100 mg b.i.d., with considerable overlap in pharmacokinetic parameters being observed between these dosing regimens. No dose relationships were observed in the occurrence of adverse events, and no consistent changes were observed in biochemistry or hematology parameters. The results of Study TMC114-C207 demonstrated that DRV co-administered with low-dose rtv in HIV-1 infected subjects achieved adequate exposure to DRV with q.d. or b.i.d. dosing regimens for a significant virologic response.

On the basis of these results, together with the favorable safety profile, that efficacy, safety, and pharmacokinetics of DRV co-administered with low-dose rtv, were investigated in Phase IIb Studies **TMC114-C202** and **TMC114-C213** using dosing regimens of 400/100 mg and 800/100 mg q.d., and 400/100 mg and 600/100 mg bid with the (F016) tablet formulation of DRV.

The **primary 24-week efficacy analysis of the integrated** data from these Phase IIb studies showed that all doses of DRV co-administered with low-dose rtv and an OBR had an unprecedented efficacy in treatment-experienced subjects with advanced HIV-1 infection, with the 600/100 mg bid dosing regimen providing the best virologic and immunologic response. The analysis of the PK and PK/PD relationships also provided evidence to substantiate the decision to recommend use of the 600/100 mg bid dosing regimen in treatment-experienced HIV-1 infected subjects.

Population pharmacokinetic analysis (based on sparse sampling) showed that exposure to DRV appeared to increase less than dose proportionally for the qd and bid regimens. For example, the 100% increase in darunavir dose between the two q.d. groups resulted in an approximately 60% increase in median exposure (AUC24h), and the 50% increase in DRV dose between the two bid groups resulted in an approximately 29% increase in median exposure. For each treatment group, the mean trough concentration of DRV in plasma *exceeded* the *predefined target trough concentration of 550 ng/mL (i.e., the EC_{50} value for PI-resistant HIV-1 strains when corrected for protein binding).* This target trough concentration was exceeded in all

subjects treated in the bid groups. In addition, the highest IQ values were seen with the 600/100 mg dosing regimen.

In evaluating the most appropriate dosing regimen for the treatment of HIV-1 infected subjects with prior experience of treatment (DRV/rtv 600/100 mg bid), higher doses would result in a less than dose proportional increase in DRV exposure. In addition, the results from the ANCOVA analyses (for assessing PK/PD relationships) suggest that to obtain approximately an additional 0.5 $\log_{10}$ decrease in viral load would require an approximately 10-fold increase in DRV exposure, which is not feasible. Therefore, a further increase in the DRV/rtv dose beyond 600/100 mg bid is not expected to provide a clinically meaningful increase in virologic response.

PK/PD relationships showed that there was a strong relationship between IQ and antiviral activity and virologic response (> 1.0 $\log_{10}$ decrease in viral load). The relationship between IQ and virologic response is driven primarily by the baseline DRV fold change (FC), as the pharmacokinetics of darunavir showed a less significant association with response compared to the darunavir FC. Thus, DRV FC is a much stronger predictor of virologic response than exposure to DRV.

There were no apparent relationships between DRV exposure and maximum changes in laboratory safety parameters, vital signs, or ECG parameters. No associations were found between DRV exposure and changes in liver function tests or lipids. There were also no relationships between DRV exposure and the occurrence of adverse events.

The 600/100 mg bid regimen also provides for a margin of forgiveness in case the exposure to DRV should be reduced in the context of potential drug-drug interactions.
On the basis of these characteristics, the DRV/rtv 600/100 mg bid dosing regimen has been selected for the treatment of HIV-1 infected subjects with prior experience of treatment and marketing approval is being sought for this dosing regimen.

The exposure response analysis of phase IIb studies consistently demonstrated that the probability of a patient's response to DRV/rtv treatment is related to inhibitory quotient (IQ = Cmin/corrected IC50).
DRV/rtv 600/100 mg bid is administered with food. This dose was selected as the recommended dose. This decision was driven by the fact that treatment outcomes were superior with this dose, including in those subjects who had the most advanced baseline disease characteristics.

8.2 Drug-Drug Interactions

Please refer to Dr Vikram Arya's Clinical Pharmacology review for further details on Drug-drug interaction.

PK results from 14 drug-drug interaction studies were included in the label. These included eight studies with other HIV drugs, namely atazanavir, indinavir, kaletra, ritonavir, unboosted and boosted saquinavir, efavirenz, neverapine, and tenofovir. Additionally, six studies were

conducted with non-HIV drugs; including clarithromycin, ketoconazole, omeprazole, paroxetine, ranitidine and sertraline.

Most of the drug-drug interaction data was generated at the 300 mg and the 400 mg dose of DRV administered with RTV bid. The "to be marketed dose" of DRV/rtv is 600/100 mg bid. It is felt that the effect of interacting drug on DRV exposure would not be very different, as most of the drug-drug interaction studies conduced using DRV/rtv 400/100 mg showed no clinically significant impact on DRV exposures, and there was also a significant overlap in exposures between the exposures between the 400/100 and the 600/100 mg bid TMC/114/rtv regimens.

The drug interactions occurring with darunavir/rtv should be considered in two groups:

1) Drugs that are absolutely contraindicated to be co-administered with darunavir/rtv – (See Table 8.2.1)
2) Drugs that show potentially significant drug interactions based on drug interaction studies or predicted interaction., with possible alterations in dose of DRV/rtv (See Table 8.2.2)

Both darunavir and ritonavir are CYP3A inhibitors. Coadministration of darunavir/rtv is **contraindicated** with drugs that are highly dependent on CPY3A4 for clearance.

Table 8.2.1 : LIST OF DRUGS BY CLASS THAT SHOULD NOT BE COADMINISTERED WITH DARUNAVIR/RTV

Drug Class: Drug Name	Clinical Comment
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. DRV/rtv should not be used in combination with phenobarbital, phenytoin, or carbamazepine as coadministration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.

Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because coadministration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to DRV/rtv.
HIV-Protease Inhibitor: lopinavir/ritonavir	An interaction trial between darunavir (300 mg twice daily), low-dose ritonavir (100 mg twice daily), and lopinavir/ritonavir (400/100 mg twice daily) demonstrated that exposure to darunavir decreased by 53% when administered concomitantly with lopinavir/ritonavir (with or without an additional dose of 100 mg ritonavir). The exposure to lopinavir decreased by 19% when coadministered with darunavir alone, and increased by 37% when coadministered with darunavir/ritonavir. It is not recommended to coadminister lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
HIV-Protease Inhibitor: saquinavir	An interaction trial between darunavir (400 mg twice daily), saquinavir (1000 mg twice daily), and low-dose ritonavir (100 mg twice daily) demonstrated that darunavir exposure was decreased by 26% when coadministered with saquinavir and ritonavir; saquinavir exposure was not affected when administered concomitantly with darunavir/ritonavir. It is not recommended to coadminister saquinavir and PREZISTA, with or without low-dose ritonavir.

HMG-CoA Reductase Inhibitors: lovastatin, [redacted]	HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A4 metabolism, are expected to have markedly increased plasma concentrations when coadministered with darunavir/ritonavir. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA/rtv with lovastatin or simvastatin is not recommended. An interaction trial between darunavir (600 mg twice daily), low-dose ritonavir (100 mg twice daily), and pravastatin (40 mg single dose) demonstrated that exposure to pravastatin increased by 81%, but only in a subset of patients. The clinical relevance of this interaction is currently unknown. Until more information is available regarding this interaction and the underlying mechanism, it is not recommended to coadminister pravastatin with DRV/rtv:
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

TABLE 8.2.2 SHOWING: POTENTIALLY SIGNIFICANT DRUG INTERACTIONS, BASED ON DRUG INTERACTION STUDIES OR PREDICTED INTERACTION-ALTERATIONS IN DOSE MAY BE RECOMMENDED

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and Cmin by 31%. The AUC of efavirenz increased by 21% and Cmin increased by 17%. The clinical significance of the reduction in Cmin is unclear, hence, the combination of DRV/rtv and efavirenz should be used with caution.
Nevirapine	↔ darunavir ↑ nevirapine	Exposure to nevirapine increased by 27% when administered in combination with DRV/rtv. DRV/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		Didanosine is administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after DRV/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate (TFV)	↔ darunavir ↑ tenofovir	When TFV is administered with DRV/rtv, exposure to TFV was increased by 22%. This finding is not considered to be clinically relevant. The combination of DRV/rtv and TFV can be used without dose adjustments.

HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir	↔ darunavir ↔ atazanavir	Atazanavir can be coadministered with PREZISTA/rtv.
Indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	Drug interaction trial between DRV, low-dose RTV (100 mg twice daily), and indinavir (800 mg twice daily) demonstrated that darunavir exposure was increased by 24% , while indinavir exposure was increased by 23% . The appropriate dose of indinavir in combination with DRV/rtv has not been established.
Lopinavir/ritonavir (LPV/rtv)	↑ darunavir ↓ Lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been established. It is not recommended to coadminister LPV/rtv and DRVwith or without an additional low-dose of ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	It is not recommended to coadminister saquinavir and DRV, with or without low-dose rtv, due to a decrease in the exposure (AUC) of DRV by 26%. Appropriate doses of the combination have not been established.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when coadministered with DRV/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with DRV/rtv.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when coadministered with DRV/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with DRV/rtv.
Anti-infective:	↑ clarithromycin	No dose adjustment of darunavir or

clarithromycin		clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↑ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of ketoconazole, itraconazole and DRV/rtv may increase plasma concentrations of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of DRV/rtv. When coadministration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: rifabutin	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and DRV in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once *every other* day when coadministered with DRV/rtv.

Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when DRV/rtv are coadministered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone fluticasone propionate	↓ darunavir ↑ fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A4 and can thereby decrease DRV plasma concentrations. This may result in loss of therapeutic effect to DRV. Concomitant use of inhaled fluticasone propionate and DRV/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.
Estrogen-based Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by rtv. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are coadministered with DRV/rtv.
HMG-CoA Reductase Inhibitors: atorvastatin	↑ HMG-CoA reductase inhibitors	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole, ranitidine	↔ darunavir	DRV/rtv can be coadministered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when coadministered with DRV/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when coadministered with DRV/rtv.

Narcotic Analgesic: methadone	↓ methadone	When methadone is coadministered with DRV/rtv, patients should be monitored for opiate abstinence syndrome, as rtvis known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	When methadone is coadministered with DRV/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is coadministered with DRV/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Other NRTIs:

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and darunavir/rtv.

Other protease inhibitors:

The coadministration of darunavir/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such coadministration is not recommended.

Multiple drug formulations were used during the clinical development program of darunavir. The interaction profile is not expected to change due to higher exposures from the commercial formulation (F016), as the safety profile of subjects in trials TMC114-C202 and TMC114-C213 was similar before and after the switch to the commercial formulation (F016), and there was no

apparent relationship observed between exposure and safety endpoints for the roll-over study TMC114-C215. More than 400 subjects were treated with the commercial formulation (F016).

The population PK analysis showed minor differences (approximately 18%) in HIV-1 infected subjects. Similar exposures were noted between the solution and tablet under fed conditions and with RTV co-administration. Data extrapolation across formulations is considered acceptable.

8.3 Special Populations

Assessment of the **safety** of darunavir/rtv in special populations was done using a pooled analysis including all data of trials TMC114-C202 and TMC114-C213, as well as trials TMC114-C215/TMC114-C208 for a total 924 subjects.

Generally, the various demographic characteristics analyzed, specifically gender, age, ethnic origin, geographic region did not appear to have an influence on the safety of DRV/rtv.

ELDERLY- Data in the elderly population (i.e., those aged 65 years and above) were obtained from the 8 subjects who initiated treatment with DRV/rtv bid. This data is too limited to draw any conclusions. The analysis by subgroups (≤40 years; 40-50 years; > 50 years of age) did not reveal any age-related trends in the safety profile of darunavir.
CHILDREN AND ADOLESCENTS- No data is currently available on the pediatric and adolescent population.
RENALLY IMPAIRED SUBJECTS- No data is currently available in renally impaired subjects. Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment.
GENDER- subgroup analyses by gender demonstrated no clear differences in the safety profiles of these subgroups.
RACE- Subgroup analyses by race demonstrated no clear differences in the safety profiles of these subgroups.
PREGNANCY- There are no adequate and well controlled studies with darunavir in pregnant women.
SUBJECTS COINFECTED WITH HEPATITIS B AND/OR HEPATITIS C VIRUS
Subjects co-infected with Hepatitis B and /or C were allowed to enroll in Study TMC114-C213. The incidence of adverse events and clinical chemistry abnormalities was not different for the limited number of subjects co-infected with hepatitis B or C virus and concurrently exposed to darunavir/rtv.

8.4 Pediatrics

Pediatric study Trial TMC114-C212 for treatment-experienced HIV-1 infected children and adolescents ages 6-17 years, with a body weight of at least 20 kg, with documented HIV-1 infection, on a stable ARV regimen for at least 12 weeks with a plasma viral >1000 copies/mL is currently enrolling subjects. Tibotec will fulfill the required pediatric assessment under 21 CFR 314.55(a) and the Pediatric Research Equity Act for the pediatric age group studied (6-17 years of age).

The sponsor has appropriately deferred the study of children less than 6 years of age for the present. [redacted]

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was not viewed by the Division as necessary, prior to accelerated approval of this drug. .

8.6 Literature Review

Literature reviewed for this NDA included current literature on the incidence and management of HIV and Hepatitis B and/or Hepatitis C co-infection.

8.7 Postmarketing Risk Management Plan

This section is not applicable since Tibotec Inc did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

The sponsor submitted two proposed proprietary names for consideration: [redacted] (primary) and Prezista (secondary). The first proposed name, [redacted] was found to be unacceptable by the Division of Drug Marketing, Advertising, and Commucations (DDMAC) on *October 11th 2005*, because the name was [redacted] The Division of Anti-Viral Drug Products (DAVP) concurred with DDMAC's objection to the name [redacted] and as a result, only the second name, "Prezista" was reviewed by the Division of Medication Errors and Technical Support (DMETS). Additionally,

DDMAC also suggested [redacted]. The Division of Antiviral Products (DAVP) concurred with DDMAC's decision and communicated this to the sponsor on *January 26th 2006.*

On April 11, 2006 , DDMAC and the Division of Medication Errors and Technical Support (DMETS) issued a letter to the sponsor stating that they found the proprietary name "Prezista" to be acceptable from a promotional perspective, and that they had no objections to the use of the proprietary name "Prezista".

The sponsor issued a Proprietary Name Rebuttal Response, explaining that they desired to achieve a ***single global proprietary name*** for darunavir, and [redacted].

The FDA via DDMAC, issued a response to this rebuttal on *May 8th 2006*. DDMAC explained

[redacted]

"Prezista" is considered to be the final trade name for darunavir/DRV/TMC114 in the United States.

9 OVERALL ASSESSMENT

9.1 Conclusions

The FDA Clinical and Statistical Reviewers concluded that in the randomized, controlled, partially blinded studies in treatment-experienced HIV-1 infected subjects patients, the combination of darunavir/ rtv 600/100 mg bid was safe and effective in the treatment of HIV infection when used in combination with another antiretroviral drugs. The safety profile of darunavir was consistent with that observed in other trials in similar patient populations. The data collection, study population, selection of primary and secondary endpoints, and primary and secondary efficacy analyses were adequate and appropriate to make the conclusion that darunavir/rtv was superior to the comparator regimen through 24 weeks of dosing. Similarly, safety was no worse than the safety of the comparator arm.

Independent FDA statistical analysis confirmed the applicant's analysis of the primary efficacy endpoint. In general there was a consistent pattern of increasing efficacy as one moved from a dose of DRV/RTV 400/100 mg qd, to the proposed dose of 600/100 mg bid, in both the primary and secondary efficacy endpoints. (See Table 6.1.4.1.H/I). The DRV/rtv 600/100 mg bid (proposed dose) achieved a 64% 1 log drop in VL compared to baseline versus a 14% 1 log drop in the control arm of Trial TMC114-C202 while in Trial TMC114-C213 study arm achieved 75% versus 24% 1 log drop in VL from baseline in the comparator arm.

Multiple secondary end point analyses also supported the conclusions of efficacy over 24 weeks of dosing. For example, the proportion of patients who achieved and maintained HIV RNA < 50 copies/mL was 36% for the DRV/rtv 600/100 mg bid versus 7% in the control arm of Trial TMC114-C202 and 57% in the 600/100 mg bid group versus 16% in control group of Trial TMC114-C213, over the course of 24 weeks of study drug dosing. Analysis of the proportion of patients who achieved and maintained HIV- RNA < 400 copies/mL also demonstrated that DRV/rtv provided a treatment benefit compared to comparator PI control arm . The mean difference in change in CD4 count from baseline to Week 24 using the DRV/rtv 600/100 mg proposed dose, and compared to control was 56 cells/mm^3 in the Trial TMC114-C202 and 100 cells/mm^3 the Trial TMC114-C213. These diffeerences were considered to be statistically significant.

The FDA's Statistical Reviewer verified the statistical significance of the observed dose response relationship by fitting logistic regressions to the three efficacy percentages, and performed sensitivity analyses to explore potential open label biases. The conclusion of darunavir's efficacy was confirmed.

The observed difference in the primary and secondary end point analysis between the two pivotal studies was likely a function of the baseline differences between the two study populations, with subjects in Trial TMC114-C213 being less advanced than the study population of TMC114-C202.

In the primary analysis of treatment outcomes, 65% of subjects in the control arm exhibited a suboptimal response, and were considered treatment failures for discontinuing their study drug, compared to 12% subjects in the study arm. These findings were statistically significant in favor of the DRV/rtv arm for all doses of DRV/rtv studied.

Four issues that might have had an impact on the outcome of the study must be considered in interpreting the results of Trials TMC114-C202 and TMC114-C213.

The first issue was the ***partially blinded study design****; With this type of study design, a disproportionately large number of study subjects may discontinue a regimen perceived to be less desirable (due to AEs, poorer potency, or dosing schedule). The FDA Statistical Reviewer conducted a series of sensitivity analyses to assess the impact of these issues on the study results.*

The second issue concerns that of the ***high attrition rate in the control group due to virologic failure****, in that 48% patients in the control versus 6.5% patients in the study arm, dropped out because of virologic failure. This phenomenon impacted exposure in the control group, and may have biased the safety data, in favor of the control group. The sponsor attempted to account for this bias by reporting incidence of AE's of all grades, SAE's and AE's leading to discontinuation, by correcting for the difference in exposure by performing an analysis per 100 patient years of exposure, when comparing the overall incidence rates between control and study group.*

The third issue is that the partially blinded study design may have impacted the "safety" analysis in yet another way, with a ***disproportionate withdrawal of control subjects*** *between randomization and first drug . The reviewer noted that there were disproportionately more control subjects who withdrew from the study* ***prior to*** *receiving first drug. The control arm lost 13% subjects before starting drug, while the DRV arm lost 3.4% subjects prior to the first dose of drug.(Please refer to Tables 2.2.3A &B of the Statistical Review).*

A fourth issue is the apparent ***Discordant Death Rate*** *between study and control arms, with 17 deaths on the study arm and zero deaths on the control arm .*
The imbalance in mortality between darunavir and control subjects can be partly explained by:

(i) The high attrition rate due to virologic failure in the control group, which had an impact on exposure. The virologic failure rate on the control arm was 65% versus a 12% rate in the study arm.

(ii) The total person time of exposure to darunavir was approximately six (6) times greater for darunavir as compared to control and the excesses of deaths on the darunavir arm may well be nothing but random variability. Study subjects were randomized 4:1 to receive darunavir versus control in DRV dose-finding studies
iii) The open-label design of the comparator arm, and the comparator arm's escape clause for lack of initial virologic response by 12-16 weeks make it somewhat difficult to discern treatment differences in some efficacy and safety parameters beyond 12 weeks of treatment.
iv) There were disproportionately more control subjects who withdrew from these open label trials between randomization and first drug dose. The control arm lost 13% subjects(17/133) before starting drug, while the DRV arms lost 3.4% (17/495). This reviewer believes that it is not unreasonable to to believe that these unblinded control subjects may have deliberately opted to go for a potentially more efficacious drug option, prior to receiving the first dose of drug when they discovered that they were randomized to the control/comparator arm.

The most commonly reported clinical AEs included: nausea, vomiting, headache, constipation and diarrhea. Most of these AEs were described as mild or moderate in severity (Grade 1 or 2). Adverse events (AEs) that were judged to be severe or life-threatening (Grade 3 or 4) were proportionally similar in study and control arms. A review of SAEs and other AEs of special interest revealed few differences between the safety profiles of the treatment arms; The rate of serious AEs was similar between the treatment arms.

Review of the laboratory monitoring data did not reveal any significant differences between the study arm and the comparator arm.except for dose related increases in serum cholesterol, LDL and amylase/lipase levels.

Similar proportions of patients in each treatment group experienced a post-baseline Grade 3 or 4 laboratory abnormality while receiving their assigned study drug

9.2 Recommendation on Regulatory Action

Based on the results of the efficacy and safety review of DRV/rtv in NDA submission 21-976, this submission is judged to be approvable on the basis of the Week 24 efficacy results, and the Week 48 safety results. The overall relative short term virologic and immunologic benefit of DRV potential outweighs the risks of DRV, when DRV is combined with another active ARV.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Although Tibotec Inc did not submit a formal risk management plan there are many risk

management activites planned for darunavir/rtv post accelerated approval.
• As a requirement for traditional approval under 21 CFR 314 subpart H the applicant must submit the 48-week data for their two pivotal Phase 3 trials, TMC114-C214 and TMC114-C211 which will provide more safety data for analysis of known and unknown DRV/rtv related toxicities.
• Also as a requirement of accelerated approval under 21 CFR 314 subpart H the applicant must submit periodic safety reports for review.
• The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.
• Additionally, the Office of Drug Safety has been involved with this NDA submission, and if warranted will be consulted formally to evaluate any new or increased post marketing safety signals.

9.3.2 Required Phase 4 Commitments

As a condition of darunavir /rtv accelerated approval, Tibotec Inc agrees to submit 96-week safety and efficacy data on the ongoing Phase IIb trials TMC114-C202, TMC114-C213, TMC114-C215 and TMC114-C208. Additionally, 48-week data from the Phase III trials TMC114-C214 in HIV-1 treatment-experienced subjects and TMC114-C211 in treatment naive subjects by December 31st, 2007 to support the traditional approval of DRV/rtv.

Tibotec Inc has committed to conducting several Phase 4 (Post-marketing) commitment studies designed to provide additional efficacy, safety and durability of response and the FDA has agreed to the following:

Required Phase 4 Commitments:
1) 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: by June 30, 2008

2) Additionally, the Division has deferred submission of pediatric studies in the under 6 years age group until June 30, 2011. These studies were deferred under PREA for the treatment of HIV-1 infection in pediatric patients ages less than 6 years. Tibotec Inc. has been asked to 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 old children in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

Protocol Submission: by December 2008
Final Report Submission: by June 2011

Pharmacology/Toxicology

3) Complete ongoing carcinogenicity study in mice and submit final report.
Protocol Submission: Completed
Final report Submission: by December 2007

4) Complete ongoing carcinogenicity study in rats and submit final report.
Protocol Submission: Completed
Final Report submission: by December 2007

Drug-Drug Interaction Trials

5) Drug interaction study between DRV/rtv and carbamazepine
Protocol Submission: by December 2006
Final report submission: by January 2008

6) Drug interaction study between DRV/rtv and buprenorphine/naloxone.
Protocol Submission: by December 2006
Final report submission: by January 2008

7) Conduct an *in vivo* drug-drug interaction study between Darunavir/rtv b.i.d. and rifabutin.
Protocol Submission: by July 2006
Final Report Submission: by June 2007

Pharmacokinetics

8) Please conduct a cocktail study to determine the effects of steady state Darunavir/rtv 600/100 mg b.i.d. on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.
Protocol Submission: by December 2006
Final report submission: by January 2008

Special Populations

9) Evaluate the pharmacokinetics of Darunavir/rtv in subjects with varying degrees of hepatic impairment in order to determine dosing recommendations
Protocol Submission: by July 2006
Final report submission: by March 2007

10) Conduct a study of darunavir in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

Protocol Submission: December 2006
Final Report Submission: December 2008

9.3.3 Other Phase 4 Requests

The following are ***not*** postmarketing study commitments, however we request the following information to be submitted:

1) The following represent clinical **drug-drug interaction studies** that have been planned by Tibotec, Inc. to be conducted with darunavir. The Division acknowledges the following planned studies:

- TMC114-C127: drug-drug interaction study between darunavir/rtv bid and methadone.
- [redacted]

Clinical

2) In addition to the required periodic adverse drug experience reports [21 CFR 314.80(c)(2)], please submit a separate periodic adverse drug experience report for rash.

Microbiology

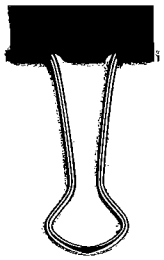
3) Determine response rates based upon presence of specific cleavage site mutations at baseline and submit this analysis with the PREZISTA traditional approval application.

4) Determine the protease cleavage site mutations that occur most frequently (>10%) in virologic failure isolates and submit this analysis with the PREZISTA traditional approval application.

5) Determine if the most frequently occurring protease cleavage site mutations contributed to decreases in darunavir susceptibility through site-directed mutagenesis and submit this analysis with the PREZISTA traditional approval application.

9.4 Labeling Review

[redacted]



39 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1

10 APPENDICES

10.1 Review of Individual Study Reports

TABLE OF CONTENTS-INDIVIDUAL STUDY REPORTS

INDIVIDUAL STUDY REPORT TMC114-C201

A. STUDY DESIGN

Trial TMC114-C201 was a Trial IIa proof-of-principle randomized study designed to determine the antiviral activity of DRV, by assessing the viral load decay rate, during a treatment with daily doses of DRV 400 mg bid, 800 mg bid, 800 mg tid or 1200 mg tid for 13 days. The formulation used was a 20 mg/ml [redacted] (TF019). The study was conducted in Austria, Germany, Great Britain, Italy, Poland, Russia and Switzerland.

The control group continued their current therapy until the end of the treatment period, while the DRV treatment groups received DRV as a substitute for all the PIs in the failing therapy, according to one of the following dose levels: 400 mg or 800 mg bid, or 800 mg or 1200 mg tid, for 13 days, followed by a single dose on day 14. Antiretroviral activity, safety, tolerability, pharmacokinetics, immunologic change, and the development of resistance to DRV were assessed.

Prior to randomization, subjects must have had documented resistance against at least 2 of the currently used PIs, confirmed by virtual phenotyping at screening (fold resistance equal or above 10). Apart from screening, phenotype and genotyping were performed before dosing (day 1), at the end of the treatment period (day 15) and 3 weeks following the last medication intake. The inclusion criteria consisted of adults with a plasma viral load of > 2000 HIV-1 RNA copies/mL, who were currently failing a ARV regimen of 1 or more NRTI's combined with 1 or more PI's for at least 8 weeks prior to screening; Excluded were subjects with a CD4 of < 50 cells/mm^3, those with a NNRTI in the current failing ARV regimen, those with a history of allergy to PEG400 and with a life expectancy of < 6 months, and with significant hematologic, renal or hepatic impairment.

B. STUDY POPULATION AND DISPOSITION

1) Study Population

Thirty four (34) subjects, consisting of 30 males and 4 females entered the study. The median age of the study population was 39.5 years, with a range of 24-62 years. Three subjects, one in each of the DRV discontinued the trial because of gastrointestinal adverse events.

2) Treatment History

At baseline, 12% to 33 % of subjects in each treatment arm were sensitive to PI's, and 25% to 57% subjects in each treatment group were sensitive to two or more PI's (based on baseline phenotype on baseline Antivirogram).

C. PHARMACOKINETIC ANALYSIS

The baseline DRV fold change (FC) in EC50 values was predictive of the change in viral load on Day 14, while the number of protease mutations at baseline was not. Comparisons of baseline and end-of-treatment phenotypes, revealed no significant change in DRV FC.

D. RESULTS OF EFFICACY PARAMETERS

Primary parameter

The primary efficacy parameter was the decrease in viral load (decay rate).

Median change in VL (by treatment dose group) at the end of the 14 days of dosing was as follows:

- DRV 400 mg bid – -0.313 $\log_{10}$ copies/mL (range
- DRV 800 mg bid – -0.818 $\log_{10}$ copies/mL (range
- DRV 800 mg tid – -1.124 $\log_{10}$ copies/mL (range
- DRV 1200 mg tid - -0.691 $\log_{10}$ copies/mL (range
- Control - -0.212 $\log_{10}$ copies/mL (range

Secondary parameters

1) Nadir of the viral load.
2) Change in CD4 cell count.
3) Change in CD4% counts

The findings for viral load decay, viral load DAVG, and nadir of the change in log10 viral load generally confirmed the findings for the change in $\log_{10}$ viral load.

E. ANALYSIS OF SAFETY

All 4 DRV dose regimens were generally safe and well tolerated; in general, the safety and tolerability profile of DRV was similar for all 4 dose groups.The most frequent AE occurring in this population was diarrhea (55%), headache (28%), nausea 10%), and abdominal distension (7%).

MO COMMENT: *The high incidence of diarrhea occurring in this population was likely a function of the PEG400 constituents in the (F019) oral solution formulation. Otherwise the frequency of AE's were similar to those observed in the Phase IIb studies.*

F. OVERALL CONCLUSIONS

1) For all 4 dose groups, C_{min}, C_{max}, and AUC24h increased with the total daily dose of DRV on Day 14.
2) Treatment with DRV 800 mg bid, 800 mg tid and 1200 mg tid for 14 days resulted in a reduction of viral load when compared to the control group. (Treatment with DRV 400 mg bid, the reduction in VL was smaller but still significant compared to the control group at treatment endpoint).
3) The baseline DRV FC was predictive for the change in viral load on Day 14, while the number of protease mutations at baseline (all, PI resistance associated, or primary) was not.
4) Statistically significant larger decreases in $\log_{10}$ VL were observed with higher values for AUC24h and various measures of IQ. The data suggested that the decrease in $\log_{10}$ VL was smaller for subjects with C_{min} below plasma protein binding corrected EC50 than for subjects with C min above plasma protein binding corrected EC50.

MO COMMENT: These results need to be interpreted with caution in view of the small sample size in this proof of concept study.

INDIVIDUAL STUDY REPORT TMC114-C207

A. STUDY DESIGN

TMC114-C207 was a Phase IIa, open label, controlled, randomized trial conducted in HIV-1 positive subjects with multiple PI-resistant strains, receiving either control treatment or DRV/rtv at various dosages for 13 days. An open trial design was chosen because blinding was not possible, as ritonavir (RTV) placebo was unavailable, and blinding for the DRV/rtv regimen was not possible. There was no stratification. The study was conducted Austria, Belgium, Germany, UK, Italy, Poland, and Switzerland.

Subjects were randomized to 1 of 4 groups. The dose regimens of DRV/rtv were:

1) DRV/rtv 300/100 mg bid (13 subjects)
2) DRV/rtv 600/100 mg bid (12 subjects)
3) DRV/rtv 900/100 mg qd (13 subjects).
4) Control group (n=12 subjects) continued on their screening therapy.

The total sample size N was 50 subjects. Adult HIV-1 infected subjects, with HIV-1 RNA copies of > 2000 copies/mL, without a current AIDS defining illness, were randomized to control group, or one of the 3 DRV/rtv treatment arms, for 14 days. Subjects with a CD4 of < 50 cells/mm^3, those with a NNRTI in the current failing regimen, those with a history of allergy to PEG400 and with a life expectancy of < 6 months, and with significant hematologic, renal or hepatic impairment were excluded from the study.

The underlying NRTI regimen remained unchanged until the end of the treatment period.

Subjects in the DRV treatment groups received darunavir (TF019, oral solution, 20 mg/mL) co-administered with low-dose ritonavir (100 mg) as a substitute for all PIs in their failing therapy for 13 days followed by a single morning dose on Day 14.

B. STUDY RESULTS

1) STUDY POPULATION

The 50 subjects treated were HIV-1 infected subjects, exposed to at least 2 and no more than 4 different PIs for a period of at least 2 months per PI; were on a PI-containing regimen for at least 8 weeks prior to screening and on a failing PI-containing regimen at the time of randomization. All subjects had a screening plasma viral load > 2000 HIV-1 RNA copies/mL.

The baseline characteristics of the subjects showed that this was a PI-experienced population with advanced HIV-1 disease. Forty-six percent (46%) of the subjects had a CDC category C (AIDS) HIV-infection at time of diagnosis of HIV-1 infection. The mean duration of HIV-1 infection was 9.6 years, with a mean baseline $\log_{10}$ viral load of

4.26 copies/mL and a median CD4+ cell count of 305 x 10^6 cells/L. The median number of susceptible NNRTIs (not allowed during the treatment period) was 3, the median number of susceptible NRTIs (excluding NtRTIs) was 4. The median number of susceptible NtRTIs was 1, and the median number of susceptible PIs was 1.

Overall, 25 (51%) subjects had virus resistant to all approved PIs at that time; 11 subjects (22%) were susceptible to 1 PI and 13 (27%) were susceptible 2 or more PIs. The overall median darunavir FC at baseline was 1.7 and was comparable for all 4 treatment groups, ranging from 1.5 to 2.0. Fifty-three percent of the subjects had 3 or more primary PI mutations at baseline.

2) STUDY DISPOSITION

One subject in the control group was lost to follow up, leaving 11 control subjects to complete the 14 days of dosing. Three subjects in the DRV/rtv 300/100 mg group withdrew consent, one subject in the 600/100 mg bid group developed an AE, and 2 subjects in the 900/100 mg group developed AE's, and 1 subject in this cohort withdrew consent. The subjects who withdrew from the trial developed gastrointestinal AE's.

C. PHARMACOKINETIC ANALYSIS

Darunavir was rapidly absorbed and the C_{max} was reached between 0.25 hours and 2 hours post dose for all dose regimens. DRV steady state plasma concentrations were generally reached within 4 days of dosing with low dose RTV. At Day 14, median AUC_{24h} and C_{min} were 50528 ng.h/mL and 1259ng/mL for the 300/100 mg bid group, 62854 ng/mL and 1430 ng/mL for the 600/100 mg bid dose group, and 68602 ng.h/mL for the 900/100 mg qd dose group, respectively.

Individual DRV C_{min}, C_{max} and AUC and $C_{ss\ av}$ values for different dose regimens overlapped considerably. The fluctuation index (FI) was slightly higher for the 900/100 mg qd dose group. There was no clear correlation between DRV PK parameters and virologic activity.

Steady-state concentrations of RTV were reached within 3 days of dosing of DRV and RTV. At Day14, RTV C_{max} was reached, a delay in the absorption of RTV was observed in most subjects and C_{max} was attained between 0.5 and 0.8 hours for all dose levels. Median AUC_{24h} were 6972, 5370 and 3188 ng.h/mL for the 300/100 mg bid, 600/100 mg bid and the 900/100 mg qd groups respectively.

Please refer to Dr Vikram Arya's report for further details.

D. ANALYSIS OF EFFICACY

The study end points were as follows:

i) For the subjects assigned to the DRV arms, the proportion of subjects with 0.5 and 1.0 log_{10} drop in plasma VL was 97% and 63% respectively.

ii) The median DAVG change in VL over the 14 day treatment period was -0.70 log_{10} for the DRV/rtv groups as compared to -0.03 log_{10} in the control group. (The median DAVG response in the 3 DRV/rtv groups ranged from -0.56 log_{10} to -0.81 log_{10}.)

All studied doses of DRV/rtv had statistically significant ($p < 0.001$) decreases in plasma HIV-1 RNA compared to baseline at 14 days (LOCF). There was almost no change from baseline in the control group.

Table 10.1.D noted below, compares the virologic response rates, defined as a at least 0.5 log_{10} or 1.0 log_{10} decrease in viral load from baseline. Proportion of study population demonstrating a virologic response were in general higher for subjects treated with DRV co-administered with low-dose rtv (Trial TMC114-C207) compared to the response rates observed when treated with darunavir alone (TMC114-C201).

TABLE 10.1.D: COMPARING THE VIROLOGIC RESPONSE RATE at Day 14 for subjects treated with unboosted DRV in TRIAL TMC114-C201 compared with DRV/rtv in TMC114-C207

Response category, n (%)	**All DRV treated subjects (TMC114-C201)**	**All DRV/rtv treated subjects (TMC114-C207)**
Decrease of $\geq$ 0.5 log_{10} in Viral load	14 (56)	34 (97)
Decrease of $\geq$ 1 log_{10} in Viral load	7 (28)	22(63)

Source: Appendix 2.7.3.7.21 and Appendix 2.7.3.7.22

None of the subjects in either control group of Trials TMC114-C201 and TMC114-C207 had a decrease in viral load of at least 0.5 log10 at Day 14.

The findings for viral load decay rate, viral load time averaged difference (DAVG), and nadir of the change in log_{10} viral load generally confirmed the findings for the changes in log10 viral load.

E. ANALYSIS OF SAFETY

The most common AE's were in the gastrointestinal and central nervous system. There were 2 treatment discontinuations in the TMC/rtv groups; 1 subject showed grade 2 and 3 CNS and GI related events, while the other subject showed HIV related esophageal candidiasis and stenosis.

One SAE of hepatotoxicity (*CRF # C207-0019*) was reported in the DRV/rtv 600/100 mg bid group, and is discussed in detail in the hepatic SAE section.

F. STUDY CONCLUSION

The results of the second Proof-of-Principle trial demonstrated that a 14-day treatment with DRV exhibits potent antiviral activity in treatment-experienced subjects, and exposure and antiviral activity was higher when DRV was co-administered with 100 mg RTV. Decreases in HIV-1 RNA were observed in multiple PI resistant subjects treated with DRV.

MO COMMENT: *From this point onward, the clinical development of DRV was performed in conjunction with low dose rtv therapy, in order to boost the therapeutic DRV levels, by increasing the DRV exposure and prolonging the serum half life of DRV.*

INDIVIDUAL STUDY REPORT TMC114-C213 and TMC114-C202

These Phase IIb randomized, controlled, partially blinded trials to investigate the efficacy, safety, and dose-response relationship of DRV/rtv in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of DRV/rtv.
Trial TMC114-C213 was conducted in Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Italy, Portugal, Spain, Switzerland, and the United Kingdom, while Trial TMC114-C202 was conducted in the USA and Argentina.

A. STUDY DESIGN

These randomized, controlled, partially blinded, Phase IIb studies were designed to evaluate:

1) The dose response relationship of antiviral activity between the four DRV/rtv treatment groups at 24 weeks,

2) The safety, tolerability and the durability of the antiviral activity of DRV, formulated as an oral tablet, and administered with low dose rtv over a 48 week treatment period. The DRV/rtv arms were compared to control arm.

The studies were conducted as a two part hybrid where subjects failing a PI based regimen were randomized to one of five treatment groups, consisting of a control group or one of 4 DRV/rtv treatment groups. The control group had a screening period (maximum of 6 weeks long) that included a two week period post randomization during which time subjects remained on their current regimen (Part A). This period was followed by 48 weeks of treatment with the investigator selected PI + OBR (Part B). The subjects randomized to DRV/rtv had a screening period that included a two week period post randomization during which time subjects remained on their current regimen (Part A). Part A was followed by part B1: a functional monotherapy period of 2 weeks. Subjects substituted their PIs for their randomized dose of DRV/rtv, 400/100 mg qd, 800/100mg qd, 400/100mg bid, or 600/100 mg bid in addition to their current background regimen of NRTIs +/- T20. Subjects were blinded as to the dose of DRV they were receiving. Part B2 consisted of a 46 week treatment period during which time subjects will continue on their randomized DRV/rtv treatment and change their background NRTIs to the OBR.

All groups were followed up for 4 weeks after the 48 week treatment period.

Prior to randomization investigators chose a PI based regimen plus an optimized background regimen (OBR). NNRTIs were excluded because there was insufficient data regarding drug interactions between DRV and NNRTIs. Abacavir(ABC) was excluded because rash was common with both ABC and DRV use. Use of T20/enfurvitide was allowed.

MO COMMENT: *The two-part hybrid design was to allow demonstration of the short term antiviral activity of DRV/rtv compared to control during the two week functional monotherapy portion of the trial and long term durability of DRV/rtv as part of an ARV regimen during the 46 week treatment period of DRV/rtv + OBR vs. PI + OBR. .*

Subjects were seen at baseline, week 1, 2, 3, 4, every 2 weeks from week 4 to week 12 and from this visit onwards, every 4 weeks until week 24. From week 24 subjects were seen every 8 weeks until week 48 or withdrawal. Blood was drawn at each site visit for safety labs. Other assessments at some or all of the visits included physical exam, urinalysis, viral load, immunology labs, ECG, pharmacokinetics and ARV bioanalysis, phenotype and genotype determination and QOL, body image and compliance questionaires. There were detailed management guidelines for selected AEs, namely rash, LFT abnormalities, nausea and diarrhea.

Pharmacokinetic (PK) assessment and an optional PK sub study was performed subjects randomized to a DRV treatment arm were eligible to participate in this sub study. Participating subjects will have a 12-hour (bid dose regimen) or 24-hour (q.d. dose regimen) PK sampling period at week 4, at week 24 and optionally at week 40. The sponsor planned to enroll 60 subjects in all (30 on bid regimens and 30 on qd. regimens). A complete PK analysis was performed on all of the samples.

There were a number of secondary endpoints dealing with the rate, extent and durability of VL decline (See Section D – Analysis of efficacy).,

HIV-1 infected subjects who were at least 3-class-experienced and who were on a stable PI-containing regimen at screening for at least 8 weeks and who had plasma HIV-1 RNA > 1000 copies/mL were eligible. 'Three-class experienced' was defined as prior treatment with 2 or more NRTIs for at least 3 months in total and 1 or more NNRTI as part of a failing regimen. Subjects had to have received at least one PI for at least 3 months in the past and have at least 1 primary PI mutation at screening. The number of subjects with 3 or more primary PI mutations was limited to 30% of the total number of subjects. Prior use of enfurvirtide (T-20) was allowed. Two interim analyses were performed as defined by protocol. The recommended dose (DRV/rtv 600/100 mg bid) was selected based on the first combined interim analysis including 150 subjects each in the TMC114-C213 trial and TMC114-C202 who reached Week 16 or discontinued earlier. The selection of the recommended dose was confirmed in a second combined interim analysis, performed when 150 subjects in each of the trials reached Week 24 or discontinued earlier.

Around the cut-off date of the primary efficacy analysis, the recommended dose was communicated to relevant parties and subjects were instructed to switch to the recommended dose of DRV/rtv after this date. The primary efficacy analysis was performed on all 318 subjects enrolled in the trial. The amended primary objective of the dose-finding part of the trial was to compare all DRV/rtv groups to the control group by means of the confirmed virologic response at Week 24, defined as a drop in viral load of at least 1.0 $\log_{10}$ versus baseline. In addition, long term safety, tolerability and the durability of antiviral efficacy of DRV/RTV in 3-class-experienced HIV-1 infected subjects were evaluated.

The trial included screening period of a maximum of 6 weeks, and a 96-week treatment period followed by a 4-week follow-up period.

Virological End points

i) PRIMARY EFFICACY VARIABLE- was the confirmed virologic response at Week 24, defined as a drop in viral load (copies/mL) of at least 1.0 log10 versus baseline, and the proportion of subjects with at least 1.0 $\log_{10}$ in plasma viral load. Subjects who never achieved were censored at their last available time point

ii) SECONDARY EFFICACY VARIABLES included the following:

a. ***Proportion of subjects with 0.5 $\log_{10}$ drop (TLOVR) in plasma viral load (compared to baseline)*** at each time point and time to achieve this. Subjects who never achieved this were censored at their last available time point.
b. ***Proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL*** (TLOVR) at each time point and time to achieve this. Subjects who never reached plasma HIV-1 RNA levels < 50 copies/mL were censored at their last available time point.
c. ***Proportion of subjects with plasma HIV-1 RNA levels < 400 copies/mL*** (TLOVR) at each time point and time to achieve this. Subjects who never reached plasma HIV-1 RNA levels < 400 copies/mL were censored at their last available time point.
d. ***Time to loss of virologic response for each of the 4 definitions of virologic response*** (as mentioned above) over the 96-week treatment period.

e. ***DAVG (time averaged difference) of $\log_{10}$ plasma viral load*** over 24 weeks, which was defined as the AUC of the change in $\log_{10}$ plasma viral load from baseline divided by the time treated in the trial. Plasma viral load values below 50 copies/mL were scored as 49 in the calculation of the DAVG.
f. Change in CD4+ cell count (absolute and %)
g. Change in CD8+ cell count (absolute and %)
h. Change in CD4+/CD8+ ratio

B. STUDY RESULTS

1. Study Population

a) Baseline characteristics- include demographics and baseline disease characteristics

The baseline characteristics of the subjects included in this trial demonstrated that the study population was one with advanced HIV disease with limited to no treatment options.

The majority of subjects enrolled into the trial were males (n = 273; 86%). The median age was 42 years, with a range of 20-71 years. Eighty-one percent (81%) of the subjects were Caucasian (n = 256). The mean baseline $\log_{10}$ viral load for all subjects was 4.48 $\log_{10}$ copies/mL ranging from 4.33 to 4.59 $\log_{10}$ copies/mL for the different treatment groups. The median baseline CD4+ cell count and percentage of CD4+ cells for all subjects was 179 x 10 cells/mm^3 (range: 3-816) and 12% (range: 1-48), respectively. Overall, 140 (44%) subjects had a CDC category C (AIDS) HIV infection at time of HIV diagnosis. The average time since HIV-1 infection diagnosis was 11.6 years.

Overall, 44 (14%) subjects were co-infected with hepatitis B or C virus. The infection status was active which for 32 of these 44 subjects. Demographic data and baseline disease characteristics were comparable across the treatment groups, except for a higher percentage of subjects co-infected with hepatitis B or C virus in the control group compared to the DRV/rtv groups (21% versus 12%).

b) Previous ARV Experience

Overall, the mean number of ARVs previously used was 11.0. The majority of the subjects with a history of having used 2 or more PIs (excluding low-dose RTV) was (97%), 1 or more NNRTIs (95%) and 4 or more NRTIs (96%). The mean number of PIs, NNRTIs and NRTIs used was 4.1 (excluding low-dose RTV), 1.3 and 5.4, respectively. The mean duration of treatment with PIs, NNRTIs and NRTIs was 5.8, 2.1 and 8.7 years, respectively. The fusion inhibitor T-20 had been used by 11% of the subjects, with a mean T-20 treatment duration of 1.2 year.

2) Subject disposition

A total of 334 patients were randomized to Trial TMC114-C213, of whom 318 received treatment. The Tables 10.1 A and 10.1.B summarize the primary reasons for discontinuation at Week 24 of both trials. (These tables were developed by FDA's Statistician, and utilize the data from the applicant's computer files and are not the printed tables from the submission).

TABLE 10.1. A SHOWING DISPOSITION OF SUBJECTS IN TRIAL TMC114-213 @24 WEEKS

	DRV/rtv 400/100 mg qd	DRV/rtv 800/100 mg qd	DRV/rtv 400/100 mg bid	DRV/rtv 600/100 mg bid	All DRV/rtv	CONTROL
Randomized	65	64	65	67	261	73
Treated	64	63	63	65	255	63
Discontinued	14	10	17	6	47	47
▪ *AE*	2	1	8	2	13	4
▪ *Virologic failure*	9	8	9	4	30	42
▪ *Lost to follow up*	3	1	0	0	4	1

A total of 340 patients were randomized to Trial TMC114-C202, of whom 319 received treatment. The applicant conducted an interim analysis using only patients enrolled by the end of December 2004. Two hundred and ninety four (294) randomized patients were in this interim group, of whom 278 received treatment.

TABLE 10.1.B SHOWING DISPOSITION OF SUBJECTS IN TRIAL TMC114-C202 (@24 weeks)

	DRV/rtv 400/100 mg qd	DRV/rtv 800/100 mg qd	DRV/rtv 400/100 mg bid	DRV/rtv 600/100 mg bid	All DRV/rtv	CONTROL
Randomized	66	66	68	69	269	71
Treated	65	64	63	66	258	61
Discontinued	24	19	14	17	74	51
▪ *AE*	6	7	4	7	24	2
▪ *Virologic failure*	12	7	5	6	30	39
▪ *Lost to follow up*	6	5	5	4	20	10

C. PHARMACOKINETIC ANALYSIS (PK)

Please see Dr Vikram Arya's analysis for complete analysis of pharmacokinetic data.

Exposure to DRV increased with increasing dose of DRV/rtv, however the increase appeared to be less than dose proportional for the qd and bid regimens. The highest daily exposure to DRV/rtv was observed after DRV/rtv 600/100 mg bid.

The estimated pharmacokinetic parameters for DRV from the population PK analysis for the different dose regimens were in the same range as those observed in the pharmacokinetic sub study. The AUC 12h ranged from 46777 - 55952 ng.h/mL, and the C0h ranged from 3203 to 5495 ng/ml for subjects on the DRV/rtv 600/100 mg bid dose.
For each dose group, the mean trough concentration of DRV in plasma exceeded the predefined target trough concentration of 550 ng/mL. All subjects in the bid dosing regimens of DRV/rtv had a plasma trough concentration of DRV exceeding 550 ng/mL. A trend of higher DRV exposure was observed for subjects with higher concentrations of AAG in plasma at baseline for all dose regimens.

D. ANALYSIS OF EFFICACY

Further details of efficacy analysis are shown in Section 6.1.4 of this report.
Additionally, Dr T Hammerstrom's statistical analysis is also available.

This report describes the primary efficacy analysis. The cut-off date for this analysis was February 1, 2005. At that time, 301 subjects in the TMC114-C213 trial reached 24 weeks of treatment or discontinued earlier (318 subjects were included in the primary efficacy analysis; 17 subjects had not reached 24 weeks of treatment).

In general, across both primary and secondary efficacy end points, there was a consistent pattern of increasing efficacy as one moved from a dose of DRV/rtv 400/100 mg qd to the "to-be-marketed dose" of 600/100 mg bid, in both the primary and secondary efficacy endpoints. (See Table 10.1.D)
(Exceptions to the pattern are marked with asterixes *).

TABLE 10.1.D: SHOWING THE PATTERN OF INCREASING EFFICACY WITH INCREASING DOSE OF DRV/rtv FOR THREE EFFICACY ENDPOINTS: PERCENT OF SUBJECTS WITH HIV RNA < BASELINE - 1 LOG HIV RNA <400 AND <50 COPIES/ML AND COMPARED TO CONTROL.

Treatment Arm	<1 log drop in HIV RNA	VL<400 copies/mL	VL<50 copies/mL
Trial TMC114-C202			
400/100 qd	31/65=48%	25/65=38%	16/65=25%
800/100 qd	33/64=52%	26/64=41%	16/64=25%
400/100 bid	38/63=60%	33/63=52%	23/63=37%
600/100 bid	42/66=64%	37/66=56%	24/66=36% *
CONTROL	6/42= 14%	7/61 = 11%	4/61 =7%
Trial TMC114-C213			
400/100 qd	45/64=70%	40/64=63%	27/64=42%
800/100 qd	45/63=71%	39/63=62% *	31/63=49%
400/100 bid	45/63=71%	43/63=68%	34/63=54%
600/100 bid	49/65=75%	45/65=69%	37/65=57%
CONTROL	15/60= 25%	15/63=24%	10/63 =16%

Source: Adapted from analysis by FDA Statistical Reviewer- Dr T. Hammerstrom

When the above proportions are compared to those of controls, only 7% to 14% of controls in TMC114-C202 , and 16% to 25% of controls in Trial TMC114-C213 are able to successfully achieve virologic suppression at Week 24.

E. ANALYSIS OF SAFETY

1) Extent of Exposure to study drug

Overall the mean duration of DRV/rtv treatment ranged from 38.3 to 40.6 weeks for the different treatment groups. The mean duration of treatment in the control group was shorter (26.3 weeks), due to the high discontinuation rate in this group.

Total patient years exposure at 1 February 2005 to any DRV/RTV dose was 195 years and the total exposure to DRV/rtv 600/100 mg bid dose was 51 years. Total patient years exposure to trial medication in the control group was 31.9 years.

2) Protocol Deviations

Major protocol deviations were noted in 11 subjects (4%). Six subjects in the TMC/rtv treatment groups and 3 in the control group took forbidden therapy.

MO COMMENT: The proportion of subjects with protocol deviations was small; None of these deviations described above were considered to have a relevant influence on the outcome of the trial.

The common adverse events reported in greater than 10% subjects were mainly gastrointestinal and included nausea, abdominal pain and discomfort, diarrhea; headache, fatigue and upper respiratory tract infections were also commonly reported.

F. OVERALL STUDY CONCLUSIONS

1) DRV/rtv co-administered with an individually optimized OBR was highly effective in this advanced population with limited to no treatment options, as compared with individually optimized ARV regimens used in the control group (OBR + selected PIs).

2) All DRV/rtv dose regimens were associated with a significantly higher proportion of subjects achieving at least a 1.0 $\log_{10}$ reduction in viral load relative to baseline. Greater reductions in $\log_{10}$ viral load, a substantially higher proportion of subjects in the other categories of virologic response, and a larger increase in CD4+ cell count were observed in all DRV/rtv groups as compared with the control group.

3) Overall, the DRV/rtv 600/100 mg bid dose provided the greatest efficacy. In this population, it appears that the additional effect of T-20 was limited in subjects who received DRV/RTV 600/100 mg bid.

4) All doses of DRV/rtv were safe and well tolerated and showed an adverse event profile comparable to the control group. Exposure to study medication was approximately 50% higher in the DRV/rtv groups. No trends related to dose and incidence of AEs, laboratory abnormalities and/or abnormal investigations were apparent. The DRV/rtv 600/100 mg bid dose was shown to have a similar safety profile as the other DRV/rtv doses evaluated in this trial.

INDIVIDUAL STUDY REPORT TRIAL TMC114-C215/TMC114-C208

A. DESIGN

Trials TMC114-C215 and TMC114-C208 were designed as open-label, ongoing trials evaluating the efficacy of the recommended dose of DRV/rtv 600/100 mg bid with the commercial tablet formulation (F016).

Due to the small number of subjects in trial TMC114-C208, data from this trial was combined with the data from the similar Trial TMC114-C215 were combined for analysis; Pooling was permissible as all subjects were treatment-experienced HIV-1-infected subjects with no or limited treatment options, all subjects received the same dose of DRV/rtv (recommended dose) from initial randomization, and both trials had similar inclusion/exclusion factors, and baseline characteristics. As a result there were 3 independent component groups for analysis, as follows:
1) De novo (N=327): The group of primary focus was that of subjects starting treatment in TMC114-C215 or in TMC114-C208 directly with the recommended dose of DRV/RTV 600/100 mg bid. This group comprised mostly of new subjects who had not previously participated in any DRV trial (N=303) and some subjects previously participating in the control arm of the original trials (N=27).
2) *Control/darunavir (N=59):* This group is composed of subjects who were randomized to control in the original trials but who were subsequently treated with any TMC/rtv dose other than the recommended dose.
3)*Darunavir/darunavir* (N=74): Subjects who failed on darunavir and rolled-over from any darunavir dose in the preceding trials to the recommended dose of darunavir/ritonavir 600/100 mg bid.

MO COMMENT: This subsection review will focus on the results of the TMC114-C215/TMC114-C208 de novo group, as it provides additional data on the efficacy and safety of DRV/rtv at the recommended 600/100 mg bid dose of DRV/rtv.

B. STUDY RESULTS

1) Study Population – baseline characteristics and treatment history

The results in the DRV *de novo* group (N=327) is the group of primary interest in Trial TMC114-C215/C208, in that subjects in this group were those subjects starting DRV/rtv treatment with the recommended dose of DRV/rtv, in its commercial formulation (F016), and in the largest numbers.

Analysis of the baseline characteristics of this study population showed that 87% of the study population was male, and 75% Caucasian, with a mean duration of infection of 12.8 years, a mean VL $\log_{10}$ of 4.62 $x10^6$ copies/ mL, and a median CD4 cell count of 115 cells/mm^3.

In this *de novo* population, the mean duration of NRTI exposure was 112 months, and 27 months for mean duration of NNRTI exposure. Previous use of ENF was slightly lower in the DRV group from trial TMC114- C215/C208 (24.5%) and compared to trials TMC114-C202 (31.8%) and TMC114-C213 (32.3%). Fewer subjects had ≥1 susceptible PI commercially available at the time of the trial in TMC114-C215/C208 (20%) compared to TMC114-C202 (33%) or TMC114-C213 (39%).

The number of subjects with >1 susceptible NRTI in the OBR was comparable for trials in TMC114- C215/C208 (61%) and TMC114-C202 (67%) and less compared to TMC114-C213 (77%).

MO COMMENT: *The baseline demographic characteristics and the treatment history of the DRV/rtv de novo subjects in TMC114-C215/C208, were comparable with those of the pivotal trials TMC114-C202 and TMC114-C213, with the exception of prior tipranavir/ aptivus (TPV) use; This baseline difference is related to the date of TPV approval in mid-2005, and the date of enrollment of Trial TMC114-C215/C208 . Thirty-one percent (31%) of subjects TMC114-C215/C208 had used TPV previously, compared to only 5% and 3.1% subjects respectively in the earlier enrolling TMC114-C202 or TMC114-C213 Trials.*

2. **Subject Disposition**

The rate of discontinuation for the DRV-treated subjects was lower in TMC114-C215/C208 (7.6%) than in either TMC114-C202 (27.3%) or TMC114-C213 (15.4%). This was true for discontinuations due to adverse event/HIV related events and discontinuations due to reaching virologic endpoints.

MO COMMENT: *The lower duration of exposure in trial TMC114-C215/C208 (see Table 65 below) is probably a factor contributing to the lower rate of discontinuation in this trial.*

TABLE SHOWING DISPOSITION OF *de novo* SUBJECTS IN TRIAL TMC114-C215/C208 AND COMPARED WITH CONTROL GROUP

PARAMETER	DRV/rtv	CONTROL TMC114-C202 and TMC114-C13
RANDOMIZED		144
TREATED	327	124
DISCONTINUED	25	98
▪ ***AE***	9 (2.8%)	6 (6.6%)
▪ ***Virologic failure***	7 (2.1)	81 (65.3%)
▪ ***Lost to follow up***	9	11

C. PHARMACOKINETIC ANALYSIS

There is no available PK data available for Trial TMC114-C208, and for subjects starting on TMC/RTV 400/100 mg bid in TMC-C215. In the de novo group, the mean AUC was 65791 ng.h/mL and mean C_{0h} was 3897 ng/mL. All subjects had plasma trough concentrations of TMC > 550ng/mL, which was consistent with the results obtained in TMC114-C202 and TMC114-C213.

Please refer to Dr Vikram Arya's review for further details.

D. ANALYSIS OF EFFICACY

The primary population for the analyses was the ITT population, (defined as all treated subjects with regardless of their compliance with the protocol).

i) Primary efficacy endpoint – Week 24 of treatment
- Sixty five percent (65%) of subjects exhibited a 1.0 log drop in the viral load at Week 24.

ii) **Secondary efficacy end points** – 24 weeks of treatment
- 40 % subjects exhibited a VL<50 copies/mL
- 57 % exhibited a VL < 400 copies/mL
- The mean decrease in VL below baseline was -1.67
- Mean change in baseline CD4 cell count 79.8 cells/mm^3

MO COMMENT: *The results of the primary efficacy responses were comparable to that noted in TMC114-C202 (64%). There were also comparable to the secondary efficacy responses (viral*

load < 50 copies/mL, < 400 copies/mL, and CD4+ count versus baseline noted above. A higher response rate was seen in trial TMC114-C213, and is likely to be related to the more favorable prognostic factors.

Overall, the TMC114-C215/C208 results confirm the viral load reductions and CD4+ increases observed in the controlled trials (TMC114-C202 and TMC114-C213) performed in a similar population of treatment-experienced subjects with advanced HIV-1 disease.

E. ANALYSIS OF SAFETY

The most frequent reported AE's in the DRV/rtv bid *de novo* subjects were:

1) Diarrhea (14%)
2) Nausea (10 %)
3) Nasopharyngitis (11%)
4) Seven subjects died from this group, of which 5 were from the TMC/RTV de novo group. (See detailed Analysis of Death in the Mortality Section)
5) Eight subjects (2%) of the *de novo* group discontinued the trial due to treatment emergent AE's. The AE's leading to discontinuation were; pancytopenia, vomiting, pyrexia, leishmaniasis, septic shock, ALT and AST increased, metabolic acidosis, lymphocytopenia, encephalitis, confusional state, renal insufficiency, acute respiratory failure and dermatitis medicamentosa.
6) Most graded laboratory abnormalities were grade 1 or 2 severity. The incidence of treatment-emergent grade 3 or 4 abnormalities were as follows:
    - WBC abnormalities (7%)
    - Pancreatic amylase (7%)
    - Triglycerides (6%)
    - Total cholesterol (4%)
    - Pancreatic lipase (3%)
    - AST elevation (2%)
    - ALT elevation (2%)
    - Hyperglycemia (1%)

MO COMMENT: Detailed analyses of the AE's leading to discontinuation, and grade 3 or 4 laboratory toxicities is discussed in detail in Safety section of the Clinical Review Template.

F. CONCLUSION

1) The efficacy results of the long-term parts of TMC114-C202 and TMC114-C213 demonstrated continuing and significant clinical benefit of the recommended dose of DRV/rtv (600/100 mg bid) in treatment-experienced HIV-1-infected subjects with no or limited treatment options of likely clinical benefit; the antiretroviral efficacy was superior when compared with the control group.

2) The results for the primary efficacy parameter (decrease in viral load versus baseline of ≥1.0 log10) were supported by those of the secondary parameters (other virologic responses and increases in CD4+ cell counts). The responses were greater in the DRV group compared to control at all time points;

MO COMMENT: The 24-week efficacy observed in the de novo subjects from TMC114-C215/C208 was similar to that seen in TMC114-C202 and TMC114-C213, thus supporting viral load reduction and CD4+ increase in the primary efficacy analysis of a larger sample size.

REPORT ON THE SINGLE AND MULTIPLE DOSE PK PHASE I STUDIES
by Anitra Denson MD

The applicant provided safety and pharmacokinetic data from 35 studies. Of these studies, 15 were single dose studies. The doses received in these studies ranged from 100 mg to 3200 mg of darunavir both with and without ritonavir. The remainder of the studies were multiple dose studies with doses ranging from 200 mg once daily to 1200 mg three times daily, most in the presence of ritonavir.

Single Dose Studies

A total of 284 healthy subjects were exposed to darunavir in single dose studies. Of these 184 (64.8%) reported at least one adverse event (AE). There were 38 reported Grade 3 or 4 AE in 31 subjects. There was one reported serious adverse event which was not related to the study drug. One subject had surgical removal of a lipoma during follow-up. Overall, the most commonly reported AEs were in the gastrointestinal system or nervous system. One hundred twenty subjects (42.3%) reported gastrointestinal AEs, of which diarrhea was the most common. Eighty-nine subjects (31.3%) reported AEs of the nervous system, of which the most common was headache.

Gastrointestinal Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	24 (8.4%)	7 (2.5%)	6 (2.1%)	0
Vomiting	12 (4.2%)	6 (2.1%)	2 (<1%)	0
Nausea	8 (2.8%)	17 (6%)	4 (1.4%)	0
Flatulence	7 (2.5%)	1 (<1%)	0	0
Abdominal pain	5 (1.8%)	2 (<1%)	1 (<1%)	0
Abdominal distention	3 (1%)	1 (<1%)	0	0

Nervous System Events

	Grade 1	Grade 2	Grade 3	Grade 4
Headache	31 (10.9%)	20 (7%)	9 (3.2%)	0
Paraesthesia	6 (2.1%)	3 (1%)	1 (<1%)	0
Dizziness	5 (1.8%)	3 (1%)	1 (<1%)	0
Somnolence	3 (1%)	3 (1%)	0	0

Rash/Allergic reaction
There were ten subjects that had reported an AE of either rash (2), erythema (1) or dermatitis (4). All these events were mild in severity. Two of the events appeared to be reaction to electrodes. There were also three subjects that reported pruritus. Again, all episodes were mild in severity. One subject with rash also had pruritus.

Clinical laboratory
There were no clinically significant changes over time in clinical laboratory values noticed in the single dose studies. Most of the laboratory abnormalities were Grade 1 or 2 in severity.

Laboratory Abnormalities ≥ Grade 2

	Grade 2	Grade 3	Grade 4
Hypercholestrolemia	22	2	0
Amylase	5	4	0
Lipase	4	4	0
Albumin (decr)	4	0	0
Hyperbilirubinemia	2	0	0
CPK	0	2	1

Urinalyses were performed during the course of the studies as well. There were no clinically significant changes noticed through any of the studies.

Vital Signs

There were no clinically significant changes in vital signs over time during the conduct of the single dose studies.

Cardiovascular

ECGs were performed during these Phase I studies. In all but four studies, post-baseline changes were seen. The most common change was an increase in the QTc interval of 30-60 ms. Most of the values remained within normal limits. Three subjects had increases >60 ms. There were also three subjects with prolonged QTc intervals. None of these changes were reported as adverse events. There does not appear to be any correlation with dose and change in QTc.

Multiple Dose Studies

A total of 444 healthy subjects were enrolled the multiple dose studies. Of theses, 363 (81.8%) reported at least one adverse event. 82 (18.5%) subjects were discontinued. There were 70 Grade 3/4 AEs reported by 48 subjects exposed to darunavir. Overall the most commonly reported AEs were in the gastrointestinal system and nervous system.

A total of 297 (66.9%) subjects reported at least one gastrointestinal adverse event with diarrhea being the most common. Most of these events were grade 1 or 2 in severity. A total of 210 (47.3%) subjects reported at least one nervous system event, with headache being the most common.

Gastrointestinal Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	56 (12.6%)	15 (3.4%)	3 (<1%)	0
Nausea	37 (8.3%)	15 (4.3%)	0	0
Loose stools	32 (7.2%)	0	0	0
Flatulence	32 (7.2%)	3 (<1%)	0	0
Abdominal pain	26 (5.9%)	9 (2%)	1 (<1%)	0
Vomiting	17 (3.8%)	10 (2.3%)	0	0
Dry mouth	10 (2.3%)	0	0	0
Stomach upset	9 (2%)	0	0	0
Abnormal bowel sounds	7 (1.6%)	2 (<1%)	0	0

Nervous System Events

	Grade 1	Grade 2	Grade 3	Grade 4
Headache	81 (18.2%)	18 (4%)	2 (<1%)	0
Dizziness	28 (6.3%)	3 (<1%)	2 (<1%)	0
Dyseusia	22 (5%)	0	0	0
Somnolence	18 (4%)	3 (<1%)	0	0
Paraesthesia	16 (3.6%)	0	0	0
Disturbance in attention	6 (1.4%)	0	0	0
Syncope	3 (<1%)	0	0	0

Allergic reaction/Rash

During the course of these studies, 42 (8.3%) subjects developed rash. The median time to onset of the rash was 8 days. The majority of the rash events were grade 1 or 2 in severity. The rash was generally described as a maculo-papular rash. One subject was graded as Grade 4 because of oral mucosal involvement. This subject also had fever and mild elevation of liver enzymes. There was one other subject that had fever occur with the rash. Many of the subjects that developed rash had pruritus as well. Except for the one subject mentioned above there were no laboratory abnormalities associated with the occurrence of rash. In addition to those subjects that developed rash, two subjects developed urticaria.

Skin Events

	Grade 1	Grade 2	Grade 3	Grade 4
Rash	12	23	1	1
Pruritus	24	5	1	0
Erythema	5	1	0	0
Urticaria	0	2	0	0
Contact dermatitis	1	0	0	0

Clinical Laboratory

Safety laboratory studies were carried out during these trials. The most common treatment emergent laboratory abnormalities were in lipid metabolism. In the individual studies, there were no obvious trends in laboratory abnormalities.

Laboratory Abnormalities ≥ Grade 2

	Grade 2	Grade 3	Grade 4
Hypercholesterolemia	51 (11.5%)	16 (3.6%)	0
Hypertriglyceridemia	21 (4.7%)	5 (1.1%)	0
Hyperbilirubinemia	17 (3.8%)	13 (2.9%)	3 (<1%)
Lipase	4 (<1%)	9 (2%)	0
Amylase	5 (1.1%)	2 (<1%)	0
CPK	2 (<1%)	0	3 (<1%)

Of note, increased bilirubin was not often seen in treatment arms of darunavir alone or in darunavir with low dose ritonavir. Fourteen of the cases of grade 2 hyperbilirubinemia occurred when darunavir was being co-administered with indinavir (7), atazanavir (4), or saquinavir (3). Twelve of the grade 3 cases occurred when darunavir was co-administered with atazanavir (10), indinavir (1), and saquinavir (1). For all of the grade 4 cases darunavir was co-administered with atazanavir.

Urinalyses were performed during the course of the studies as well. There were no clinically significant changes noticed through any of the studies.

Vital signs
There were no clinically significant changes in vital signs over time during the conduct of the single dose studies.

Cardiovascular
All subjects had ECGs performed during the course of these studies. In all but one study, changes were seen in QTc interval. Most of these changes were an increase of QTcB or QTcF by 30-60 ms. There were 3 subjects that had > 60 ms increase. There nine instances of prolonged QTc, and one instance of pathologically prolonged QTc. None of these changes were reported as AEs. There does not appear to be a correlation with dose and change in QTc. Overall, the ECG changes do not appear to be clinically significant.

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