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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-814

Medical Review(s)

TEAM LEADER MEMORANDUM

DATE:	June 22, 2005
TO:	Division File for NDA 21-814
FROM:	Rosemary Johann-Liang, M.D. Medical Officer Team Leader. Division of Antiviral Drug Products HFD-530
DRUG:	APTIVUS (tipranavir), 250 mg capsules,
PROPOSED INDICATION:	[ ]
GRANTED INDICATION:	APTIVUS, co-administered with [ ] ritonavir, 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.
APPLICANT:	Boehringer Ingelheim Pharmaceuticals, Inc

The New Drug Application (NDA) 21-814 for APTIVUS (tipranavir, a non-peptidic protease inhibitor) 250 mg capsules, is being recommended for regulatory approval under accelerated approval regulations: 21 CFR 314.510 Subpart H. This decision is based upon the surrogate endpoint analyses of plasma HIV RNA levels in controlled studies up to 24 weeks duration. In the current NDA, the applicant has provided evidence of APTIVUS' initial antiviral effect when co-administered with [ ] ritonavir and used in combination with other antiretroviral drugs for the treatment of HIV-1 infected, three-antiretroviral class-experienced patients with ongoing measurable viremia and with limited therapeutic options. I concur with the clinical review prepared by Dr. Andrea James (primary medical reviewer) with assistance from Dr. Melisse Baylor (on Phase 1, pediatric and naïve studies) and from Dr. Neville Gibbs (on Phase 2 studies). As stated in Dr. James' review, the applicant has demonstrated that APTIVUS co-administered with [ ] ritonavir, at the proposed doses for marketing (500 mg APTIVUS/200 mg ritonavir), has a benefit (antiviral effect over multiple protease-inhibitor resistant virus) which at this time of accelerated approval outweighs the safety concerns (particularly hepatotoxicity, drug-drug interactions, lipid abnormalities, and rash) in the HIV-1 population studied in their Phase 3 randomized trials (1182.12 and 1182.48, i.e. heavily pretreated with limited therapeutic options). Thus, this drug is being approved under the Subpart H regulations with the indication being restricted to the clinically advanced, highly treatment experienced and multiple protease inhibitor resistant HIV-1 infected population with limited treatment options and ongoing measurable

viremia. This restricted indication was recommended by the FDA Antiviral Advisory Committee which convened on this drug product (May 19, 2005). In this desperate population, novel and effective antiretroviral drug therapies are especially needed to suppress HIV-1 replication and thus arrest progression of/to AIDS.

Background

The 24 week virologic data from the two pivotal on-going open-label controlled trials (1182.12 and 1182.48) forms the basis of this accelerated approval. This new molecular entity NDA for tipranavir was submitted originally in October of 2004. Due to a number of difficult issues with the reviewability of the Applicant's raw datasets by the FDA, the applicant chose to withdraw their New Drug Application (NDA) in December of 2004. The Applicant resubmitted this NDA on December 22, 2004 after resolving a number of the dataset issues. Data reviewed by the FDA from the December submission covered the tipranavir/ritonavir (TPV/r) development program up to June 11, 2004 (the data cutoff date for 24 week submission). This NDA was granted a priority (6 month) review period. A consultation to the FDA's Antiviral Advisory Committee also occurred during the 5th month of review.

In addition to the two Phase 3 trials, the NDA submission contained information from two roll-over (from Phase 3) open label safety studies (1182.17 and 1182.58), five Phase 2 trials (1182.2, 1182.4, 1182.6, 1182.51 and 1182.52), twenty-eight Phase 1 trials in HIV-negative healthy individuals, one limited pediatric safety and efficacy data (1182.14), and preliminary serious safety data on newly enrolling Phase 3 trial (1182.33) in antiretroviral treatment-naïve population. A safety update to the NDA was submitted by the Applicant on February 22, 2005. This additional submission provided safety data in the TPV/r development program through September 30, 2004.

Mechanism of action

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor (PI) that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

EFFICACY

Design and Baseline Characteristics

Of the 20 approved antiretroviral package inserts with CLINICAL STUDIES sections (last query to the Physician's Desk Reference: March 3005), 15 unique registrational trials from 13 drugs are described under subsections entitled, "treatment-experienced" population. The two TPV/r Phase 3 studies will be make 17 unique registrational trials from 14 drugs. The design and baseline characteristics of TPV/r's "treatment-experienced" studies are quite different from the other approved drugs due to the fact that this population was heavily pretreated with no treatment options while the other "treatment experienced" trials are either in populations with lesser amounts of antiretroviral pretreatment and/or with available treatment options. The design and population of TPV/r trials were in fact similar to the enfurvitide (ENF) registrational trials which were also conducted in the heavily pretreated subjects (See NDA 21-481 Team Leader Memorandum, October 2004, by this author).

Studies 1182.12 and 1182.48 are ongoing, randomized, controlled, open-label, multi-center studies in HIV-positive, triple antiretroviral class experienced subjects. All subjects were

required to have previously received at least two protease inhibitor (PI)-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry with baseline HIV RNA of at least 1000 copies/mL and any CD4 cell count. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90.

These studies evaluated treatment response at 24 weeks in a total of 1159 subjects receiving either TPV/r plus optimized background regimen (OBR) versus a control group receiving ritonavir-boosted PIs (lopinavir, amprenavir, saquinavir or indinavir) plus OBR . Prior to randomization, subjects were pre-assigned to either receive or not receive enfurvitide. After Week 8, subjects in the control group receiving ritonavir-boosted PIs (CPIs) who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to TPV/r in a separate roll-over study.

Demographics and baseline characteristics were balanced between the TPV arm and control arm. In both studies combined, the 1159 subjects had a median age of 43 years (range 17-80), were 88% male, 73% white, 14% black and 1% Asian. The median baseline plasma HIV RNA was 4.82 (range 2 to 6.8) $\log_{10}$ copies/mL and median baseline CD4 cell count was 155 (range 1 to 1893) cells/mm^3. Forty percent (40%) of subjects had a baseline HIV RNA of >= 100,000 copies/mL, 61% had a baseline CD4 cell count <200 cells/mm^3, and 57% had prior AIDS defining Class C event at baseline.

Subjects had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs with 12% of subjects having previously used enfurvitide. Overall at baseline, 97% of the isolates were resistant to at least one PI, 95% of the isolates were resistant to at least one NRTI, and >75% of the isolates were resistant to at least one NNRTI.

The individually pre-selected protease inhibitor based on genotypic testing and the subject's medical history was lopinavir in 50%, amprenavir in 26%, saquinavir in 20% and indinavir in 4% of subjects in both studies combined. Eighty-six (86%) percent of control subjects in both studies combined were possibly resistant or resistant to the pre-selected comparator PIs.

A total of 25% of subjects in both studies used enfurvitide during study. There were differences between Studies 1182.12 and 1182.48 in investigative sites, the use of the protease inhibitors, and in the use of enfurvitide (please see Dr. Rafia Bhore's Statistical Review for complete descriptions and analyses).

Since the two pivotal clinical trials are similar in design and baseline characteristics and the resulting outcomes were also similar, the following summary outcome table is presented with pooled data. The principal analysis population was the modified intent-to-treat population (appropriate since these studies were designed as superiority trials) defined as all randomized patients (with the disease) who took at least one dose of the study and had at least one follow-up visit post baseline. The primary efficacy endpoint for week 24 was the proportion of subjects with a confirmed 1 log drop in HIV RNA without any prior evidence of treatment failure due to 1) death, 2) loss-to-follow up, 3) confirmed virologic failure, 4) permanent discontinuation of study drug, or 5) introduction of a new ARV drug for reasons other than toxicity to the background ARV. These proportions were calculated based on the FDA-defined Time to Loss of Virologic Response algorithm.

Disposition and Outcomes

TPV/r + OBR arm was superior in efficacy over the control arm of suboptimal CPI/r + OBR at 24 weeks (see Primary Outcomes Table below) with a treatment difference of 22% (95% CI, 17%, 27%). For two secondary virologic endpoints, the proportion of subjects in the TPV/r arm compared to the comparator PI/ritonavir arm with HIV RNA < 400 copies/mL was 34% and 16% respectively, and with HIV RNA < 50 copies/mL was 23% and 9% respectively.

Primary Outcomes at Week 24 (Pooled Data 1182.12 and 1182.48)

	TPV/r + OBR N (%)	CPI/r + OBR N (%)
Total treated	582 (100)	577 (100)
Treatment response at Week 24	**234 (40)**	**103 (18)**
No confirmed 1 log10 drop from baseline	**312 (54)**	**456 (79)**
Initial Lack of Virologic Response by Week 8	203 (35)	340 (59)
Rebound	68 (12)	67 (11)
Never suppressed	41 (7)	49 (8)
Added ARV drug	**22 (4)**	**9 (2)**

The following table compares the treatment differences between primary and secondary virologic endpoints across the two NDAs which examined antiretroviral efficacy in heavily pretreated subjects with limited treatment options at 24 weeks. Results are slightly better for enfurvitide but consistent overall. As discussed in my enfurvitide Team Leader Memorandum, these treatment margins may be useful for cross-study comparisons and/or setting the delta for non-inferiority margins.

Virologic Outcome Treatment Differences between test drug and control arms at 24 weeks

Virologic endpoint results at 24weeks	ENF Phase 3 trials combined	TPV/r Phase 3 trials combined
Primary: 1 log↓ in viral load	26% (95% CI: 20%, 32%)	22% (95% CI: 17%, 27%)
Secondary: <400 copies/mL	21% (95% CI: 16%, 32%)	18% (95% CI: 13%, 23%)
Secondary: <50 copies/mL	14% (95% CI: 9%, 18%)	14% (95% CI: 10%, 18%)

The examination of outcome by the use of enfurvitide (representative of another virologically active compound) in the TPV/r trials was an important analysis. The justification of this subgroup analysis is that these trials demonstrated superiority in their primary outcome analysis and that enfurvitide use was a pre-specified stratification prior to randomization. Patients in the TPV/r arm achieved a significantly better virologic outcome than patients in the CPI/arm when TPV/r was combined with enfuvirtide.

Proportion of Treatment Responders Through Week 24 by ENF use (pooled results)

% subjects with ENF use during study	TPV/r + OBR (N=582)	CPI/r + OBR (N=577)	Treatment Difference with CI
Yes (25%)	48%	19%	29.4% (19%, 30%)
No (75%)	29%	13%	15.6% (10%, 21%)

Issue of Early Escape Clause: Due to the heavily pretreated subjects under study, an escape clause to protect the subjects in the control arm was necessary. However, this important aspect of the study design impacted the outcome assessments of the study. The following are two examples. 1) The primary efficacy endpoint was the proportion of subjects with confirmed 1 log RNA drop from baseline at week 24 without evidence of treatment failure. The study was designed with an escape clause to allow subjects in the comparator arm who had a lack of initial virologic response at week 8 to discontinue the RESIST trial and receive TPV in a rollover safety study; lack of initial virologic response was defined as decrease in viral load < 0.5 log10 and failure to achieve a viral load of <100,000 copies/mL during the first 8 weeks of treatment despite a 0.5 log10 drop after 8 weeks of treatment. These same discontinued subjects in the comparator arm were considered as treatment failures at week 24 primarily accounting for the treatment difference in the primary efficacy endpoint. The initial virologic treatment difference (24%) between the two arms shown at week 8 explains the virologic treatment difference (22%) between the two arms at week 24. 2) Because 59% of the control arm left the study through virologic criteria at 8 weeks, assessment of the important immunologic parameter (secondary outcome of median change in CD4+ cell count from baseline) was limited. Neither the use of as-treated (AsT) analysis nor the last observation carried forward (LOCF) analyses are optimal; but, both taken together present useful information to the health care provider. If AsT analysis is used, the median change in CD4+ cell count from baseline was +40 cells/mm3 in the TPV/r arm (N=436) and +32 cells/mm3 in the CPI/r arm (N=248) at week 24. If the LOCF is used, the median change from baseline in CD4+ cell count in patients receiving TPV/r (N=582) versus CPI/r (N=577) was +34 and +4 cells/mm3 at Week 24, respectively.

Issue of clinical endpoints in heavily pretreated subjects: The use of HIV-1 virologic suppression as the surrogate measurement of clinical outcome has been the mainstay of HIV drug trials during the last decade due to correlations between viral suppression and improved clinical outcome and since aggressive treatment of HIV has resulted in too few clinical events for adequate comparisons in short-term drug trials. The heavily pretreated population of enfurvitide drug trials and now the TPV/r drug trials are evolving populations in HIV drug trials, different from the HIV-1 clinical populations during the beginning of the epidemic. The subjects in TPV/r Phase 3 trials are clinically advanced with lower CD4 counts and high baseline viral loads with prolonged exposures to multiple drug therapeutics and subsequent multi-resistance to antiretrovirals and/or accumulation of drug toxicities. The natural history of this advanced and complicated population is unknown, but it is probable (and the accumulating data shows) that clinical events are occurring. Diligence is required to capture as much clinical information as possible in these trials so that we can better understand the relationship of clinical outcome to viral surrogates in this population. In this TPV/r Phase 3 studies, using all-cause mortality as a definitive clinical event (AIDS-defining events were captured in these trials as adverse events only and not separately captured or adjudicated and thus difficult to compare), it was noted that the number of on-treatment deaths (15 TPV/r versus 13 CPI/r) were similar between the two arms. The added virologic benefit (as measured by the surrogate of plasma HIV RNA) did not translate into any reduction in mortality at the 24 week time-point. These results may be explained by the fact that these studies were not powered for mortality and the 24 week time-point is too premature to see any clinical endpoint differences. In addition, due to the open-label

nature of these RESIST trials with all the inherent bias as well as the built in escape clause for the comparator arm at 8 weeks after lack of initial virologic response, it is difficult to discern meaningful comparative clinical efficacy data beyond 8 weeks of treatment.

Issue of Bias Due to Open-Label Study Design with an Early Escape Clause: The interpretations of the data from the two Phase 3 TPV/r trials are confounded by this issue. The inevitable introduction of bias to trials where both the subjects and the investigator have knowledge of the treatment arm is particularly enhanced in a desperate population needing novel therapeutics. Subjects in the CPI/r arm know that their (HIV) virus is resistant to the control drugs and that they have TPV/r as a new treatment option if they fail early on the CPI/r drug. In contrast, subjects in the TPV/r arm do not have alternatives if they fail. This may result in different levels of compliance in the two treatment groups. There were several potential sources of open-label bias identified by the FDA review team including 1) Post-randomization changes in the Optimized Background Regimen 2) Post-randomization changes in the Randomization Strata 3) Early discontinuation of treatment arm due to initial lack of virologic response at Week 8 4) Protocol Violations 5) Potential lack of treatment compliance identified by low blood concentrations of drug level. An example to illustrate this issue is the concomitant use of enfurvitide (ENF).

Post-randomization Changes in Randomization Strata of ENF

Pre-selected ENF (No) but Actual ENF (Yes)			Pre-selected ENF (Yes) but Actual ENF (No)		
TPV/r N=427	CPI/r N=430	Total N=857	TPV/r N=155	CPI/r N=147	Total N=302
11 (3%)	4 (1%)	15 (2%)	8 (5%)	23 (16%)	31 (10%)

As shown in the table above, there were 857 subjects who were pre-assigned to not take enfurvitide. Among the subjects who were not assigned to take enfurvitide, 3% of the subjects in TPV group actually took enfurvitide and 1% in the control group took enfurvitide. In the second type of mismatch, there were 302 subjects who were pre-assigned to use enfurvitide. Among these patients, 5% of the TPV subjects chose not to use enfurvitide, while in the comparator group 16% of the subjects did not use enfurvitide. When we compared the behavior of subjects in the comparator PI group in the first type of mismatch versus second, there is a significant difference (based on McNemar's test for mismatches; see Statistical Review). Upon our discussion with the applicant, we found that subjects who were in the comparator PI group did not take enfurvitide even when they were assigned because they wanted to take 2 new drugs after Week 8 through the escape clause if their viral load did not drop.

Issue of baseline viral resistance impacting outcome: It is important to note that in both 1182.12 and 1182.48 trials combined, 86% of the subjects were possibly/definitely resistant to the assigned comparator PIs. Thus, although these pivotal trials are being presented as TPV/r + Optimized background regimen (OBR) versus CPI/r + OBR, in actuality, the results should be interpreted more as TPV/r versus suboptimal control with both arms utilizing a large variety of OBR (n = 161 different drug combinations as per FDA statistical analysis). TPV/r showed significantly greater treatment effect than CPI/r when subjects were already resistant (possibly or definitely) to their treatment CPI. TPV/r did not appear to offer antiviral benefit over CPI/r for subjects in the comparator arm who were sensitive to their PIs.

Baseline HIV-1 resistance profile impacting outcome (pooled 1182.12 and 1182.48)

	TPV/r	CPI/r	
Not Resistant	23/76 (30%)	17/80 (21%)	9% (-4.6%, 22.7%)
Possibly Resistant	56/135 (41%)	23/112 (21%)	21% (9.8%, 32.1%)
Resistant	119/369 (32%)	43/385 (11%)	21.1% (15.4%, 26.8%)

Issue of baseline genotype/phenotype impact on outcome: Resistance characterization at baseline was analyzed by the FDA microbiologist (Please see Dr. Lisa Naeger's review) to explore the impact on 24 week outcome since genotypic and/or phenotypic analysis of baseline virus may aid in determining TPV susceptibility before initiation of TPV/r therapy, particularly in heavily-pretreated subjects. Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virologic outcome. Both the number and type of baseline PI mutations as well as concomitant ENF use affected TPV/r response rates in studies 1182.12 and 1182.48 through Week 24 of treatment. Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline substitution at position I13, V32, M36, I47, Q58, D60, I84 or substitutions V82L/I/S/F. The reduction in virologic responses for these baseline substitutions was most prominent when subjects did not receive ENF with TPV/r. In addition, subjects with substitutions at V82 including V82A or T and an I84V mutation in their HIV-1 had reduced response rates. Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. Response rates were reduced if five or more PI-associated mutations (at positions - D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 or L90) were present at baseline and subjects did not receive concomitant enfurvitide with TPV. TPV/r response rates were also assessed by baseline TPV phenotype. Analyses exploring relationships between baseline phenotypic susceptibility to TPV, the number of baseline protease mutations at amino acids 33, 82, 84 and 90, and response to TPV/r therapy at week 24 are summarized in the table below.

Response by Baseline TPV phenotype in the RESIST Trials

Baseline TPV Phenotype	Proportion of Responders[a] with No ENF Use	# of Baseline Mutations at 33, 82, 84, 90	TPV Susceptibility
0-3	45% (74/163)	0-2	Susceptible
>3-10	21% (10/47)	3	Decreased Susceptibility
>10	0% (0/8)	4	Resistant

[a]**confirmed 1 $\log_{10}$ decrease at Week 24**

These baseline phenotype groups do not represent definitive clinical susceptibility breakpoints for TPV/r because it is based on a selective patient population. This information represents the

analyses of data from studies 1182.12 and 1182.48 to show likelihood of virologic success based on pretreatment susceptibility to TPV/r in heavily pretreated PI-experienced patients.

SAFETY

The overall safety profile is based on 3195 subjects (June 2004 data cutoff) who received at least 1 dose of TPV during various clinical trials. This includes 2430 HIV positive and 765 HIV negative subjects. In the safety update submission (September 2004 data cutoff), an additional 793 HIV positive subjects had been added to the program, predominantly from the on-going 1182.33 trial in HIV-1 infected treatment naïve population and the emergency use/expanded access programs. Specific issues relating to safety results that arose from the review of this supplemental application are briefly highlighted below. Please see Dr. Andrea James' integrated safety review for the complete discussion.

Drug-drug interaction: The drug-drug interaction potential of 500 mg of TPV in combination with 200 mg of ritonavir is extensive. TPV/r can alter plasma exposure of other drugs and other drugs can alter plasma exposure of TPV/r. Please see Dr. Derek Zhang, clinical pharmacologist's review for the complete and very complicated discussion. The known and potential interactions between TPV/r and other HIV medications as well as TPV/r potential for interactions with other classes of drugs are presented in his tables. His conclusions include the following: 1) Administration of TPV/r can increase plasma concentrations of agents that are primarily metabolized by CYP3A, because TPV/r is a net inhibitor of CYP3A. 2) The applicant did not evaluate the effect of TPV/r on substrates for enzymes other than CYP3A. In vitro studies indicate TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Due to the known effect of RTV on CYP2D6, the potential net effect of TPV/r is CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. 3) In vivo data suggest that the net effect of TPV/r on P-glycoprotein is induction. Based on current data, it is difficult to predict the net effect of TPV/r on oral bioavailability and plasma exposure of drugs that are dual substrates of CYP3A and P-gp. 4) TPV is a CYP3A substrate as well as a P-gp substrate. Therefore, co-administration of TPV/r and drugs that induce CYP3A and/or P-gp may decrease TPV plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of TPV/r and drugs that inhibit P-gp may increase TPV plasma concentrations and increase or prolong its therapeutic and adverse effects. Co-administration of TPV/r and drugs that inhibit CYP3A may not further increase TPV plasma concentrations, based on the results of a submitted mass balance study.

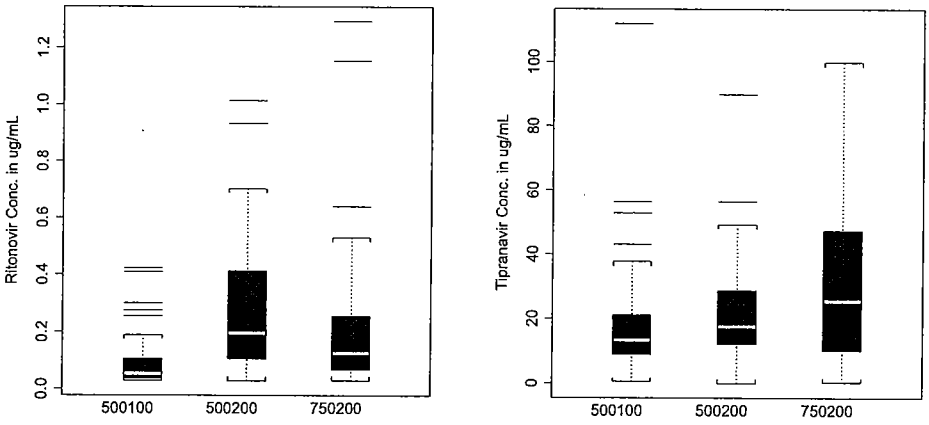
Dose-related exposure analysis between TPV and RTV: The following excerpts are taken from various reviewers to make the point that as TPV dose increases, TPV exposure increases but RTV exposure decreases. Thus, based upon the review of the submitted data, the dose-related safety events are attributable to TPV and not to the low-dose RTV boost.

Medical Officer Review by Dr. Melisse Baylor: Phase 1 Study P & U 015 of TPV in HIV-infected subjects. She writes in her conclusion of this study review that "*TPV exposure increased with RTV boosting and with increase of TPV dose, while RTV levels decreased with increasing TPV levels. This pharmacokinetic finding allowed determination of dose response for activity and for safety. Adverse events, particularly diarrhea and nausea were common. Less common AEs of significance were increased ALT values and increases in lipid values; the frequency of these AEs was exposure related.*"

Medical Officer Review by Dr. Neville Gibbs: Phase 2 study 1182.4 of TPV in HIV-infected subjects. He writes in his conclusion of this study review that *"Pharmacokinetic analyses in*

this study showed that RTV concentrations in the higher dose groups (TPV/r 1250/100mg) were substantially lower when compared to the TPV/r 500/100 mg group. This decrease may be attributed to CYP3A induction by the higher dose of TPV, which results in increased metabolism of RTV. The overall safety profile of TPV co-administered with RTV was similar to that observed in previous tipranavir trials in both HIV-1-negative healthy volunteers and HIV-1-positive adults. Low dose TPV/r was easier to tolerate than high dose due to the increased frequency of GI adverse events in the high dose TPV/r group. The tolerability and safety profile of TPV/r was similar to that of SQV/r, however, there was an increased frequency of GI adverse events, rash, and hepatotoxicity in subjects receiving TPV/r compared to those receiving SQV/r.

Pharmacometrics Review by Dr. Jenny Zheng: Phase 2 study 1182.52, the dose finding study in HIV-infected subjects. She writes regarding the dose-related transaminase rises *"in order to understand whether ALT elevation is related to TPV or ritonavir, the exposures of both TPV and RTV were compared across treatments. The median RTVr concentration is lower (0.281 μg/mL vs. 0.217 μg/mL) and TPV concentration is higher (21.26 μg/mL vs. 30.75 μg/mL) after the 750/200 mg dose compared to the 500/200 mg dose. In spite of this, the 750/200 mg dose group had a higher proportion of subjects with grade 3/4 ALT elevations."*



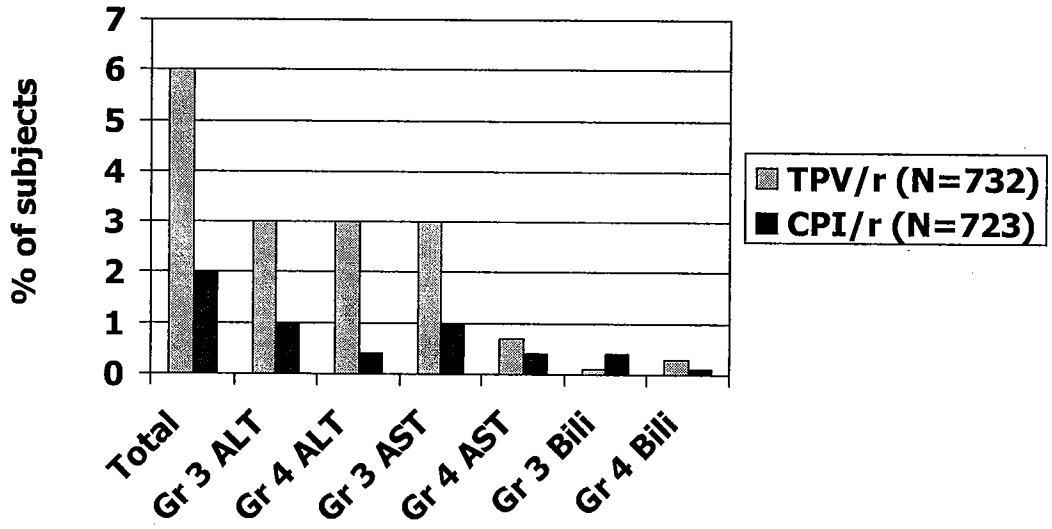
Range of trough (Cmin) RTV and TPV concentrations at the 3 dose levels. The median concentrations of TPV are 17.46 μg/mL (n=60), 21.26 μg/mL (n=63) and 30.75 μg/mL (n=56), respectively.

Hepatotoxicity: Initial hepatotoxicity signals were observed throughout the 18 Phase 1 studies in healthy volunteers. A total of 36 (5.5%) healthy HIV-negative subjects experienced treatment emergent grade 3 or 4 liver abnormalities (rise in ALT) in the Phase 1 studies. Comparison of the 500/200 mg and 750/200 mg dose groups in Study 1182.52, the dose finding Phase 2 study, provided further strong evidence that TPV independent of, but in the presence of, ritonavir causes grade 3/4 ALT elevations in a dose dependent manner.

Proportion of subjects with grade 3/4 ALT elevations for each dose group.

Dose Group	Proportion of Subjects with Grade 3/4 ALT elevations (number/total)
500/100 mg	4.3% (3/69)
500/200 mg	11.1% (8/72)
750/200 mg	23% (16/69)

In the RESIST trials, 10% of subjects on the TPV/r arm compared to 3% on the CPI/r arm developed treatment emergent grade 3 or 4 ALT or AST elevations.



For 1182.12, time to first DAIDS Grade 3 or 4 ALT elevation was significantly different between the two arms with subjects in the TPV/r arm more likely to develop Grade 3 or 4 elevations in ALT and at a significantly faster rate than those in the CPI/r arm. For 1182.48, time to first Grade 3 or 4 ALT elevation was significantly shorter for subjects in the TPV/r arm compared those for subjects in the CPI/r arm (Please see Dr. Susan Zhou's Statistical Review on Phase 2 laboratory parameters).

Very few subjects had documented concurrent symptoms and the following table depicts outcomes of the grade 3 and 4 ALT/AST elevations.

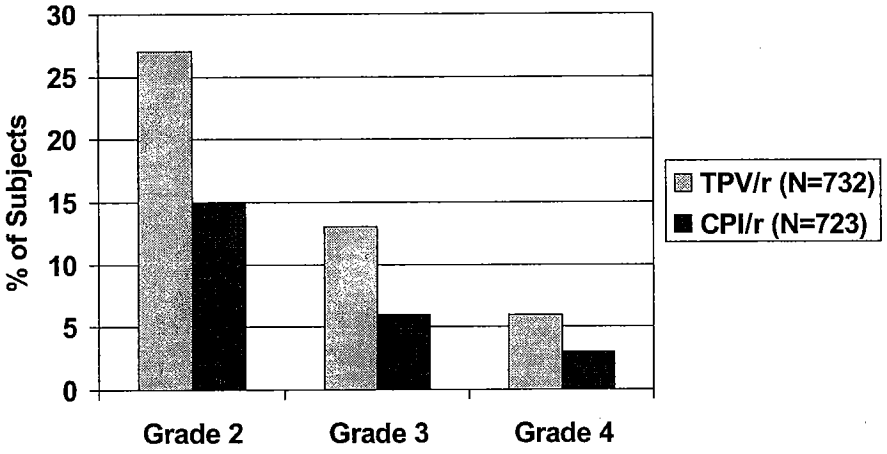
	TPV/r N = 732	CPI/r N = 723
Grade 3/4 ALT/AST Elevation	45 (6%)	18 (2%)
Discontinued	12 (27%)	0
Resolved On tx Off tx	29 (64%) 19 (42%) 10 (22%)	17 (94%) 17 (94%) 0
Unresolved On tx Off tx	16 (35%) 14 (31%) 2 (4%)	1 (6%) 1 (6%) 0

A possible risk factor may be baseline hepatitis. The % frequency of grade 3 and 4 ALT elevations among subjects with baseline hepatitis B or C was 9/76 (12%) in the combined TPV/r arm versus 6/113 (5%) in the CPI/r arm. Thus, the case is certainly made that LFT elevations are attributable to TPV. On the other hand, the data we have thus far does not show a clinical picture

of these laboratory abnormalities resulting in acute liver injury with fulminant liver failure. However, the contributory effect of drug-induced transaminitis on subacute liver injury impacting on the ultimate negative clinical sequelae is possible, especially in the context of multiple drug-drug interactions and the medically fragile population.

Furthermore, the Applicant has submitted 7 fatal cases in their Safety Update who had a hepatic component to the fatality. Causal determination of death events to TPV hepatotoxicity cannot be determined; but, contribution of the drug toxicity to the death events also cannot be ruled out. Specific warnings, precautions, and monitoring are indicated. Since the Phase 3 trials excluded subjects with evidence of active liver disease, it will be important to request Phase IV commitments from the Sponsor to study patients with underlying liver disease including hepatitis B or C HIV-1 co-infected patients to better characterize this safety concern.

Lipid Abnormalities: More subjects in the TPV/r arm developed Grade 3 or 4 laboratory lipid abnormalities than those in the CPI/r arm and at a significantly faster rate. For combined Phase 3 datasets, 21% of subjects developed treatment emergent grade 3 or 4 triglycerides compared to 11% of subjects on the CPI/r arm. The following figure depicts the % of subjects with treatment emergent rise in triglycerides.



Analyses of 1182.12 laboratory data showed that the time to first Grade 3 or 4 in total cholesterol or triglycerides were significantly different between the two arms. Analyses of 1182.48 laboratory data showed that the time to first Grade 3 or 4 elevation in total cholesterol or triglycerides were shorter for subjects in the TPV/r arm. The significant differences in the frequency of Grade 3 or 4 lipid or transaminase elevations between the TPV/r and CPI/r arms may be due to differences in follow-up between the two arms. The escape clause in these studies resulted in a differential duration of randomized treatment exposure and laboratory monitoring between the two arms. On the other hand, it is important to keep in mind many subjects randomized to the CPI/r arms (13%) already had a long duration of exposure to the CPI drug because they entered the study and continued on their current PI.

Cutaneous reaction (adverse event of "rash"): was another safety event of special interest in this review due to a substantial Phase 1 signal from an oral contraceptive study in healthy HIV negative women (Study 1182.22). Seventeen subjects (33%) developed a rash while receiving TPV. This high and unexplained incidence of rash in healthy, female volunteers raised the

possibility that gender and immune status may have an impact on the frequency and types of adverse events (AEs) observed with TPV/r use. Other phase 1 trials in healthy HIV-negative volunteers showed that rash was seen in 14/390 (3.6%) males as compared to 34/265 (13%) females. In Phase 2 trials of HIV infected subjects, one large study (1182.51) showed a rash rate of 10.2% (32/315). Rash was only reported in males but the study population was 93% male. In another large phase 2 study (1182.52), 8.6% (18/216) of subjects in the study developed treatment-emergent rash. Dose relation was suggested because there were 10 subjects who developed rash in TPV/r 750/200 mg group, including one discontinuation, whereas there were 5 subjects in the TPV/r 500/200 mg group and 3 subjects in the TPV/r 500/100 mg group. Relationship of the development of rash to an intact immune system (as indicated by preserved CD4 cell counts) could not be examined in these two large Phase 2 studies because these subjects were heavily pretreated and advanced in HIV disease with median CD4 cell count of 133 (1182.51) and 178 (1182.52). Phase 2 trials enrolled predominantly males: however of the limited data available, females on the TPV/r in phase 2 trials had higher incidence of rash (15/114 or 13.2%) as compared to males (59/745 or 7.9%).

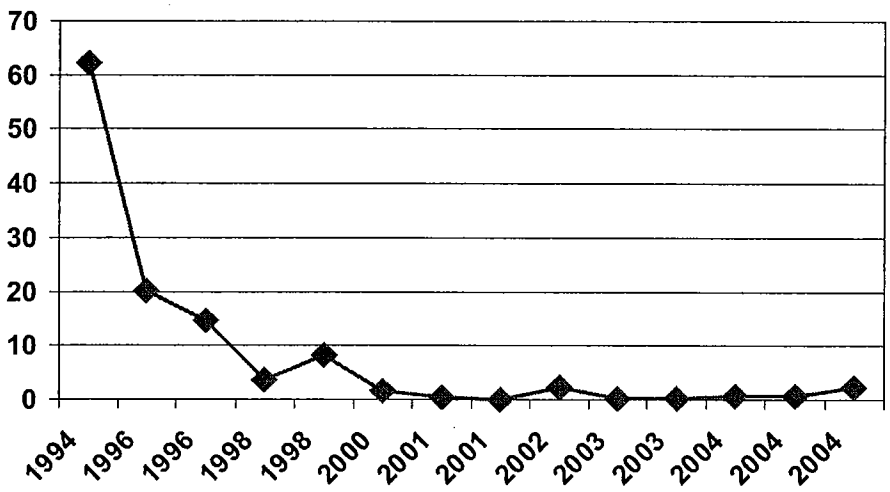
In the Phase 3 trials, the overall incidence of rash was similar in both arms (11% TPV/r versus 10% CPI/r). The severity and need for treatment were also similar between the two arms. Since the Phase 3 trial population was immunologically depleted, adequate exploration of the impact of immune competence on the frequency of rash was limited. An exploratory analysis of females in the Phase 3 trials (n=118 TPV/r; n=90 CPI/r) showed that the females on the TPV/r arm had a higher incidence of rash (14%) as compared to the females on the CPI/r arm (9%). However, the small number of women in these trials made it impossible to draw any definitive conclusions. Although BI is currently conducting a study in antiretroviral naïve subjects, the study is already fully enrolled with only about 20% of female subjects (similar to the 1182.12 and 1182.48 trials) and based on baseline CD4+ count, viral load and AIDS defining illnesses, these naïve subjects have advanced HIV disease. Therefore, it appears unlikely that the current naïve trial will provide definitive answers to whether or not TPV/r affects women and/or immunocompetent subjects differently than the remainder of the HIV+ population. A Phase IV commitment will be requested to further explore and study this safety concern.

Mortality: One hundred and two subjects died during the entire TPV clinical development program up through the database lock on June 11, 2004. In total, 12 subjects died during the pretreatment phase and 90 subjects died after being exposed to at least one dose of drug (post-drug exposure). For most deaths, subjects had advanced HIV disease and multiple concomitant medications. Three of the 90 post-drug exposure subject deaths were considered to be possibly TPV/r treatment related by the Applicant. However, FDA could not rule out relatedness or a possible contribution of the effects of TPV in most death cases. This unclear ascertainment of study drug's relationship to mortality (and to morbidity) is due to the nature of the population under study, and in many cases, was due to the lack of available information surrounding the death cases.

Overall, there were more deaths in 1182.12 than in 1182.48 (22 versus 11), and there were more deaths on the TPV/r arms compared to the CPI/r arms (19 versus 14). The *on-treatment* deaths (15 TPV/r versus 13 CPI/r) in Phase 3 trials were similar between the two arms. AIDS defining or AIDS progression events were captured in Phase 3 trials as adverse events only and not specifically abstracted or adjudicated. The added virologic benefit of TPV/r over CPI/r (as measured by the surrogate of plasma HIV RNA) did not translate into any reduction in mortality at the 24 week time-point. However, these Phase 3 trials were not designed to assess clinical endpoints. The escape clause at 8 weeks precluded optimal evaluation of longer term clinical efficacy and safety.

Analyses of mortality rates in the NDA database of all "treatment-experienced" trials which led to approval of an antiretroviral from the archives of DAVDP were conducted to place TPV/r Phase 3 trials' mortality rates into perspective. Fourteen unique studies from 13 registrational drug programs were found to meet our search. Mortality rate per study in 100 subject-years by year of DAVDP approval are shown in the figure below.

Mortaltiy Rates (100 subject-years) per NDA study in "treatment-experienced" population shown by year of approval by DAVDP



Examination of subject baseline characteristics showed that the population enrolled in enfurvitide phase 3 studies which most closely approximated the TPV phase 3 studies was the enfurvitide trials population (http://www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm). All on-treatment TPV deaths were reviewed and only those deaths which occurred within the window of 24 weeks treatment + 28 days follow-up were counted as raw numbers. This was how enfurvitide deaths were counted in enfurvitide's accelerated approval NDA review at 24 weeks. Both mortality rates (#death/100 subject-years) using data through 24 weeks were calculated for both NDAs. As shown below, raw numbers of deaths or mortality rates between the test and control arms were similar for both the TPV and enfurvitide (ENF) NDAs at 24 weeks.

FDA Analysis of the Comparison of deaths at 24 weeks (Phase 3 data)

TPV numbers at 24 weeks		ENF numbers at 24 weeks	
TPV/r + OBR	CPI/r + OBR	ENF+ OBR	Placebo + OBR
12/582 (2.0%)	7/577 (1.2%)	10/663 (1.5%)	5/334 (1.5%)
Mortality rate = 4.5	Mortality rate = 2.6	Mortality rate = 3.3	Mortality rate = 3.3

These comparative mortality rates between the TPV/r and CPI/r arms, as well as between two different drug programs (ENF and TPV/r), reassured us at this point in the review (24 week

analyses) that the death rates observed in the TPV drug program were within similar range to the already reviewed ENF trials' death rates.

Special Populations: Pediatrics – Based upon the preliminary results of study 1182.14, Dr.Melisse Baylor's conclusions are as follows: *"The applicant has proposed* [redacted] *At this time, there is insufficient efficacy data* [redacted] *Furthermore, very few data points were collected to support* [redacted] *Therefore, in this reviewer's opinion, there are not sufficient data* [redacted] *at this time."* Further work on appropriate formulations, safety and dosing information are needed to treat this population.

Gender Difference: Females – It has been discussed above and throughout multiple reviews that females may have a higher risk of rash when taking TPV/r. It is interesting to note that PK and efficacy analysis by gender also show gender differences. Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice daily for 2 to 4 weeks and without meal restriction produced the following PK parameters.

Pharmacokinetic parameters[a] of TPV/r 500/200 mg for HIV+ patients by gender

	Females (n = 14)	Males (n = 106)
Cp_{trough} (μM)	41.6 ± 24.3	35.6 ± 16.7
Cmax (μM)	94.8 ± 22.8	77.6 ± 16.6
Tmax (h)	2.9	3.0
$AUC_{0\text{-}12h}$ (μM•h)	851 ± 309	710 ± 207
CL (L/h)	1.15	1.27
V (L)	7.7	10.2
$t_{1/2}$ (h)	5.5	6.0

[a]Population pharmacokinetic parameters reported as mean ± standard deviation

In Dr. Bhore's statistical analysis, she reported the following results which show that for both Phase 3 studies, response rates were higher for females.

Subgroup Analysis by Gender on Treatment Response through 24 weeks (confirmed 1 log_{10} drop in viral load)

Gender	TPV/r + OBR	CPI/r + OBR	Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval)[†]	Test for treatment by subgroup interaction p-value[‡]
1182.12				
Male (91%)	112/278 (40%)	62/287 (22%)	19% (11%, 26%)	0.378
Female (9%)	14/33 (42%)	3/22 (14%)	29% (7%, 51%)	
1182. 48				
Male (84%)	79/225 (35%)	31/229 (13%)	22% (14%, 29%)	0.151
Female (16%)	29/46 (63%)	7/39 (18%)	45% (27%, 64%)	