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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

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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 5<sup>th</sup> 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<sub>10</sub> copies/mL and median baseline CD4 cell count was 155 (range 1 to 1893) cells/mm<sup>3</sup>. Forty percent (40%) of subjects had a baseline HIV RNA of  $\geq$  100,000 copies/mL, 61% had a baseline CD4 cell count  $<$ 200 cells/mm<sup>3</sup>, 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)
<b>Treatment response at Week 24</b>	<b>234 (40)</b>	<b>103 (18)</b>
<b>No confirmed 1 log<sub>10</sub> drop from baseline</b>	<b>312 (54)</b>	<b>456 (79)</b>
Initial Lack of Virologic Response by Week 8	203 (35)	340 (59)
Rebound	68 (12)	67 (11)
Never suppressed	41 (7)	49 (8)
<b>Added ARV drug</b>	<b>22 (4)</b>	<b>9 (2)</b>

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 <sub>10</sub> ↓ 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 enfurvitide.

**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  $< 0.5 \log_{10}$  and failure to achieve a viral load of  $< 100,000$  copies/mL during the first 8 weeks of treatment despite a  $0.5 \log_{10}$  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/mm<sup>3</sup> in the TPV/r arm (N=436) and +32 cells/mm<sup>3</sup> 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/mm<sup>3</sup> 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 <sup>a</sup> 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

<sup>a</sup>confirmed 1 log<sub>10</sub> 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.

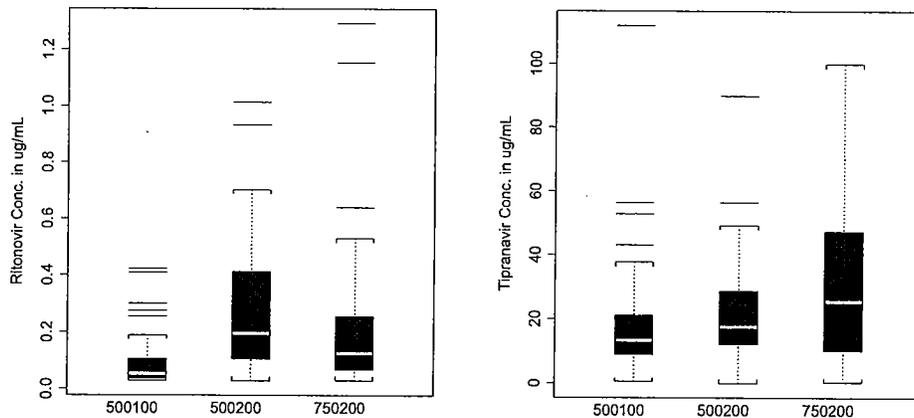
**Dose-related exposure analysis between TPV and RTV:** The following excerpts are taken from various reviewers to make the point that as TPV dose increases, TPV exposure increases but RTV exposure decreases. Thus, based upon the review of the submitted data, the dose-related safety events are attributable 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.”



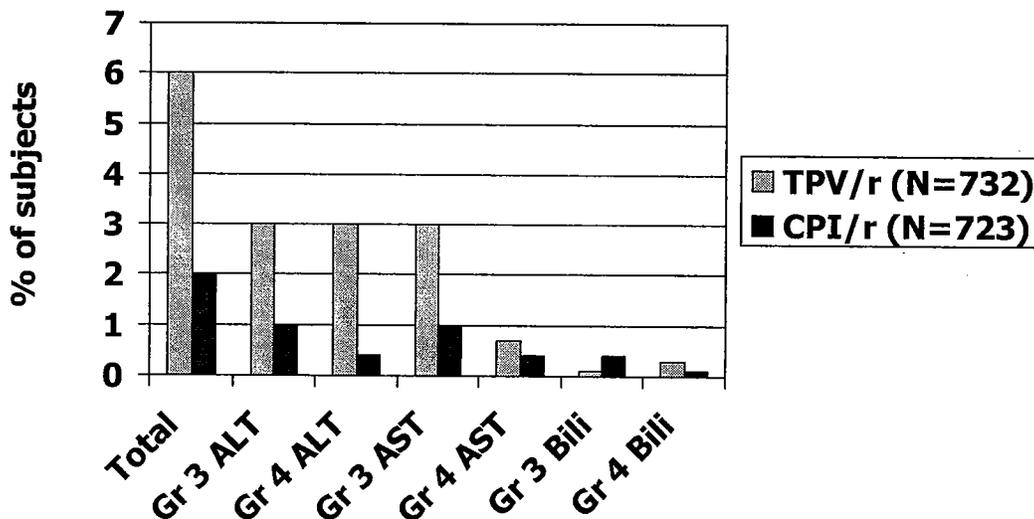
Range of trough (C<sub>min</sub>) RTV and TPV concentrations at the 3 dose levels. The median concentrations of TPV are 17.46 µg/mL (n=60), 21.26 µg/mL (n=63) and 30.75 µg/mL (n=56), respectively.

**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.

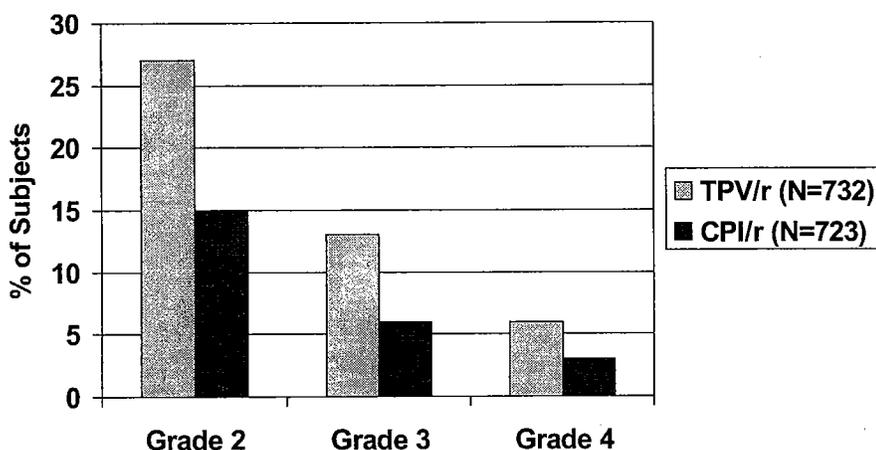
	TPV/r N = 732	CPI/r N = 723
Grade 3/4 ALT/AST Elevation	45 (6%)	18 (2%)
Discontinued	12 (27%)	0
Resolved	29 (64%)	17 (94%)
On tx	19 (42%)	17 (94%)
Off tx	10 (22%)	0
Unresolved	16 (35%)	1 (6%)
On tx	14 (31%)	1 (6%)
Off tx	2 (4%)	0

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%).

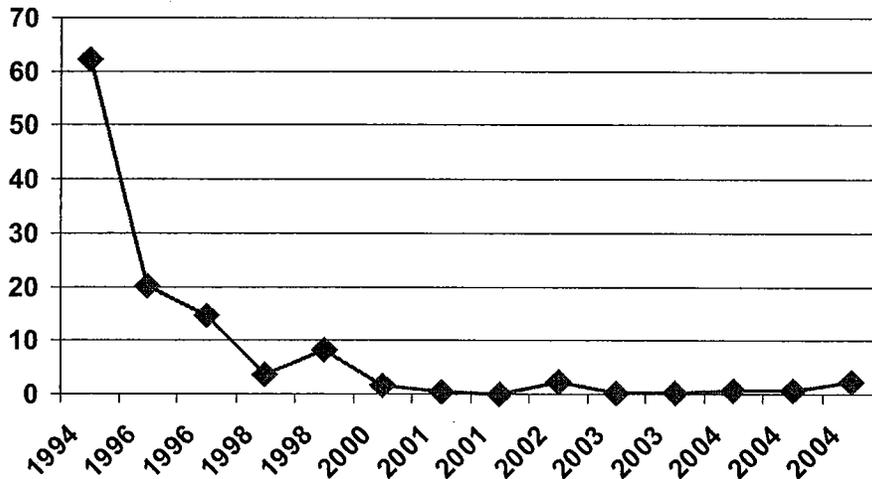
In the Phase 3 trials, the overall incidence of rash was similar in both arms (11% TPV/r versus 10% CPI/r). The severity and need for treatment were also similar between the two arms. Since the Phase 3 trial population was immunologically depleted, adequate exploration of the impact of immune competence 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.

**Mortality 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](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:

insufficient efficacy data  
 very few data points were collected to support  
 there are not sufficient data  
 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<sup>a</sup> of TPV/r 500/200 mg for HIV+ patients by gender**

	Females (n = 14)	Males (n = 106)
C <sub>p</sub> trough (µM)	41.6 ± 24.3	35.6 ± 16.7
C <sub>max</sub> (µM)	94.8 ± 22.8	77.6 ± 16.6
T <sub>max</sub> (h)	2.9	3.0
AUC <sub>0-12h</sub> (µM•h)	851 ± 309	710 ± 207
CL (L/h)	1.15	1.27
V (L)	7.7	10.2
t <sub>1/2</sub> (h)	5.5	6.0

<sup>a</sup>Population pharmacokinetic parameters reported as mean ± standard deviation

In Dr. Bhole'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<sub>10</sub> drop in viral load)**

Gender	1182.12		Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval) <sup>†</sup>	Test for treatment by subgroup interaction p-value <sup>‡</sup>
	TPV/r + OBR	CPI/r + OBR		
Male (91%)	112/278 (40%)	62/287 (22%)	19% (11%, 26%)	0.378
Female (9%)	14/33 (42%)	3/22 (14%)	29% (7%, 51%)	
<b>1182.48</b>				
Male (84%)	79/225 (35%)	31/229 (13%)	22% (14%, 29%)	0.151
Female (16%)	29/46 (63%)	7/39 (18%)	45% (27%, 64%)	

## RECOMMENDATION

This new molecular entity NDA for APTIVUS (tipranavir, TPV), co-administered with **Ⓛ** **Ⓝ** ritonavir is being recommended for accelerated regulatory approval under subpart H regulations. In the current NDA, the applicant has provided evidence of APTIVUS' antiviral effect (assessed at 24 weeks duration) when used in combination with other antiretroviral drugs for the treatment of HIV-1 infected, heavily antiretroviral treatment-experienced subjects. The two pivotal trials both demonstrated superior efficacy of APTIVUS + low dose ritonavir when compared to partially active control PI + optimized background regimen in subjects with multiple PI resistant virus and with limited therapeutic options. Experience gained from the review of this NDA should assist in better design and implementation of pivotal clinical trials in the heavily antiretroviral treatment experienced patients. Hepatotoxicity, hyperlipidemia, and cutaneous reactions, as well as extensive drug-drug interactions are the major safety concerns with this drug product. I concur with the clinical reviews prepared by Dr. Andrea James, Dr. Neville Gibbs, and Dr. Melissa Baylor (and advice from the FDA Anti-advisory Committee) that this drug should be approved awaiting 48 week confirmatory data. Further, as advised, the indications and usage should reflect the limitations of the current knowledge and communicate what is known about the risk/benefit balance at this time. A box warning regarding hepatotoxicity has been recommended by the Advisory Committee. The following is the recommended wording for the Box Warning and the Indications and Usage sections for the proposed package insert. Also in the proposed label, specific drug-drug interaction tables as well as detailed resistance information are recommended to guide the prescribing physician. As the drug is released to the market and the Applicant pursues further efficacy and safety studies, pharmacovigilance programs as well as post-marketing risk management strategies should be initiated in concert with the Applicant and the Agency's Office of Drug Safety.

### Box Warning

<p>APTIVUS CO-ADMINISTERED WITH <b>Ⓛ</b> <b>Ⓝ</b> RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. SEE WARNINGS.</p>
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### Indications

APTIVUS (tipranavir), 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. This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of tipranavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class

antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

### Usage

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response (see CLINICAL PHARMACOLOGY: Microbiology, DESCRIPTION OF CLINICAL STUDIES.)
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir. The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir (see CLINICAL PHARMACOLOGY: Microbiology).
- Liver function testing should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment (see WARNINGS).
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, Hepatitis B or C co-infection or other underlying hepatic impairment (see WARNINGS).
- The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS)
- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

### PHASE IV 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. This commitment is listed below.

1. By September 30, 2006, please submit study reports for the 48 week data of the two ongoing Phase 3 studies, RESIST-1 (1182.12) and RESIST-2 (1182.48).

In addition, the Applicant has committed to the following postmarketing studies.

#### Drug-Drug Interaction Trials

2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and atazanavir.

Protocol Submission: Study completed

Final Report Submission: Submitted by December 31, 2005

3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and buprenorphine/naloxone.

Protocol Submission: July 15, 2005.

Final Report Submission: Submitted by June 30, 2006

4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and carbamazepine.

Protocol Submission: July 15, 2005

Final Report Submission: Submitted by September 30, 2006

5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and tadalafil.

Protocol Submission: August 31, 2005

Final Report Submission: Submitted by December 31, 2006

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and ribavirin/pegylated IFN alpha 2a.

Protocol Submission: August 31, 2005.

Final Report Submission: Submitted by June 30, 2007

7. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and methadone.

Protocol Submission: Study completed.

Final Report Submission: Submitted by September 30, 2005

#### **Pharmacology/Toxicology**

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

Protocol Submission: Completed

Final Report Submission: December 31, 2006

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

Protocol Submission: Completed

Final Report submission: December 31, 2005

#### **Special Populations**

10. Assess the long term (48 week) antiviral efficacy and safety of tipranavir/ritonavir in ARV treatment naive patients through the conduct of study 1182.33.

Protocol Submission: Completed

Final Report Submission: September 30, 2006

Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33), please submit data in resistance template.

Protocol Submission: Completed  
Final Report Submission: September 30, 2006

Assess metabolic changes being studied in sub-study of 1182.33.

Protocol Submission: Completed  
Final Report Submission: September 30, 2006

11. Conduct a 48-week prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count.

Protocol Submission: March 30, 2006  
Final Report Submission: September 1, 2008

12. Conduct a 48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

Protocol Submission: March 30, 2006  
Final Report Submission: July 1, 2008

13. Assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.

Protocol Submission: December 31, 2006  
Final Report Submission: December 31, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring the submission of the Applicant's pediatric studies for ages 2 weeks to 2 years until January 31, 2009. Also, we are deferring the submission of the Applicant's pediatric studies for ages 2 years to 18 years until June 30, 2006. These submissions are also postmarketing study commitments (pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments) and they are listed below.

14. Assess two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety, in ARV naive and experienced children and adolescents between 2 and 18 years of age.

Protocol Submission: Completed  
Final Report Submission: June 30, 2006

15. Evaluate dose requirements and safety in pediatric patients age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA).

Protocol Submission: September 30, 2006

Final Report Submission: January 31, 2009

**Pharmacokinetics**

16. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

Protocol Submission: September 30, 2005  
Final Report Submission: December 31, 2006

**Clinical**

17. Conduct a formal QT prolongation study.

Protocol Submission: Special Protocol Assessment Complete  
Final report Submission: June 30, 2006

In addition to the post-marketing commitments, the Applicant has agreed to the following studies.

**Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and bupropion.
2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]

**Pharmacokinetics**

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with tipranavir/ritonavir twice daily.

**Clinical**

8. Conduct a long-term cardiovascular safety evaluation of Protease Inhibitor/ritonavir (including tipranavir) from epidemiologic databases.

**Microbiology**

9. Evaluate cleavage site mutations in rebound samples on tipranavir.

**Therapeutic Drug Monitoring**

10. The Applicant will meet with the Division of Antiviral Drug Products (DAVDP) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIVinfected patients receiving tipranavir/ritonavir. The study will be conducted and the results will be used to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for patients taking APTIVUS/ritonavir.

Concurrence

ODE IV/DepOffDir/ECox

HFD-530/DivDirector/DBirnkrant

HFD-530/DepDivDir/JMurray

Cc: NDA 21-814 and NDA 21-822

ODE IV/OfficeDirector/MGoldberger

HFD-530/MO/AJames

HFD-530/MO/MBaylor

HFD-530/MO/NGibbs

HFD-530/PM/TSinha

Stats/RBhore/SZhou

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this page is the manifestation of the electronic signature.**  
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/s/

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Rosemary Johann-Liang  
6/22/05 02:04:54 PM  
MEDICAL OFFICER

this is the Capsule TLmemo

Debra Birnkrant  
6/22/05 02:19:47 PM  
MEDICAL OFFICER

Edward Cox  
6/22/05 04:27:29 PM  
MEDICAL OFFICER

+

## CLINICAL REVIEW

Application Type 21-814  
Submission Number 000  
Submission Code N

Letter Date December 22, 2004  
Stamp Date December 22, 2004  
PDUFA Goal Date June 22, 2005

Reviewer Name Andrea N. James, MD  
Review Completion Date June 22, 2005

Established Name Tipranavir  
(Proposed) Trade Name Aptivus  
Therapeutic Class Antiretrovirals  
Applicant Boehringer Ingelheim

Priority Designation P

Formulation 1. Tablet

Dosing Regimen 1. 500mg orally twice daily

Indication Treatment of HIV-1 infection  
Intended Population HIV-1 infected

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

This reviewer recommends the accelerated approval (21 CFR 314 subpart H) of tipranavir (TPV) 500mg boosted by 200 mg of ritonavir (r) 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 TPV/r to construct a viable antiretroviral regimen. This recommendation is based on review of the efficacy and safety data submitted by Boehringer Ingelheim Pharmaceutical, Inc (BIPI or the applicant) for this New Drug Application (NDA). Additionally, this reviewer heavily weighed in the overall recommendation of the Antiviral Drug Advisory Committee (ADAC), whose expert panel voted 11 to 3, to approve TPV/r for the population described above. The ADAC believes, as does the FDA, that this patient population is in desperate need of treatment alternatives and that that need outweighs the currently identified risk associated with TPV/r's use.

This reviewer's recommendation is made with reservation because the hepatotoxicity known to be associated with TPV/r use is not well characterized and the best monitoring and management strategy is unknown. Based on the data provided with this NDA submission there were over 50% of patients in the pivotal Phase 3 trials who violated the protocol entry or study criteria thereby gaining access to the RESIST studies and potentially gaining access to TPV/r. This type of disregard for study conduct denotes a potentially desperate patient and healthcare provider population. This reviewer has real concern that this drug may be used inappropriately (either in the wrong patient population or without adequate monitoring) and this may increase the safety risk of using the drug so that it outweighs the efficacy benefit. Overall, however, this reviewer believes that this drug warrants approval as it will fill a need for a population with a life-threatening disease where other treatment options are limited.

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

Tipranavir was studied in two adequate and controlled Phase 3 clinical trials 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).

The FDA review confirmed that TPV/r was superior to a suboptimal, partially-active control arm (consisting of four ritonavir boosted comparator protease inhibitors (CPI/r) to which the vast majority of patients were resistant at baseline) in achieving the primary composite endpoint of the proportion of patients with a confirmed HIV-1 RNA viral load measurement  $\geq 1 \log_{10}$  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. This treatment effect was consistent across gender, age, geographic region and important HIV baseline disease characteristics. This treatment effect was not consistent across race and requires further evaluation. Tipranavir/r also had a statistically significant increase in CD4+ cell count (a secondary endpoint) from baseline compared to the CPI/r arm.

The FDA review of the TPV/r safety data found TPV/r safe for its intended use in a very restricted patient population as stated in the labeling. In general TPV/r had more adverse events and more adverse events leading to discontinuation as compared to the CPI/r. Additionally, a major safety concern identified prior to and confirmed during the safety review is TPV/r associated hepatotoxicity (namely grade 3 and 4 ALT and AST elevations). Tipranavir/r hepatotoxicity was observed in all phases of drug development. Tipranavir/r associated hepatotoxicity is exposure and dose related, and generally presents asymptotically, occurring throughout the dosing period of the drug. In rare cases hepatotoxicity that developed while using TPV/r lead to hepatic decompensation and death in HIV+ infected patients; drug relatedness to these events cannot be ruled out. Other safety concerns identified include rash in women and hyperlipidemia.

Tipranavir/r has an extensive drug interaction profile and complete knowledge of how or if to dose TPV/r with certain drugs is lacking. The potential for interactions to occur when TPV/r is co-administered with other drugs is high and must be considered prior to and during TPV/r use.

The overall relative short term (24-week) virologic and immunologic benefits of TPV potentially outweigh the risk of TPV in this restricted patient population especially when TPV is combined with another active ARV (for example, T20) and patients are monitored closely for toxicities and other untoward side effects of the drug.

## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

Although BIPI did not submit a formal risk management plan there are many risk management activities planned for TPV/r post accelerated approval.

- As a requirement of accelerated approval under 21 CFR 312 subpart H the applicant must submit the 48 Week data for their two pivotal Phase 3 trials, which will provide more safety data for analysis of known and unknown TPV/r related toxicities.
- Also as a requirement of accelerated approval under 21 CFR 312 subpart H the applicant must submit periodic safety reports for review.
- The labeled indication for TPV/r is very restricted in an effort to minimize the risk/benefit ratio associated with the use of this product.

- The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.
- The product has been contraindicated in patients with moderate to severe (Child-Pugh B and C) liver disease in light of the known hepatotoxicity associated with TPV/r and a lack of data in this patient population.

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

As a condition of TPV/r's accelerated approval, BIPI agrees to submit 48 Week safety and efficacy data on 1182.12 and 1182.48 by September 30, 2006 to support the traditional approval of TPV/r. Additionally, BIPI 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:

#### **Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and atazanavir.

Protocol Submission: Study completed

Final report Submission: Submitted by December 31, 2005

2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and buprenorphine/naloxone.

Protocol Submission: July 15, 2005.

Final report Submission: Submitted by June 30, 2006

3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and carbamazepine.

Protocol Submission: July 15, 2005

Final report Submission: Submitted by September 30, 2006

4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and tadalafil.

Protocol Submission: August 31, 2005

Final report Submission: Submitted by December 31, 2006

5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and ribavirin/pegylated IFN alpha 2a.

Protocol Submission: August 31, 2005.

Final report Submission: Submitted by June 30, 2007

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and methadone.

Protocol Submission: Study completed.

Final report Submission: Submitted by September 30, 2005

Pharmacology/Toxicology

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

Protocol Submission: Completed

Final report Submission: December 31, 2006

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

Protocol Submission: Completed

Final Report submission: December 31, 2005

### **Special Populations**

9. Assess the long term (48 week) antiviral efficacy and safety of tipranavir/ritonavir in ARV treatment naive patients through the conduct of study 1182.33.

Protocol Submission: Completed

Final report Submission: September 30, 2006

- Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33), please submit data in resistance template.

Protocol Submission: Completed

Final report Submission: September 30, 2006

- Assess metabolic changes being studied in sub-study of 1182.33.

Protocol Submission: Completed

Final report Submission: September 30, 2006

10. Conduct a 48-week prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count.

Protocol Submission: March 30, 2006

Final report Submission: September 1, 2008

11. Conduct a 48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

Protocol Submission: March 30, 2006

Final report Submission: July 1, 2008

12. Assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.

Protocol Submission: December 31, 2006

Final report Submission: December 31, 2007

BIPI understands that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. In the original NDA submission, BI requested deferral of submission of their pediatric studies for ages 2 weeks to 2 years until January 31, 2009. BI also requested deferral of submission of their pediatric studies for ages 2 to 18 years until June 30, 2006.

BIPI understands that the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments as per the Written Request for pediatric exclusivity and any proposed changes in the Written Request for pediatric studies. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

13. Assess two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety in ARV naive and experienced children and adolescents between 2 and 18 years of age.

Protocol submission: Completed

Final report submission: June 30, 2006

14. Evaluate dose requirements and safety in pediatric patients age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA).

Protocol submission: September 30, 2006

Final report submission: January 31, 2009

BI commits to submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) will be clearly designated "Required Pediatric Study Commitments".

#### **Pharmacokinetics**

15. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

Protocol Submission: September 30, 2005

Final report Submission: December 31, 2006

#### **Clinical**

16. Conduct a formal QT prolongation study.

Protocol Submission: Special Protocol Assessment Complete

Final report Submission: June 30, 2006

#### **1.2.3 Other Phase 4 Requests**

The following are not postmarketing study commitments, but in a letter dated June 7, 2005, BIPI agreed to conduct the studies listed below:

### **Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and bupropion.
2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]

### **Pharmacokinetics**

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with tipranavir/ritonavir twice daily.

### **Clinical**

8. Conduct a long-term cardiovascular safety evaluation of Protease Inhibitor/ritonavir (including tipranavir) from epidemiologic databases.

### **Microbiology**

9. Evaluate cleavage site mutations in rebound samples on tipranavir.

### **Therapeutic Drug Monitoring**

10. BI will meet with the Division of Antiviral Drug Products (DAVDP) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIV-infected patients receiving tipranavir/ritonavir. The study will be conducted and the results will be used to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for patients taking APTIVUS/ritonavir.

## **1.3 Summary of Clinical Findings**

### **1.3.1 Brief Overview of Clinical Program**

Tipranavir (TPV, APTIVUS™) is a new molecular entity (NME), a new of non-peptidic protease inhibitor (PI). Tipranavir 500 mg, co-administered with 200 mg of ritonavir (r) 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 24 Week data from two, Phase 3 studies (1182.12 or RESIST 1 and 1182.48 or RESIST 2) multinational, randomized, controlled trials in which 3309 patients were enrolled; 1159 were randomized and 1483 received at least one dose of study drug. Both pivotal trials were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The studies were designed to continue through 96 weeks. At Week 8 patients in the CPI/r group, who had a lack of initial virologic response (defined as a  $< 0.5 \log_{10}$  decrease or  $\geq 0.5 \log_{10}$  decrease, but viral load not less than 100,000 copies/mL) were allowed to enroll in the roll-over trial, 1182.17, where all patients received TPV/r 500mg/200mg. The studies were initially designed to show non-inferiority of TPV/r compared to the CPI/r. However, Amendment 2 changed the protocol so that patients, who were pan-resistant, as per their genotype, to all available PIs could be enrolled into RESIST 1 and 2, which changed the statistical analysis plan from a non-inferiority analysis to a superiority analysis.

In addition to the two pivotal efficacy and safety trials, the applicant submitted 37 clinical trials that provided supportive safety data.

At the time of the original NDA database closure, June 11, 2004, the TPV/r safety database (all 39 clinical trials) included a total of 3195 patients or subjects (2430 HIV-positive patients and 765 HIVnegative subjects) who were exposed to at least 1 dose of TPV. In total, 1397 HIV-positive patients have received TPV/r at the intended market dose of 500 mg/200 mg for a total of 685.1 exposure years; 761 of these patients have been exposed to TPV/r for 24 weeks. In the pivotal RESIST trials at the time of database cut-off 746 patients had received at least one dose of TPV/r. In the pivotal RESIST trials approximately 82% of the patients on the TPV/r arm versus 53% of patients on the CPI/r arm completed 24 weeks of study. This safety database is consistent with that requested in Agency Guidance Documents and is similar in size to previously approved drugs at the time of accelerated approval.

### 1.3.2 Efficacy

The primary endpoint for the integrated interim analyses of the RESIST trials was treatment response at Week 24. Treatment response is a composite endpoint of the proportion of patients with confirmed virologic response (defined as two consecutive VL measurements  $\geq 1 \log_{10}$  below baseline) without prior:

- Evidence of confirmed virological failure (defined as two consecutive VL measurements of  $<1 \log_{10}$  below baseline, or one VL measurement of  $<1 \log_{10}$  followed by permanent discontinuation or loss to follow-up), or
- Introduction of a new ARV to the regimen for reasons other than toxicity or intolerance clearly attributable to a background drug, but not the study drug or its control, or
- Permanent study drug discontinuation, or
- Death, or
- Loss to follow-up.

The FDA statistical analysis confirmed the applicant's analysis of the primary efficacy endpoint at Week 24, namely that in both studies combined, the TPV/r arms had a statistically significantly higher proportion of patients who achieved a treatment response (40%) versus the CPI/r arm (18%).

Over half the patients (51%) in the RESIST trials had what was deemed to be a relevant protocol violation; however sensitivity analyses showed that despite these violations TPV/r maintained its superior treatment effect over the CPI/r arm.

Key secondary analyses of the primary endpoint by age, race, and gender revealed that TPV/r performed differently in non-whites (specifically blacks since the other race groups were too small to analyze) in RESIST 1, namely there was no treatment difference between blacks on TPV/r and blacks on the partially active CPI/r arm. Subgroup analyses by race in RESIST 2 revealed no differences in treatment response; however in RESIST 2 only 5% of the study population was black and 26% of race information was missing or unavailable due to laws governing the collection of this data in foreign countries.

The microbiology evaluation for emergence of resistance found that the most common protease mutations that developed in  $>20\%$  of isolates from treatment-experienced patients who failed on TPV/r treatment were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V. Both the number and type of baseline PI mutations affected response rates to TPV/r in RESIST 1 and 2. Virologic response rates in TPV/RTV-treated patients were reduced when isolates with substitutions at positions I13, V32, M36, I47, Q58, D60 or I84 and substitutions V82S/F/I/L were present at baseline. Virologic responses to TPV/r at week 24 decreased when the number of baseline PI mutation was 5 or more. Patients taking enfuvirtide with TPV/r were able to achieve  $>1.5 \log_{10}$  reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations. Virologic responses to TPV/r decreased in RESIST 1 and 2 when the baseline phenotype for TPV was  $>3$ . The resistance profile in treatment-naive patients has not yet been characterized.

### 1.3.3 Safety

FDA reviewers evaluating the safety data concluded that TPV/r was safe for the intended restricted patient population. In the RESIST trials overall patients on TPV/r reported slightly more adverse events (AEs) (82.4% versus 77.2%), AEs leading to discontinuation (8.0% versus 4.9%) and SAEs (13% versus 12%) than patients on the CPI/r arm. The pattern of AEs, however, was very similar between the two treatment groups. Gastrointestinal AEs (predominantly diarrhea, nausea, and vomiting) and Infectious AEs comprised the majority of AEs observed. There was some variability in the type and frequency of AEs observed in evaluation of AEs by age, gender, race and geographic location. However, clinically the only unusual or concerning pattern was that black patients receiving TPV/r (58.5%) had a considerably higher percentage of AEs in the MedDRA system organ class (MSOC) infections and infestations compared with white patients (40.6%) taking TPV/r. The reason for this difference is not known, and may simply reflect a much smaller sample size of black patient compared to white patients, but need further investigation.

Three drug related safety issues are highlighted in this review: hepatotoxicity, rash, and hyperlipidemia.

Hepatotoxicity: Initial signals were observed throughout the 18 Phase 1 studies in healthy volunteers. A total of 19% of healthy HIV-negative subjects experienced ALT elevations above the upper limit of normal, and 6% of subjects experienced a treatment emergent grade 3 or 4 increase in ALT in the Phase 1 studies. The Phase 2 dose-finding study 1182.52 showed that ALT increases were TPV dose dependent. The proportions of patients who had grade 3/4 ALT increases in three treatment arms, TPV/r 500/100 mg, TPV/r 500/200mg, and TPV/r 750/200mg, were 4%, 11%, and 23%, respectively. TPV and RTV exposure data analysis suggests that these ALT increases are associated with increased TPV exposures and not RTV exposures.

In the RESIST trials, 6.1% of patients on the TPV/r arm compared to 2.4% on the CPI/r arm developed treatment emergent grade 3 or 4 ALT or AST elevations. For RESIST 1, time to first DAIDS Grade 3 or 4 ALT elevation ( $p=0.0028$ ) was significantly different between the two arms with patients 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 RESIST 2, time to first Grade 3 or 4 ALT elevation ( $p=0.0255$ ) was significantly shorter for patients in the TPV/r arm compared to that for patients in the CPI/r arm. In general, patients were asymptomatic with their ALT/AST elevations, and these elevations emerged throughout the entire study period. Most patients were able to resolve their ALT/AST elevations while continuing on study; however, 27% of TPV/r patients with ALT/AST elevations (12 of 45) discontinued study drug as a result of the ALT/AST elevations. In rare cases hepatotoxicity that developed while using TPV/r lead to hepatic decompensation and death in HIV+ infected patients; drug relatedness to these fatal events cannot be ruled out.

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.

In Phase 2 trials of HIV infected patients, 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 patients in the study developed treatment-emergent rash. 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 patients were heavily pretreated and advanced in HIV disease with median CD4 cell count of 133 (1182.51) and 178 (1182.52).

Females had a higher rate of rash as compared to males throughout the entire TPV development program. Females in the Phase 1 (N=265) and 2 (N=114) trials developed rash at a rate of 13% while in comparison 3.6% of males in the Phase 1 trials and 7.9% of males in the Phase 2 trials developed rash.

In the dose finding study, 1182.52, 8.6% (18/216) of patients in the study developed treatment-emergent rash. A dose relationship for the frequency of rash was suggested because there were 10 patients who developed rash in TPV/r 750/200 mg group, including one discontinuation, whereas there were 5 patients in the TPV/r 500/200 mg group and 3 patients in the TPV/r 500/100 mg group.

In the Phase 3 RESIST 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 RESIST trial population was immunologically depleted, adequate exploration of the frequency of rash based on baseline CD4 counts was limited. An exploratory analysis of females in the RESIST 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%). Although the small number of women (19.1%) in the TPV development program, make it impossible to draw any definitive conclusions about the true risk of rash in this population, the consistent rate of rash in women at 13-14% throughout the phases of development is a good indication that the increased frequency of rash in females is a real phenomenon.

Hyperlipidemia: Overall 46% of TPV/r patients in the RESIST trials had Grade 2-4 treatment emergent hypertriglyceridemia versus 24% of CPI/r patients, and 15% of TPV/r patients had Grade 2-4 treatment emergent hypercholesterolemia versus 5% of CPI/r patients. Grade 2 cholesterol and triglycerides were included in this analysis because clinically this is the point at which clinicians would likely intervene with cholesterol or triglyceride lowering agents.

Deaths: One hundred-and-two patients died in the entire TPV clinical development program up through the database locking of pivotal studies 1182.12 and 1182.48 on June 11, 2004. Ninety of these deaths were in patients who had received at least one dose of study drug and 12 were in patients who were in the screening period of the study. Three

deaths in the entire development program were considered TPV/r treatment related by the investigators.

In the RESIST trials there were 15 on-treatment (study day 1 through 30 days off study drug) and 4 post-treatment (> 30 days off study drug) deaths on the TPV/r arm and 13 on-treatment and 1 post-treatment deaths on the CPI/r arm. None of these deaths were considered treatment related by the investigators. The characteristics of the patients who died reflect those of an advanced HIV-1 infected population with the majority of patients having very low CD4+ counts as the time of study entry and death. Although in many cases there was not enough information to determine the cause of death when the cause of death could be determined it was often due to an AIDS related event such as an opportunistic infection or AIDS related malignancy. In terms of mortality TPV/r has no apparent clinical benefit over the CPI/r arm; however, the RESIST trials were not designed to detect a clinical benefit. In a Safety Update containing data through September 30, 2004, an additional 29 deaths were reported: 21 on-treatment and 8 post-treatment deaths on the TPV/r arm; there were no additional deaths on the CPI/r arm.

#### 1.3.4 Dosing Regimen and Administration

Review of the data provided in the NDA supports the approval of TPV at a dose of 500mg boosted by 200mg of RTV.

The exposure response analysis of phase 2 and phase 3 studies demonstrated that the probability of a patient's response to TPV/r treatment is related to inhibitory quotient ( $IQ = C_{min}/\text{corrected } IC_{50}$ ). However, due to the variability in pharmacokinetics of the drug and the variable degree of resistant virus, the range of resulting inhibitory quotients with the fixed doses are wide, which results in unpredictable virological response for individual patients. To maximize the likelihood of a patient's response, individualized dose by monitoring IQ is an alternative to the fixed dose regimen, but it requires further prospective investigation.

#### 1.3.5 Drug-Drug Interactions

Tipranavir/r has an extensive drug interaction profile and complete knowledge of how, or if, to dose TPV/r with certain drugs is lacking. The potential for interactions to occur when TPV/r is co-administered with other drugs is high and must be considered prior to and during TPV/r use.

Tipranavir is a cytochrome P450 (CYP) 3A substrate as well as a P-glycoprotein (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.

In addition TPV/r is a net inhibitor of CYP 3A and can significantly increase exposures of drug metabolized by this pathway potentially resulting in increased adverse events or the need for dose adjustments. TPV/r is also an inducer of P-gp and could lower plasma concentrations of drugs depending on P-gp.

### 1.3.6 Special Populations

#### Pediatrics:

data provided with the NDA is insufficient to support this study, at this time. No new safety signals were identified in

Naïve patients: Study 1182.33 is an ongoing study comparing TPV/r at 500mg/100mg or 500mg/200mg with lopinavir / ritonavir 400mg/100mg BID in approximately 540 treatment naïve adult patients. Patients in all three arms are also receiving tenofovir 300mg and lamivudine 300mg once a day. Although the study population is naïve, baseline characteristics of the patients match those of a clinically advanced HIV+ population. The data submitted with this NDA is very preliminary and no safety conclusions in this population can be made.

Hepatically Impaired Population: In a study, 1182.32, comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose plasma concentrations of TPV and RTV were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of TPV administered with ritonavir has not been adequately evaluated or evaluated at all, respectively. TPV/r is contraindicated in this patients with moderate or severe (Child-Pugh B or C) hepatic disease.

Renally Impaired Population: TPV/r pharmacokinetics has not been studied in patients with renal dysfunction. However, since the renal clearance of TPV is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Established name:	Tipranavir (TPV)
Trade Name:	APTIVUS™
Chemical:	C <sub>31</sub> H <sub>33</sub> F <sub>3</sub> N <sub>2</sub> O <sub>5</sub> S
Class:	Protease inhibitor
Proposed indication:	Treatment of HIV-1 infection
Dose and regimen:	adults: tipranavir 500mg boosted by 200mg ritonavir (TPV/RTV) orally twice daily
Dosage form:	250 mg tablet

Tipranavir (TPV) is a new molecular entity (NME), a non-peptidic protease inhibitor (PI), that is a sulfonamide and belongs to the class of 4-hydroxy-5,6-dihydro-2-pyrones. TPV is a potent inhibitor of both HIV-1 and HIV-2 proteases. TPV was originally discovered and developed by Pharmacia & Upjohn. Now TPV is under clinical development by Boehringer Ingelheim Pharmaceutical, Inc (BIPI) for the treatment of HIV-1 disease. The target population for this application is one that is heavily protease inhibitor experienced, and in this population successful treatment with TPV depends upon the number and type of baseline mutations as determined by genotype or phenotype.

Early in development BIPI decided that TPV would be used in conjunction with low dose ritonavir (RTV) as a booster. The addition of low dose RTV allowed for increased TPV exposure at a lower pill burden.

BIPI has evaluated and submitted data on TPV's efficacy and safety in heavily protease inhibitor (PI) experienced adults, and therefore is proposing an indication for the treatment of HIV-1 infection in PI experienced adult patients. Currently BIPI has naïve and pediatric studies ongoing.

### 2.2 Currently Available Treatment for Indications

There are now 21 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 2.2:1).

TABLE 2.2:1 Currently Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddl)	Videx®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavridine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz	Sustiva®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	saquinavir, hard gel	Invirase®
	saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir	Reyataz®
	lopinavir/ritonavir fixed dose combination	Kaletra®
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. TPV’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**

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

BIPI developed TPV to be used in conjunction with low dose 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 100-200mg 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 P-glycoprotein 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**

TPV and RTV are both PIs and as such are associated with acute and chronic side effects observed throughout the PI class, namely, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, hemolytic anemia, and increased bleeding in hemophiliacs. TPV use appears to be associated with much more hypertriglyceridemia and hypercholesterolemia than the other RTV boosted-PIs (Please see section 7.1.3.3. for a detailed review of TPV associated adverse events).

### **2.5 Presubmission Regulatory Activity**

IND 51,979 for TPV was initially submitted to the FDA in November 1996. TPV was discovered and originally developed by Pharmacia and Upjohn (P&U). The initial formulation of TPV had low bioavailability and was poorly tolerated. The majority of the Phase 1 studies conducted by P&U evaluated different formulations of TPV in an attempt to find a formulation with better bioavailability and tolerability. The development of the SEDDS (self-emulsifying drug delivery system) formulation improved the bioavailability, and co-administration of TPV with low-dose ritonavir (r or RTV) improved exposure, tolerability and allowed for twice-daily dosing.

The applicant, Boehringer Ingelheim Pharmaceuticals Incorporated (BIPI), acquired TPV in early 2000. At a Type C meeting in October 2001, the FDA and BIPI agreed on the design of the definitive dose finding study, 1182.52, the general design of the Phase 3 trial program and the drug interaction studies that needed to be performed prior to initiation of the Phase 3 program. Multiple dose finding studies were conducted by P&U and BIPI. The to-be-marketed dose, TPV/r 500/200 mg, was selected based on the results of study 1182.52. The applicant and the FDA agreed upon the dose of TPV/r 500/200mg to take into the Phase 3 studies and the overall design of the phase 3 studies at the December 17, 2002 End of Phase 2 meeting. In August 2003, the applicant submitted a special protocol assessment to study the safety, efficacy and pharmacokinetics of both the liquid formulation and SEDDS formulation of TPV/r in HIV infected children and

adolescents ages 2 – 18 years. The FDA advised the applicant that as per the Pediatric Research Equity Act (PREA) studies are required in children down to 2 weeks of age. The applicant submitted a request with this NDA submission to defer completion of pediatrics studies (please see Section 1.2.2 Required Phase 4 commitments for details).

## **2.6 Other Relevant Background Information**

TPV was recently granted accelerated approval in Switzerland. The Swissmedic, Swiss Agency for Therapeutic Products, approval letter to BIPI can be found in it's entirety in Appendix A. Swissmedic gave TPV a limited indication based on the design and results of the pivotal Phase 3 trials:

[

]

*MO comment: This reviewer agrees with Swissmedic's decision to give TPV a limited indication at the time of accelerated approval based on the relatively limited efficacy data (24 weeks) in a restricted patient population (multiply drug resistant) and based on the known and unknown drug-drug interactions and safety concerns.*

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

Please refer to Dr. Ko-Yu Lo's CMC review for a detailed analysis of TPV's chemistry, manufacturing and controls. The following issues are pertinent to the clinical review:

1. TPV contains a functional excipient, polyoxyl 35 castor oil, [ ]

The 500 mg BID dose of TPV capsules in combination with ritonavir (200 mg BID) gives a total daily exposure of polyoxyl 35 castor oil between — g/day. These exposures are the highest among all approved NDAs, but are supported by a 6-month dog study that demonstrated a 10-fold safety factor relative to the clinical exposure.

*MO comment: The level of polyoxyl 35 castor oil was a concern for mainly two reasons:*

1. *Systemic levels of this excipient have been associated with an anaphylatoid- like reaction. In the 6-month dog study there was no evidence of systemic levels of polyoxyl 35 castor oil at a dose comparable to the human administered dose.*
2. *Polyoxyl 35 castor oil could cause GI side effects; however, the analysis of the clinical safety data does not provide any evidence that GI side effects are significantly worse with TPV/r use as compared to the control group (see Section 7.1.5.4 for details of Common Adverse Events)*

2. Due to the questionable stability of the excipient [ ] at temperatures above — the NDA was amended to change the recommended storage condition from room temperature to refrigeration.

*MO comment: This recommendation for refrigeration applies only while the drug is in the pharmacy; once in patients' hands it can be stored at room temperature.*

3. TPV will be approved to have a 36-month expiration dating period based on [ ] long-term stability data at 4°C.

### 3.2 Animal Pharmacology/Toxicology

Please refer to Dr. Anita Bigger's Animal Pharmacology/Toxicology Review for a detailed analysis of the TPV pharmacology and toxicology data. The following is a summary of Dr. Bigger's findings.

#### Pharmacology

Safety pharmacology assays assessed TPV's effects on a number of organ systems including cardiovascular, central nervous, pulmonary, renal and gastrointestinal (GI) systems. Overall TPV was well tolerated with some effects in the renal and GI systems. In renal studies in rats, females exhibited increases in sodium excretion at all doses and decreases in potassium excretion at the high dose. Male rats exhibited decreases in potassium excretion at all doses. Although the changes in urinary electrolyte excretion were considered TPV-related, neither of these findings was correlated with any significant observation in a 4-week oral dose toxicity study of TPV in rats. In GI studies in rats, gastric emptying and GI propulsion were significantly decreased at all doses in males and at middle and high doses in females. Gastric fluid volume was increased at the

high dose in males and acid concentration of gastric fluid was decreased at the high dose in males and females. These GI changes were considered TPV-related. These study results suggest that TPV at therapeutic doses might elicit some effects on renal and/or GI function.

*MO comment: Regarding the renal findings in rats neither the applicant nor the FDA found any clinical correlation in humans (see Section 7.1.7 Laboratory Findings for an assessment of TPV's effect on creatinine).*

*Regarding the GI findings, animal findings does support the human data. GI toxicity, specifically diarrhea, nausea and vomiting, were a major cause of AEs throughout the TPV development program.*

TPV was assessed both in vitro and in vivo for cardiovascular toxicity potential. TPV showed an inhibitory effect in vitro on the HERG-associated potassium channel ( $IC_{50} = 2.9 \mu M$ ) but no effect on action potential duration in guinea pig papillary muscle tissue at concentrations up to  $10 \mu M$ . TPV demonstrated no drug related effects in vivo on mean arterial pressure, heart rate or ECG (including QT interval) in the beagle dog dosed with TPV up to 160 mg/kg. In addition, no evidence of cardiovascular effects was observed in toxicity studies of up to 26 weeks in dogs with TPV/RTV or up to 39 weeks in dogs with TPV alone.

*MO comment: A formal QT study of TPV/r is ongoing.*

TPV was evaluated for effects on immune function to determine if it had immunomodulatory potential. Evidence from repeat-dose studies in mice rats and dogs suggested that TPV might have immunostimulatory and/or immunosuppressive potential. In a mouse immune function study (185) a single dose of TPV inhibited anti-CD3-dependent T-cell stimulation as measured by IL-2 concentrations. Also a minimal, albeit statistically significant, T cell-driven delayed type hypersensitivity (DTH) was observed as measured in  $\text{C}$  assay. Although there were no additional appropriate assays for further investigation of immunostimulatory potential of TPV, an additional assay, the T-dependent antigen response to sheep red blood cells was performed to confirm or negate TPV's immunosuppressive potential. The results of this study showed that treatment with TPV alone or TPV/RTV did not adversely affect the functional ability of the humoral component of the immune system in female CD-1 mice, as evaluated in the IgM antibody-forming cell response to the T-dependent antigen, sheep red blood cells. These results are supportive evidence that TPV is not an immunosuppressive agent.

*MO comment: No additional in vitro tests were available to test TPV's immunostimulatory effect. Additional evidence of TPV's immunostimulatory effect will need to come from clinical studies.*

TPV was also evaluated in a biochemical receptor screen ( $\text{C}$  ) and in general showed a low inhibitory profile against a variety of receptor targets at

concentrations up to 10 $\mu$ M. The only exception was the cholecystokinin-A (CCK-A) receptor binding assay where TPV was shown to bind with "modest affinity" (82%) at 10 $\mu$ M. The significance of TPV binding to the CCK-A receptor at this level is unknown.

General toxicology: The minimum lethal doses of TPV identified in single dose toxicology studies were 3000 mg/kg free acid equivalents (FAE) in mice, 2330 mg/kg FAE in male rats and 1500 mg/kg FAE in female rats and >500 mg/kg FAE in beagle dogs. Gastrointestinal symptoms (emesis, soft stools and/or diarrhea) were common findings among the species tested. In rats, elevations of coagulation parameters were noted in females after single administration of 1500 to 3000 mg/kg.

The primary TPV target organs identified through repeat-dose toxicology studies in mice, rats, dogs and/or monkeys are the liver and gastrointestinal tract.

*MO comment: Again the animal studies support the findings in the clinical trials where GI toxicity is amongst the most common causes of AEs and liver toxicity is the most concerning*

Additional organs that were affected included the thyroid gland, testes and to a lesser extent the adrenal gland, kidneys, spleen and heart. Co-administration of TPV and RTV in rats and dogs revealed only target organs or signs of toxicity seen when each compound was administered alone. Neither drug exacerbated the toxicity of the other.

It should be noted that in rats and dogs, TPV exposure in animals at the NOAEL doses is equivalent to or slightly above exposure in humans at the clinical dose of 500/200 TPV/RTV BID. Early toxicity studies were performed with TPV alone. Once the decision was made for co-administration with RTV in the clinic, bridging toxicity studies with both compounds were performed. Co-administration does increase the exposure of TPV, especially at low doses, but the effect is lower at higher doses. In animals the boosting effect of co-administration with RTV is generally lower than in humans (11-fold increase) and in particular much lower at NOAEL doses in repeat-dose toxicology studies: mice (12- to 22-fold), rats (6- to 7-fold), dogs (3- to 13-fold) and monkeys (2-fold). However, toxicities seen in repeat-dose toxicology studies are not considered to preclude chronic administration of TPV to the intended patients, even though plasma levels are equivalent to or below human exposure. These toxicities are reversible, manageable, species specific and/or considered secondary to species-specific hepatic enzyme-inducing effects of TPV in the rodent.

Gastrointestinal effects included emesis, soft stools, diarrhea and/or excessive salivation after dosing and were observed in all species tested. These effects probably effect local actions since no correlative macroscopic or microscopic changes in the GI tract were observed in mice, rats or dogs. GI effects in rodents included soft stool, diarrhea, increased salivation after dosing (attributed to the bitter taste of TPV during gavage administration) and decreases in food consumption. In dogs and monkeys, soft stool, diarrhea, as well as emesis were observed. The frequency of these GI effects increased with TPV dose level and these signs decreased or ceased completely when TPV dosing

was stopped. There was a decrease in emesis and post-dose salivation when TPV was administered in the SEDDS formulation to dogs by capsule, rather than by oral gavage. This supports the theory that the bitter taste of TPV leads to post-dose salivation and emesis. It should be noted that in a 26-week safety study in dogs with varying amounts of a SEDDS vehicle equivalent to the bulk fill solution, an increase in soft stools was noted during the Pretest Phase when only SEDDS vehicle was administered to dogs. This occurrence of soft stools was related to the volume of SEDDS vehicle which was approximately 30-fold (mg/kg basis) that of humans at a dose level of 500/200 mg/kg TPV/RTV BID.

TPV is a microsomal enzyme inducer and has been shown to increase activity of CYP 3A and CYP 3B in rats and dogs. Changes associated with hepatic enzyme induction, increased liver weights, hepatocellular hypertrophy and increases in smooth endoplasmic reticulum have been seen in nonclinical studies in mice, rats and dogs. Additional changes considered secondary to enzyme induction and specific to rodents were seen generally at high doses and included hepatocellular degeneration, vacuolation, necrosis and mineral deposition in mice and multinucleated hepatocytes in rats. Karyomegaly, an effect of RTV in rats, was observed at a low incidence in the 26-week TPV/RTV study. Histological changes specific to dogs included bile duct hyperplasia and gallbladder cystic hyperplasia at a high dose in the 39-week TPV alone study. This effect was not seen in the 26-week TPV/RTV dog study. These effects were reversible and enzyme induction caused by TPV with resultant hepatocellular hypertrophy is considered an adaptive response and not evidence of toxicity.

The rat is the more inducible species, with males showing more activity than females. This is reflected in the fact that females have higher plasma concentrations of TPV than males after repeated doses of TPV. Additional effects seen in the rat could be secondary to hepatic microsomal enzyme induction. These include increased metabolism and clearance of thyroid hormones, slight increase in plasma proteins and potentially effects on coagulation parameters. Increases in plasma proteins were seen in rat studies as increases in total protein, albumin (accompanied by a slight increase in plasma calcium in several studies) and/or globulin. Increased thyroid gland weights, thyroid follicular hypertrophy, increases in TSH and decreases in T3 and T4 were seen in rat studies and are considered to reflect a rodent specific increase in thyroid hormone metabolism secondary to induction of hepatic enzymes. Changes in thyroid parameters were monitored in the clinic in early trials. The changes seen in rodents in nonclinical studies were not seen in humans. TPV clearly increases coagulation parameters (prothrombin time and activated partial thromboplastin time) in rodents but the mechanism is unknown. It may be caused by an indirect mechanism related to hepatic enzyme induction in rodents. No similar changes were seen in dog studies. Monitoring of PT was performed in clinical trials and no significant changes in this parameter were observed in humans.

Dogs exposed to TPV or TPV/RTV exhibited mild increases in liver alkaline phosphatase (AP) isoenzymes and this suggests an effect on the liver. Histopathological effects in dogs included gallbladder cystic glandular hyperplasia and bile duct hyperplasia in long term repeat dose studies. These effects are common in older beagle dogs but were

increased in TPV treated dogs. In the absence of more severe histopathology, such as biliary stasis or cholestasis, these changes raise little concern for humans. This is also in contrast to the observation that rats exhibited decreased serum AP at higher dose levels in a number of studies.

In mice, enzyme leakage (ALT, AST) at high dose levels was correlated with hepatocellular necrosis. Increases in AST and/or ALT were observed minimally or not at all in toxicology studies on rats and dogs. Based on this difference in species, the importance for humans is not clear. However, liver function can be easily monitored in humans and the nonclinical studies support monitoring as a way of managing this potential human toxicity.

Testicular effects consisting of decreased weights and bilateral seminiferous tubule degeneration and/or atrophy were observed in a 26-week TPV/RTV study in rats and a 39-week TPV study in dogs. In the 26-week TPV/RTV study in rats, mean testicular weights were decreased 19% in males receiving the highest dose of 1200/320 mg/kg/day TPV/RTV but not at 1200 mg/kg/day TPV or 160 mg/kg/day RTV. Bilateral seminiferous tubule degeneration was seen in 3/15 male rats. The 1200/320 mg/kg/day TPV/RTV dose level caused high mortality. No other studies in rats, including the 26-week study with TPV alone, resulted in testicular changes. The low incidence of testicular findings together with the high incidence of mortality in the 1200/320 TPV/RTV group, coupled with hemorrhagic events, decreased food consumption and body weight gain, suggest that the testicular degeneration seen in rats in this study is related to stress. However, a direct effect of the drugs cannot be discounted. Testicular changes consisting of vacuolar degeneration of the epithelial lining and atrophy of the seminiferous tubules were noted in ¾ male dogs after administration of 320 mg/kg/day TPV for 39 weeks. Following a recovery period, 1.3 males at this dose level still displayed degeneration of the seminiferous tubules as well as abnormal germ cells and decreased number of sperm within the ducts of the epididymides. No testicular changes were noted in other studies in dogs with TPV or TPV/RTV. After the submission of the NDA, the sponsor submitted Study Number U04-3531 which gives the results of a re-evaluation of the data on testicular degeneration and/or atrophy by an expert panel. The panel concluded that the findings in the dog were within normal limits of variation. Based on the above information, testicular findings in one rat study at a high dose associated with high mortality are not considered to be a cause of concern in humans.

Effects were seen sporadically in adrenal gland, kidneys, spleen and heart are not considered to have predictive value for humans for the following reasons: 1) Adrenal gland effects consisted of increased adrenal weights without correlative microscopic changes, with the exception of one 4-week study in mice where hypertrophy of the zona fasciculata was observed at the highest TPV and TPV/RTV levels. These were minimal to mild effects seen at high doses and similar changes were not seen in dogs. Thus, these adrenal effects in rats were attributed to stress and not a direct effect of TPV. 2) Changes in the kidney were an increased urinary protein and exacerbation of chronic progressive nephropathy, a rodent specific spontaneous change, seen in a 26-week rat study. Kidney changes were not seen in other species or in rats in the 26-week TPV/RTV study. 3)

Increased extramedullary hematopoiesis was observed in the spleen in mice, rats and dogs but was considered secondary to mildly reduced red blood cell parameters in rats and dogs and hemorrhage in the 26-week TPV/RTV rat study. 4) Minimal to mild myocardial degeneration was observed in one study in mice when TPV was administered by diet over 13 weeks. No heart changes were seen in any gavage administration study in mice up to 13-weeks nor have heart changes been seen in any study in rats or dogs, up to 26- and 39-weeks, respectively. The significance of this finding is unclear but it is assumed that if TPV had exhibited cardiotoxicity, cardiac changes would have been seen in multiple species or consistently in one species rather than in one study.

The safety of the self-emulsifying drug delivery system (SEDSS) formulation was explored in a 26-week TPV/RTV dog study to eliminate concerns over the high dose [ ] from 500/200 mg/kg TPV/RTV BID) of Cremophor EL (CrEL) contained in this formulation. Of concern was the possibility that CrEL might pass from the GI tract into systemic circulation and thereby pose a risk of anaphylactoid reactions since CrEL is known to cause these reactions if given in high levels IV. Consequently, exposures to the SEDSS formulation were chosen to achieve 1, 10 and 30-fold exposure to CrEL in humans. Toxicities in two animals and the death of one animal treated with the high dose of SEDSS were deemed due to the effect of the formulation. The target organs noted in the early death female were the stomach, intestine and mesenteric lymph nodes. CrEL plasma levels were detectable 2 hours after the first or second dose in several animal administered 2720 mg/kg/day SEDSS and one animal receiving 910 mg/kg/day SEDSS. Plasma CrEL levels ranged from [ ] mg/ml. These levels are unlikely to cause anaphylactoid reactions. The NOEL for SEDSS is considered to be 910mg/kg/day SEDSS which supports a 10-fold safety factor for the SEDSS vehicle in the recommended human dose.

*MO comment: Cremophor EL is another name for polyoxyl 35 castor oil. Please see MO comment undere section 3.1 for clinical discussion of concern with polyoxyl 35 castor oil.*

Genetic toxicology: TPV was tested for the ability to induce point mutations in DNA (mutagenicity) and the ability to damage chromosomes (clastogenicity) in five in vitro and in vivo assays including the battery of assays specified in the ICH S2B guidance on genotoxicity. TPV was negative in these assays, indicating that TPV has no mutagenic or clastogenic potential.

In addition, a number of genetic toxicology assays were performed to qualify impurities. These studies reinforce the conclusion from the results of the standard battery assays on TPV alone that TPV, as well as impurities and degradation products tested, are not mutagenic or clastogenic.

Carcinogenicity: Carcinogenicity studies in mice and rats are ongoing.

Reproductive toxicology: A male and female fertility and early embryonic development study (oral) in Sprague-Dawley rats demonstrated that TPV did not affect

spermatogenesis, estrous cycle, copulation, conception, fertility, implantation or early embryonic development at doses up to 1000 mg/kg/day. This corresponds to a C<sub>max</sub> of 258 µM which is approximately two-fold the human C<sub>max</sub> at the proposed clinical dose of 500/200 TPV/RTV BID.

In an embryo-fetal development study in Sprague-Dawley rats, there was no evidence of TPV-related embryoletality or teratogenicity at doses of 40 to 1000 mg/kg/day. However, the NOAEL for both maternal and developmental toxicity was 40 mg/kg/day, based on findings of postdose salivation, decreased body weight and food consumption in dams and decreased body weight and sternebrae ossification in fetuses. This NOAEL corresponds to a mean C<sub>max</sub> 30.4 µM and a mean AUC of 340 µM.h, which is 0.2-fold of the expected human exposure at the proposed dose of 500/200 TPV/RTV BID.

In embryo-fetal development studies, when TPV was administered to pregnant rabbits (gestation days 6 through 20) in daily doses up to 375 mg/kg, maternal toxicity (death of one female, abortions, decreased body weight and food consumption and increased clinical signs) and developmental toxicity (slightly decreased fetal body weights, fetuses with wavy ribs and bent femurs and increased incidence of fetuses with gross malformations) were observed at the high dose. Interpretation of these fetal findings is complicated by maternal toxicity and by the fact that a single litter was responsible for the majority of the developmental toxicities, suggesting a litter effect. These gross malformations were not observed in fetuses at 375 and 759 mg/kg/day TPV in the dose range-finding study in rabbits. Therefore, it is unlikely that TPV was teratogenic at 375 mg/kg/day. Maternal toxicity (abortions) occurred at 150 mg/kg/day but no developmental toxicity was observed at that dose level. The NOAEL for maternal toxicity was 75 mg/kg/day while the NOAEL for developmental toxicity was 150 mg/kg/day. The AUCs associated with these NOAEL doses correspond to 0.04-fold and 0.08-fold, respectively, the human exposure at the proposed clinical dose of 500/200 TPV/RTV BID.

In a pre- and post-natal development study in rats, TPV was toxic to dams and suckling pups at 400 and 1000 mg/kg/day with dose-relationship. Maternal toxicity was restricted to adverse effects on body weight and food consumption. Pup toxicity consisted of slight (400 mg/kg/day) or marked (1000 mg/kg/day) progressive growth inhibition throughout lactation, resulting in persistent adverse influence on the growth of the pups up to maturity. However, none of the postweaning functions examined in F1 offspring, including reproductive ability, were compromised up to the 1000 mg/kg/day dose and there was no evidence of teratogenicity at any dose. The 40 mg/kg/day dose was an NOAEL for both the dams and offspring.

*MO comment: TPV/r will be a pregnancy category C drug and should be used only if the benefits outweigh the risks. Further, TPV will be included in the antiretroviral pregnancy registry.*

Special toxicology: Local irritation studies in rabbits demonstrated that TPV was minimally irritating to the eye and mildly irritating to abraded skin with open wound.

## 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 3 studies, RESIST 1 and RESIST 2 conducted by BIPI. Additionally, data from 1182.17 (the Rollover study) and 1182.58 (the Open Label Safety Study) were reviewed in detail for safety. Dr. Melissa Baylor reviewed in detail the supportive 18 Phase 1 studies, study 1182.33 (the Naïve study) and study 1182.14 (the pediatric study). Dr. Neville Gibbs reviewed in detail the Phase 2 studies 1182.52 (the definitive dose finding study), 1182.51 (the dual-boosted PI PK and safety study), 1182.2, 1182.4, and 1182.6. In this review data from the Phase 1 and 2 studies will be mentioned as supportive evidence of safety signals derived from the Phase 3 data.

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 developed countries in the post HAART era. DAVDP's clinical trials database was reviewed to assess the mortality rate of HIV-1 infected patients in registrational clinical trials.

Additionally minutes were reviewed from the May 19, 2005 Antiviral Advisory Committee Meeting where relevant efficacy and safety data from the TPV NDA were presented. Please refer to Section 8.5 for a detailed discussion of the outcome of the Antiviral Advisory Committee Meeting on TPV.

### 4.2 Tables of Clinical Studies

The TPV clinical development program consists of 39 clinical trials in which subjects and patients received TPV alone or TPV in combination with ritonavir (TPV/r). Of the 39 clinical studies, 13 were in HIV-positive patients and 26 were in HIV-negative subjects. Of the 39 clinical studies, 25 were conducted by BI (11 in HIV-positive patients and 14 in HIV-negative subjects) and 14 by P&U (2 in HIV-positive patients and 12 in HIV-negative subjects).

Table 4.2 -1 Trials in the TPV Clinical Development Program

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
<b>Phase 3, HIV+</b>						
1182.12	pivotal safety and efficacy	North America, Australia,	open-label, randomized, active control	TPV/r 500/200mg BID x 96 wks	620/multiple PI experienced	Ongoing

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
1182.48	pivotal safety and efficacy	Europe, South America and Mexico	open-label, randomized, active control	TPV/r 500/200mg BID x 96 wks	863/ multiple PI experienced	Ongoing
<b>Phase 2, HIV+</b>						
1182.2	safety and efficacy	US	open-label, randomized, active control	x 24 weeks	41/multiple PI experienced, NNRTI-naïve adults	Completed
1182.4	safety and efficacy	France, Italy, US	open-label, randomized, active control	x 24 weeks	79/single PI experienced + NNRTI experienced	Completed
<b>Phase 2a or 2b, multiple dose PK studies, HIV+ subjects</b>						
1182.6	PK	US, Europe	open label, sequential PK	x 3 weeks	208	Completed
1182.51	PK	Europe, North America	Open label, randomized, parallel group	x 24 weeks	315/treatment experienced	Completed
1182.52	Safety, efficacy and PK	NA, Europe, Australia	Double-blind, randomized, dose optimization	x 32 weeks	216/ multiple PI experienced	Completed
<b>Phase 1, PK, HIV-subjects</b>						
U00-3266	PK/safety	US	Single-center, randomized 3:1, double-blind, PBO-controlled, escalating dose	PBO capsules TPV hand filled capsules Doses 100 – 2000 mg	48	Completed
U00-3192	PK	US	Single-center, open-label, randomized, 4 period crossover	Single 800mg dose of TPV in 4 different formulations	12	Completed
U00-3265	PK/safety	US	Single-center, randomized 3:1, double-blind, PBO-controlled, escalating dose	TPV hand filled capsules at doses ranging from 300-2000mg	48	Completed
U00-3187	PK Food effect study	US	Single center, single dose, randomized, open-label, three-way crossover	TPV HFC	12	Completed
U00-3189	PK	U.S.	Single center, single dose, randomized, open-label, five way crossover	Multiple doses and formulations	10	Completed
U01-3059	PK/safety	U.S.	Single-center, single group, open-label, multiple dose, sequential	TPV HFC + DLV	8	Completed

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
			treatment, drug interaction			
U00-3208	PK	U.S	Open-label, multiple dose, single treatment	Multiple doses and formulation	14	Completed
U00-3267	PK/safety	U.S	Randomized, open label, crossover	Multiple doses and formulation	16	Completed
U00-3271	PK	US	Randomised, open-label, parallel-group, multiple dose	TPV 600 or 900 mg w/ an escalating dose of RTV 100-700 mg	19	Completed
U01-3058	PK/safety	US	Randomised, open-label, parallel-group, sequential treatment, multiple-dose	Multiple doses and formulation	24	Completed
U01-3056	PK/safety	US	Randomised, open-label, parallel-group,	TPV 1200mg BID different formulations	18	Completed
U01-3057	PK/safety	US	Randomised, openlabel, parallelgroup, treatment, multipledose	TPV 1250 mg BID + RTV 200mg and EFV	24	Completed
1182.55	PK/PD Drug interaction	US	Open label, randomized, parallel group	TPV and loperamide	24	Completed
1182.5	PK/safety	US	Open label, parallel group	TPV dose ranging from 250-1250mg boosted by RTV 100-200mg	113 healthy volunteers	Completed
1182.10	drug interaction	Canada	open-label	fluconazole + TPV/r	20	Completed
1182.11	drug interaction	Canada	open-label	clarithromycin + TPV/r	24	Completed
1182.21	drug interaction	Canada	open-label	atorvastatin + TPV/r	23	Completed
1182.22	drug interaction	Canada	open-label, randomized, parallel	NET/EE Ortho 1/35 + TPV/r	52	Discontinued
1182.37	drug interaction	US	open-label, randomized, parallel	TPV/r + ZDV	60	Completed
1182.41	drug interaction	US	open-label, randomized, parallel	TPV/r + EFV	68	Completed
1182.42	drug interaction	Germany	Open-label, randomized, parallel	TPV/r + ddI	23	Completed
1182.44	drug interaction	Canada	open-label	TPV/r + rifabutin	24	Ongoing

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
1182.46	drug interaction	UK	open-label, randomized, parallel	TPV/r + TDF	49	Completed
1182.45	bioavailability	Germany	open-label, single-dose, three-way, crossover trial	Liquid and SEDDS formulation	30	Completed
1182.24	ADME mass balance	US	open-label, single dose <sup>14</sup> C TPV/r	500/200mg	12	Completed
1182.32	hepatic insufficiency	Canada	open-label	single dose TPV/r 500/200mg	24	Completed
<b>Phase 2, uncontrolled, HIV+</b>						
1182.1	safety, efficacy, and PK	U.S.	Open-label, non-randomized	Multiple doses HFC x 24 weeks	40	Complete
1182.17	safety	NA, SA, Europe, Australia	open-label long term rollover trial-subjects from trials: 1182.1, 1182.2, 1182.4, 1182.6, 1182.12, 1182.48, 1182.51, 1182.52	TPV/r 500/200 mg	748	Ongoing
1182.58	safety	NA, SA, Europe, Australia	open-label safety study	TPV/r 500/200mg BID	451	Ongoing
<b>Phase I/II Pediatric</b>						
1182.14	PK and safety	NA, SA, Europe	open-label, randomized, dose finding	TPV 290mg/m <sup>2</sup> BID/r 115 mg/m <sup>2</sup> + OBR or TPV 375 mg/m <sup>2</sup> BID/r 150 mg/m <sup>2</sup> BID + OBR x 48 weeks	57/PI experienced and naïve	Ongoing
<b>Phase II Naïve studies</b>						
1182.3	safety, efficacy, and PK	US, Puerto Rico and South Africa	open-label, randomized, parallel	TPV 1200mg BID vs. TPV/r 300/200mg BID vs. TPV/r 1200/200mg BID	31/ ARV naïve	Complete
1182.33	safety and efficacy	NA, SA, Australia, Europe, Carribean, Mexico, Thailand, Uganda	open-label	TPV 500mg + 100 or 200mg of RTV vs. Kaletra w/ background of TDF + 3TC x 48 weeks	540 planned 15 enrolled/ ARV naïve	Ongoing

**Abbreviations:** APV = Amprenavir; BDIC = Bulk drug in capsule (tipranavir); Capmul® MCM = Medium chain monoglyceride emulsifier used in SEDDS solutions; CPI = Comparator protease inhibitor; DLV = Delavirdine; EFV = Efavirenz; GDO/GMO = Glyceryl di-oleate/Glyceryl mono-oleate emulsifiers used in SEDDS solutions; HFC = Hard filled capsule formulation of tipranavir; NRTI = Nucleoside reverse transcriptase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; NVP = Nevirapine; OBR = Optimised background regimen; P&U = Pharmacia & Upjohn; RTV = Ritonavir; SEC = Soft elastic capsule (tipranavir); SEDDS = Self-emulsifying drug delivery system (tipranavir); SQV = Saquinavir; TPV/r = Tipranavir boosted with ritonavir;  $\text{ }^{\text{C}}$  =  $\text{ }^{\text{C}}$  -compressed tablet (tipranavir); ZDV = Zidovudine; 3TC = Lamivudine.  
Source: SCS p. 228, NDA 21-814

### **4.3 Review Strategy**

The efficacy data were reviewed for RESIST 1 and RESIST 2. The safety data from all 39 studies were reviewed including Case Study Reports in Module 5 of the NDA, Case Report Tabulations, and Case Report Forms when available and applicable. As mentioned before, Drs. Melisse Baylor and Neville Gibbs reviewed the Phase 1, Phase 2, Pediatric, and Naïve data submitted with this NDA. Please refer to Drs. Baylor and Gibbs' reviews in Section 10.1 for detailed analyses of the aforementioned studies. Dr. Rafia Bhore performed the statistical efficacy analyses and Dr. Susan Zhou performed many of the statistical analyses of the safety data; their findings are incorporated into this review.

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**

DAVDP consulted the Division of Scientific Investigations (DSI) to inspect a sample of U.S. and International sites. There were six sites chosen: three U.S. and three International. Two of the three U.S. sites were chosen because they enrolled a large number of patients while the fourth, Dr. Blick's site, was chosen because he violated a study protocol by discontinuing an clinically deteriorating patient from one TPV study (pivotal trial, 1182.12) and enrolled him in another TPV study (Open Label Safety Study, 1182.58.) Please refer to the DSI consult report for specific details of inspection findings.

Briefly, the U.S. sites inspected were those of Dr. Blick, Dr. Jayaweera and Dr. Becker. The inspection report for Dr. Blick's site concluded that he did not conduct the study in accordance with the protocol, he did not re-consent three patients with the revised informed consent, he did not promptly report to the sponsor or the IRB adverse events and all unanticipated problems involving risk to human patients, and he did not maintain adequate and accurate [patient] records. The inspection report for Dr. Jayaweera's site concluded that she did not conduct the study in accordance with the protocol, she did not prepare and maintain adequate records of the disposition of the study drug, and she did not maintain adequate and accurate [patient] records. The inspection report for Dr. Becker concluded that he "adhered to applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects."

The International sites were all in South America and were chosen based on a combination of number of patients enrolled and the fact that very few to no patients had discontinued study by Week 24 at these sites while at most other sites between 25-50% of patients had discontinued by Week 24. The DSI inspection reports of all three International sites concluded that the investigators at each site "adhered to applicable

statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.”

*MO comment: One-third of the sites inspected by DSI had study conduct deficiencies. This is not surprising given the large number of protocol violations reported in the RESIST database (see Section 4.5). Fortunately the superior efficacy of TPV/r over a partially-active control arm was maintained despite these violations. However, this pervasive lack of rigor on the part of the investigators participating in the RESIST trials is worrisome and suggests that restrictions placed on the use of TPV/r may be ignored by healthcare providers who perceive their patients to be in great need of TPV/r despite not meeting all the criteria for its use.*

#### 4.5 Compliance with Good Clinical Practices

Over 50% of patients in each treatment group (51% in the TPV group and 56% in the CPI/r group) had “relevant protocol violations” (Table 4.5:1). BIPI appointed an independent committee for each of the RESIST trials to prospectively decide protocol deviations that had even a remote chance of affecting a subject’s efficacy evaluation.

*MO comment: This number of protocol violations is unusually high, but may be evidence of a very desperate patient population and desperate healthcare providers whose need for a new and active ARV lead them to violate inclusion and exclusion criteria and protocol defined procedures.*

**Table 4.5:1 Protocol Violations in RESIST 1 and RESIST 2 Trials**

	RESIST 1		RESIST 2		Total	
	TPV/r N=311	CPI/r N=309	TPV/r N=271	CPI/r N=268	TPV/r N=582	CPI/r 577
Number (%) of unique patients with protocol violations	141 (45%)	146 (47%)	158 (58%)	176 (66%)	299 (51%)	322 (56%)
<b>Total Number of Protocol Violations†</b>	<b>173</b>	<b>173</b>	<b>191</b>	<b>219</b>	<b>364</b>	<b>392</b>
<b>Screening Violations</b>	<b>82</b>	<b>87</b>	<b>75</b>	<b>84</b>	<b>157</b>	<b>171</b>
No protease gene mutations at codons 30 N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M	3	3	7	1	10	4
More than two protease gene mutations at	16	15	4	6	20	21

	RESIST 1		RESIST 2		Total	
	TPV/r N=311	CPI/r N=309	TPV/r N=271	CPI/r N=268	TPV/r N=582	CPI/r 577
codons 33, 82, 84, 90						
Less than 2 PIs or less than 3 months of treatment on historical HIV-1 therapy page	2	6	7	5	9	11
No NRTI with >1 month duration or no NNRTI with >1 month duration	2	5	7	5	9	10
Screening Viral Load < 1000	5	1	2	1	7	2
Triglycerides at screening > DAIDS grade 2	12	12	31	48	43	60
ALT or AST > DAIDS grade 1	11	13	6	7	17	20
Use of Immunomodulatory Drugs within 30 days before study entry or during trial (FDA only)	31	32	11	11	42	43
<b>Treatment Regimen Violations</b>	<b>91</b>	<b>85</b>	<b>105</b>	<b>125</b>	<b>196</b>	<b>210</b>
Randomized to CPI/r and pre-specified not taken throughout the trial or changed	0	3	0	6	0	9
More than one PI taken at the same time (plus RTV)	1	1	3	4	4	5
Wrong T20 stratum	13	14	7	14	20	28
Undetectable troughs at any study visit but documented intake of PI	30	19	38	41	68	60
Treatment Interruption of >28 days within 6 month period if not due to AE	0	0	0	1	0	1

	RESIST 1		RESIST 2		Total	
	TPV/r N=311	CPI/r N=309	TPV/r N=271	CPI/r N=268	TPV/r N=582	CPI/r 577
OBR of less than 2 non PI ARV drugs	1	2	7	6	8	8
No new or recycled ARV in OBR	46	46	50	53	96	99
<b>Other Violations</b>	<b>0</b>	<b>1</b>	<b>11</b>	<b>10</b>	<b>11</b>	<b>11</b>
Use of contraindicated drugs	0	0	1	1	1	1
Investigational or immunomodulatory drug use during treatment	0	1	10	9	10	10
† A patient may have one or more protocol violations. Number of protocol violations will not add up to the number of patients with protocol violations.						
Source: NDA 21-814 Amendment 060 (dated 19 April 2005)--- Response from Applicant to FDA's query on protocol violations						

*MO comment: The independent committees deciding what constituted a relevant protocol violation for RESIST 1 and RESIST 2 agreed on every category except for the category "No new or recycled ARV in OBR": the RESIST 2 committee believed that this was a relevant protocol violation while the RESIST 1 committee did not. The RESIST protocols stipulated that the OBR must be constructed of at least two new ARVs, and therefore, it makes sense to this reviewer that having an OBR that does not contain two new ARVs would be considered a protocol violation. One could argue that in this advanced population finding two new, active ARVs may be impossible; however, deciding not to adhere to that protocol defined criterion is a major decision and warrants a trial wide protocol amendment versus a case-by-case decision. Since these two trials are nearly identical in design, it makes no sense to this reviewer to apply different criteria to the trials. Therefore this reviewer chose the most conservative approach and applied the "No new or recycled ARV in OBR" to both trials.*

*Dr. Bhore performed a sensitivity analysis censoring protocol violators and showed that despite the numerous protocol violations TPV/r maintained its superior activity over the suboptimal control group (see Section 6.1.4).*

#### 4.6 Financial Disclosures

BIPI reported that they are "a subsidiary of Boehringer Ingelheim GmbH (BIGmbH), a privately held German company. As a privately held company BIGmbH is not publicly traded on any stock exchange, has no equity available to investigators and does not, as a matter of policy, provide compensation to investigators based on the outcome of studies

conducted on its behalf. In addition, no investigators can have or own a proprietary interest in a product, trademark, licensing agreement or patent owned by the company.”

BIPI identified four trials as being covered by the Financial Disclosure Rule: 1182.14, 1182.52, 1182.12 and 1182.48. BIPI reported that none of the investigators or sub-investigators involved with these studies had any financial arrangements to disclose.

## 5 CLINICAL PHARMACOLOGY

Please refer to Dr. Derek Zhang’s Clinical Pharmacology and Biopharmaceutics review for a detailed analysis of the pharmacokinetics (PK), pharmacodynamics (PD) and exposure-response relationship of TPV/r. A summary of the important PK, PD and exposure-response issues raised in Dr. Zhang’s review are presented below.

### 5.1 Pharmacokinetics

Tipranavir’s absorption in humans is limited, however, no absolute quantification of TPV’s absorption is available. Tipranavir is a substrate for cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp), so the limited absorption may be due to the effect of the intestinal CYP3A4 and the intestinal P-gp efflux transporter. Peak plasma concentrations are reached approximately 2-3 hours (range from 1 to 5 hours) after dose administration. The proposed dose of TPV 500 mg with 200 mg of RTV, a CYP3A4 inhibitor, given twice daily resulted at steady-state in an increase of the mean plasma TPV  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  by 45-fold, 4-fold, and 11-fold respectively, compared to TPV 500 mg bid given alone. The mean plasma TPV  $C_{min}$ ,  $C_{max}$ ,  $AUC_{0-12h}$  and elimination half-life was 32.6  $\mu\text{M}$ , 131  $\mu\text{M}$ , 859  $\mu\text{M}\cdot\text{h}$ , 4.8 h, respectively, at steady state following a TPV/r dose of 500 mg/200 mg twice daily with a light meal. For the SEDDS capsule formulation, the  $AUC_{0-12h}$  and  $C_{max}$  of TPV increased 31% and 16%, respectively, with a high-fat meal compared to that with a light snack.

Tipranavir protein binding is very high (approximately 99.9% at 20  $\mu\text{M}$ ) in human plasma. The degree of binding is similar over a wide concentration range from 10 to 100  $\mu\text{M}$ . TPV binds to both human serum albumin and  $\alpha$ -1-acid glycoprotein.

In vitro metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP enzyme involved in TPV metabolism. Tipranavir is also a P-gp substrate.

A mass-balance study in healthy male subjects demonstrated that, at steady-state, a median of 82.3% of the radioactivity of the  $^{14}\text{C}$ -TPV dose (TPV 500 mg/RTV 200 mg) was recovered in feces. The excretion of tipranavir via the feces could be due to a combination of unabsorbed drug as well as the biliary excretion of absorbed drugs and its metabolites. Tipranavir trough concentrations at steady-state are about 60-80% lower

than those on Day 1. Unchanged TPV accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Unchanged TPV represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of TPV. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of TPV.

### ***Special Populations***

**Hepatic Impairment:** After 7 days of 500mg/200mg bid dosing, the mean systemic exposure of TPV was higher for 9 subjects with mild hepatic insufficiency compared to that of 9 matched controls and the ranges of 90% CI were quite large, e.g., geometric mean ratios with 90% CIs for AUC, C<sub>max</sub> and C<sub>min</sub> were 1.30 (0.88, 1.92), 1.14 (0.83, 1.56) and 1.84 (0.81, 4.20), respectively. A similar change in RTV exposure was also observed. Dosage adjustment may not be warranted for this group of patients based on the moderate change in TPV and RTV systemic exposure and safety profiles observed in this study. There were insufficient data (lack of data at the steady-state) from the moderate hepatic insufficiency group to reach any conclusion.

*MO comment: TPV/r will be contraindicated in patients with Child-Pugh B and C liver disease because of inadequate data or the absence of data in this population and because of the evidence that patients with underlying liver injury are at increased risk of TPV/r associated hepatotoxicity*

**Renal Impairment:** Tipranavir pharmacokinetics have not been studied in patients with renal dysfunction. However, since the renal clearance of TPV is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

**Gender and Race:** Evaluation of steady-state plasma tipranavir trough concentrations from two pivotal phase III clinical trials indicated that females generally had higher tipranavir concentrations than males. After 4 weeks of tipranavir/ritonavir 500 mg/200 mg bid, the median plasma trough concentration of tipranavir was 43.9 µM for females and 31.1 µM for males. The range of exposure was similar for males and females. The range of tipranavir exposure was similar for males and females and between the races.

*MO comment: Although the range of exposure for males and females were similar, the median trough concentrations were higher in females than in males and may correlate clinically with the greater treatment response and higher rate of rash observed in women.*

**HIV-1 Patients:** A population pharmacokinetic analysis of steady-state TPV exposure in healthy volunteers and HIV-infected patients following administration of TPV/r 500 mg /RTV 200 mg bid suggested the mean systemic exposure of TPV was slightly lower for HIV-1 infected patients compared to that of HIV-1 negative subjects. This observation does not change conclusions of studies conducted in healthy volunteers.

**Pediatric Patients:** The pharmacokinetic profile of TPV in pediatric patients has not been established (see Section 8.4 and Appendix 10.1 for details of the Pediatric study)

### ***Drug interactions***

Potential for TPV/r to affect other drugs:

1. TPV, co-administered with low-dose RTV at the recommended dosage, is a net inhibitor of CYP3A. Thus, TPV/r may increase plasma concentrations of agents that are primarily metabolized by CYP3A and could increase or prolong their therapeutic and adverse effects. Thus, co-administration of TPV/r with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring
2. Studies in human liver microsomes indicated TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Follow-up in vivo evaluations using probe substrate drugs for these enzymes have not been conducted to rule out or confirm these potential interactions. Ritonavir is a moderate CYP2D6 inhibitor, and likely an inducer of CYP1A2, CYP2C9 and glucuronosyl transferases. The potential net effect of TPV/r on CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. Data are not available to indicate whether TPV inhibits or induces glucuronosyl transferases and whether TPV induces CYP1A2, CYP2C9 and CYP2C19.
3. Data suggest that the net effect of TPV/r at the proposed dose regimen (500 mg/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.
4. Based on items 1 and 3 above, it is difficult to predict the net effect of TPV/r on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Potential for other drugs to affect TPV/r:

1. 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.
2. Co-administration of TPV/r with drugs that inhibit CYP3A may not further increase TPV plasma concentrations, based on the results of a mass balance study.

The following tables highlight drugs that are contraindicated and not recommended for co-administration with TPV/ritonavir (Table 5.1:1) and some other established or potential drug interactions (Table 5.1:2). The information in both tables is based on drug interaction studies or is predicted based expected mechanisms of interactions. A more complete list of drug interactions will be included in the final labeling.

**Table 5.1:1 Drugs that Should Not be Co-administered with TPV/r**

<b>Drug Class/Drug Name</b>	<b>Clinical Comment</b>
<b>Antiarrhythmics:</b> Amiodarone, bepridil, flecainide, propafenone, quinidine	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
<b>Antimycobacterials:</b> rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>Ergot derivatives:</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	<b>CONTRAINDICATED</b> 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.
<b>GI motility agents:</b> Cisapride	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal products:</b> St. John's wort	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>HMG CoA reductase inhibitors:</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptics:</b> Pimozide	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Sedatives/hypnotics:</b> Midazolam, triazolam	<b>CONTRAINDICATED</b> due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

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On Original

**Table 5.1:2 Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions**

<b>Concomitant Drug Class: Drug name</b>	<b>Effect on Concentration of Tipranavir or Concomitant Drug</b>	<b>Comment</b>
<b>HIV-Antiviral Agents</b>		
Nucleoside reverse transcriptase inhibitors: Abacavir	↓Abacavir concentrations by approx. 40%	Appropriate doses for the combination of TPV/r and abacavir have not been established.
Didanosine	↓Didanosine approx 10-20%	Dosing of EC-didanosine and TPV/r should be separated by at least 2 hours. Preferably didanosine should be given just before lunch.
Zidovudine	↓Zidovudine concentrations by approx. 50%	Appropriate doses for the combination of TPV/r zidovudine have not been established. Similar interaction observed between nelfinavir and zidovudine, ritonavir and zidovudine, with no dose adjustment.
Protease inhibitors (co-administered with low-dose ritonavir): Amprenavir Lopinavir Saquinavir	↓Amprenavir approx. 50%, ↓Lopinavir 50-70%, ↓Saquinavir 70-80%,	Appropriate doses for the combination of TPV/r with amprenavir, lopinavir or saquinavir have not been established.
Other PIs	Similar degree of interaction might be expected as that of amprenavir, lopinavir or saquinavir	No information available for indinavir, nelfinavir and atazanavir
<b>Other Agents</b>		
Antacids	↓ Tipranavir approx 30%	Reduced plasma concentrations of tipranavir are expected if antacids, including buffered medications, are administered with tipranavir. Tipranavir should be administered 2 h before or 1 h after these medications.
Antidepressants: SSRIs Atypical antidepressants	Expected ↑ SSRIs Expected ↑ Atypical antidepressants	Coadministration with TPV/r has the potential to produce serious adverse events and has not been

**Table 5.1:2 Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions**

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Comment
		studied. Patients should be monitored carefully for adverse events.
Antifungals: Fluconazole Itraconazole Ketoconazole Voriconazole	↑Tipranavir, ↔Fluconazole Expected ↑Itraconazole, Expected ↑Ketoconazole Cannot predict effect of TPV/r on voriconazole	Dose adjustments are not needed, for TPV/r administered with fluconazole.  Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (>200 mg/day) are not recommended.
Anticoagulant: Warfarin	Cannot predict the effect of TPV/r on warfarin due to conflicting effect of TPV and RTV on CYP2C9	Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction. Interaction was not evaluated. Warfarin concentrations may be affected. It is recommended that INR be monitored frequently when TPV/r is initiated.
Anti-diabetic agents	The effect of TPV/r on CYP2C8, which metabolizes most glitazones, is not known.  Sulfonylureas are metabolized by CYP2C9, interaction is possible.	The interactions were not evaluated.
Antimycobacterials: Rifabutin	↓Tipranavir possible, but effect of multiple dose rifabutin was not evaluated.  ↑Rifabutin 3-fold ↑ Desacetyl-rifabutin 20-fold	Dosage reduction of rifabutin by 75% is recommended (e.g. 150 mg every other day or three times a week).
Clarithromycin	↑Tipranavir (based on cross-study comparison)  ↔Clarithromycin,	No dosage adjustments are needed.

**Table 5.1:2 Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions**

<b>Concomitant Drug Class: Drug name</b>	<b>Effect on Concentration of Tipranavir or Concomitant Drug</b>	<b>Comment</b>
	↓14-hydroxy metabolite	
Calcium Channel Blockers: e.g., diltiazem, nicardipine and verapamil	Cannot predict effect of TPV/r on calcium channel blockers due to conflicting effect of TPV/r on CYP3A and P-gp	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	Possible ↓ Tipranavir	Use with caution. TPV may be less effective due to decreased TPV plasma concentrations in patients taking these agents concomitantly.
HMG-CoA reductase inhibitors: Atorvastatin	↔Tipranavir  ↑ Atorvastatin approx 5-9-fold ↓ Hydroxy-metabolites	Start with the lowest possible dose of atorvastatin with careful monitoring, or consider HMG-CoA reductase inhibitors not metabolized by CYP3A such as pravastatin, fluvastatin or rosuvastatin.
Narcotic analgesics: Methadone	Expect ↓Methadone	Dosage of methadone may need to be increased when co- administered with TPV/r.
Meperidine	Expect ↓Meperidine, ↑Normeperidine	Dosage increase and long- term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures)
Oral contraceptives/Estrogens: Ethinyl-estradiol	↓Ethinyl-estradiol concentrations by 50%	Alternative or additional contraceptive measures are to be used when estrogen based oral contraceptives are co- administered with TPV/r.
Despiramine	Expect ↑Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.
Theophylline	Cannot predict the effect of TPV/r on theophylline due to potential conflicting effect of TPV and RTV on CYP1A2	Concentrations of theophylline may be affected. Increased therapeutic monitoring is recommended, after TPV/r is initiated.

Of all of the PK studies conducted 1182.51 is noteworthy. Study 1182.51 was conducted in conjunction with the two pivotal phase III trials, RESIST 1 and RESIST 2. Patients ineligible for enrollment into RESIST 1 and RESIST 2 because of having three or more TPV associated mutations at codons 33, 82, 84 or 90 were eligible for screening for 1182.51. The working hypothesis was that the combination of TPV/r with a second PI might increase the chances of a clinical response in a highly resistant HIV-1 infected patient population. Study 1182.51 was a preliminary PK study to investigate the potential drug interactions between TPV/r and the other RTV boosted-PIs and to provide initial clinical data for this dual PI approach. Patients were randomized to one of four arms. Each arm received the same total dose of TPV, 500mg twice daily (BID) and RTV, 200mg BID at Week 2.

The treatment arms were as follows:

TPV/r (500/200) plus OBR

LPV/r (400/100 bid) plus OBR, with TPV/r (500/100) added at week 2

APV/r (600/100 bid) plus OBR, with TPV/r (500/100) added at week 2

SQV/r (1000/100 bid) plus OBR, with TPV/r (500/100) added at week 2

The co-administration of TPV/r at 500 mg/200 mg BID decreased LPV, SQV, and APV steady-state trough plasma concentrations by 52%, 80% and 56%, respectively. These data were also consistent with the results of the intensive PK sub-study where co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased LPV, SQV, and APV steady-state trough plasma concentrations by 70%, 82% and 55%, respectively, AUC by 55%, 76% and 44%, respectively, and Cmax by 47%, 70% and 39%, respectively. TPV exposure increased slightly in the APV/r and LPV/r groups, but decreased slightly when co-administered with SQV/r. RTV trough plasma concentrations were similar in APV/r and LPV/r groups with the addition of TPV/r. However RTV trough plasma concentrations in the SQV/r group decreased by 50% with the addition of TPV/r. This decrease in RTV concentration might account for the most dramatic reduction in SQV exposure with the addition of TPV/r.

*MO comment: Study 1182.51 was a pilot study for a larger Phase 3 study of a more resistant population than that studied in the RESIST trials. This study was designed to evaluate only PK and safety, but obviously the results imply a potentially negative impact on long term efficacy and resistance. Based on the results of this study, dual-boosted PI regimens including TPV/r cannot be recommended and should be discouraged at this time. Please refer to Dr. Gibbs's review of 1182.51 in Appendix 10.2 for further details.*

## **5.2 Pharmacodynamics**

A formal QT study is underway and the results are pending.

### 5.3 Exposure-Response Relationships

Exposure response analyses were conducted using the PK data from the definitive dose-finding study (Study 1182.52, N=160) and two pivotal studies (1182.12 and 1182.48 studies; N=291).

1. **Exposure-Viral Load Analysis:** The exposure response analysis of phase 2 and phase 3 studies consistently demonstrated that the probability of a patient's response to TPV/r treatment is related to inhibitory quotient (IQ =  $C_{min}/\text{corrected } IC_{50}$ ). However, due to the variability in pharmacokinetics of the drug and the variable degree of resistant virus, the range of resulting inhibitory quotient after the fixed doses are wide, which results in unpredictable virological response for individual patients. To maximize the likelihood of a patient's response, individualized dose by monitoring IQ is an alternative to the fixed dose regimen, but requires further prospective investigation.
2. **Exposure-ALT Analysis:** The incidence of Grade 3/4 ALT elevation is associated with TPV exposure, see Section 7.1.3.3 for details.

*MO comment: The above analyses were conducted by FDA reviewers post-hoc and so this information was not available during dose selection. The to-be-marketed dose of TPV/r was established from study 1182.52 and was chosen primarily because of the 3 doses studied it had the best efficacy/toxicity profile (Please see Dr. Gibbs's review of 1182.52 in Appendix 10.1.2 for details.)*

*BIPI will be asked to further evaluate the exposure-response and exposure-toxicity relationship of TPV/r in a prospective clinical trial.*

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

BIPI proposes that TPV/r 500/200mg administered orally twice daily be indicated for the treatment of  $\square$   $\square$  HIV infected patients.

*MO comment:  $\square$   $\square$  is too broad an indication for TPV/r given the limited population the drug has been studied in and the toxicity profile of the drug. The FDA intends to indicate the drug for HIV-1 infected adults with evidence of viral replication, who are heavily treatment experienced or have HIV-1 strains that are resistant to multiple PIs.*

### 6.1.1 Methods

Week 24 interim efficacy data for the two Phase 3 pivotal trials, 1182.12 (RESIST 1) and 1182.48 (RESIST 2) were reviewed in support of the proposed indication.

### 6.1.2 General Discussion of Endpoints

The primary endpoint for the integrated interim analyses of the RESIST trials was treatment response at Week 24. Treatment response is a composite endpoint of the proportion of patients with confirmed virologic response (defined as two consecutive VL measurements  $\geq 1 \log_{10}$  below baseline) without prior:

- Evidence of confirmed virological failure (defined as two consecutive VL measurements of  $<1 \log_{10}$  below baseline, or one VL measurement of  $<1 \log_{10}$  followed by permanent discontinuation or loss to follow-up), or
- Introduction of a new ARV to the regimen for reasons other than toxicity or intolerance clearly attributable to a background drug, but not the study drug or its control, or
- Permanent study drug discontinuation, or
- Death, or
- Loss to follow-up.

Time to treatment response corresponded to the first of the two VL measurements mentioned above.

*MO comment: Viral load is a validated surrogate and has been used as the primary endpoint to assess the activity and efficacy of antiretrovirals since 1997 in lieu of a clinical outcome. The use of this endpoint is supported by analyses showing an association between change in viral load and clinical outcome.*

Secondary endpoints for the integrated analysis of the two RESIST trials were:

- Week 24 for patients reaching this endpoint by database cutoff for submission dossier preparation (see Statistical Methods below; definition of patient populations) :
- Viral load and VL change from baseline to Week 24
- Virologic response (defined as a  $\geq 1 \log_{10}$  reduction in VL from baseline)
- Occurrence of VL  $<400$  copies/mL
- Occurrence of VL  $<50$  copies/mL
- CD4+ cell count and change in CD4+ cell count from baseline to Week 24
- Week 16 for all patients randomized and treated:
- Viral load and VL change from baseline to Week 16
- Virologic response (defined as a  $\geq 1 \log_{10}$  reduction in VL from baseline)
- Occurrence of VL  $<400$  copies/mL
- Occurrence of VL  $<50$  copies/mL
- CD4+ cell count and change in CD4+ cell count from baseline to Week 16

### 6.1.3 Study Design

RESIST 1 (1182.12) and RESIST 2 (1182.48), were Phase 3 multi-center, multi-national, randomized, controlled, open-label comparative efficacy and safety study of TPV/r 500 mg/200 mg twice a day (BID) compared with a genotypically-defined RTV boosted comparator protease inhibitors (comparator PI/r or CPI/r), namely LPV/r, SQV/r, AMP/r or IDV/r.

*MO comment: These trials were designed as open-label for the following reasons: 1) Abbott Laboratories, the manufacturers of RTV, refuse to make a RTV placebo, so all trials that include RTV can never be fully blinded. 2) Given the four different PI regimens, the daily pill burden would be excessive.*

These studies were conducted in HIV-positive, multiple ARV-experienced male and female patients who were  $\geq 18$  years old. All patients must have had at least 3 consecutive months' experience with all three classes of ARVs (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], and PIs) and must have taken at least two PI-based regimens for at least 3 months, one of which was the current treatment regimen. Patients could have had any CD4+ cell count to be eligible and were to have a VL of  $>1000$  copies/mL at screening.

Patients were eligible if their genotyping demonstrated at least one protocol-specified protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and no more than two mutations at codons 33, 82, 84, or 90. Prior to randomization Investigators had to preselect the CPI/r and predetermine whether or not ENF would be used as part of the ARV regimen. LPV/r was the PI of choice if genotypically available. Genotype resistance assessments were performed using the TruGene®, Version 1.0, HIV-1 genotyping assay; but if the initial screening sample was not successfully amplified and genotyped, the test was repeated using the TruGene®, Version 1.5, HIV-1 genotyping assay. For these ongoing trials, the primary efficacy endpoint is the proportion of patients with a treatment response ( $\geq 1 \log_{10}$  reduction in two consecutive VL measurements without prior evidence of treatment failure) at 24 weeks for the interim analysis and then again at 48 weeks for the final analysis. The studies were originally designed to continue through 96 weeks.

The two major differences between the RESIST trials were 1) RESIST 1 was conducted in the United States, Canada and Australia, while RESIST 2 was conducted in Europe and Latin America; and 2) RESIST 1 performed a 24 week interim analyses while RESIST 2 performed a 16 week interim analyses.

*MO comment: The 16 Week interim analysis in RESIST 2 was deemed adequate for accelerated approval by the EMEA; however, DAVDP did not agree that 16 week data were adequate. BIPI and DAVDP agreed at the End of Phase (EOP) 2 meeting that for this accelerated approval NDA BIPI would submit 24-week efficacy data on all 620 patients from RESIST 1 and 539 out of 863 patients, who were able to reach 24 weeks in RESIST 2.*

At Week 8 patients in the CPI/r group who had a lack of initial virologic response (defined as a  $< 0.5 \log_{10}$  decrease or  $\geq 0.5 \log_{10}$  decrease, but viral load not less than 100,000 copies/mL) were allowed to enroll in the roll-over trial, 1182.17, where all patients received TPV/r 500mg/200mg.

The studies were initially designed to show non-inferiority of TPV/r compared to the CPI/r. However, Amendment 2 changed the protocol so that patients, who were pan-resistant, as per their genotype, to all available PIs could be enrolled into RESIST 1 and 2.

*MO comment: The FDA review team strongly recommended to BIPI that in light of Amendment 2 the data be analyzed to test for superiority of efficacy of TPV/r versus CPI/r, since the control group no longer represented a completely active control.*

#### 6.1.4 Efficacy Findings

Baseline characteristics of patients enrolled in the RESIST studies are summarized in the Table below. The majority of patients in the RESIST trials were Caucasian (68-77%) males (84-91%) with a median age of 42-44 years and a median baseline VL of 4.8  $\log_{10}$ .

Table 6.1.4:1 Baseline Characteristics in RESIST 1 and RESIST 2

	RESIST 1	RESIST 2
<b># of Patients Randomized</b>	630	880
<b># of Patients Treated</b>	620	863
Age (Years)		
Mean	45	43
Median	44	42
Range	24, 80	17, 76
Sex (%)		
Male	91	84
Female	9	16
Race (%)		
Caucasian	77	68
Black	22	5
Asian	1	1
Missing	0	26
Weight (kilograms)		
Mean	76	69
Median	75	68
Range	35, 151	32, 118
CD4 Cell Count (cells/mm <sup>3</sup> )		
Mean	164	224
Median	123	189
Range		

	RESIST 1	RESIST 2
<b># of Patients Randomized</b>	630	880
<b># of Patients Treated</b>	620	863
HIV RNA (log <sub>10</sub> copies/mL)		
Mean	4.7	4.8
Median	4.8	4.8
Range	□	∩
Proportions w/ HIV RNA (copies/mL)		
< 10,000	16%	15%
≥ 10,000 to <100,000	43%	49%
≥ 100,000	41%	36%
Hepatitis B + Hepatitis C+ Hepatitis B and C+	5% 7% 0.5%	5% 14% 0.9%
Stage of HIV Infection (CDC Class)		
Class A	24%	17%
Class B	19%	27%
Class C	57%	56%
Protease Inhibitor Stratum		
APV	14%	40%
IDV	4%	3%
LPV	61%	38%
SQV	21%	20%
Genotypic Resistance to Pre- selected PI		
Not Resistant	8%	20%
Possibly Resistant	35%	6%
Resistant	57%	74%
Actual use of ENF		
Yes	36%	12%
No	64%	88%

The two pivotal trials were essentially balanced with a few notable exceptions (highlighted text in table). There were more female subjects enrolled in RESIST 2 as compared to RESIST 1 (16% versus 9%).

*MO comment: Overall both studies enrolled very few women, which is not unusual in studies of advanced HIV patient. However, BIPI reports that no special efforts or considerations were made to increase the enrollment of women in the RESIST studies.*

RESIST 1 appeared to have a slightly more advanced population with a lower median CD4 cell count (123 versus 189 cells/mm<sup>3</sup>) and more patients having VL > 100,000

copies/mL (41% versus 36%) as compared to RESIST 2. There was also twice as much Hepatitis C co-infection on RESIST 2 as compared to RESIST 1 (14% versus 7%).

*MO comment: Although RESIST 2 had double the amount of Hepatitis C co-infection as RESIST 1, overall the rate of Hepatitis C co-infection was low compared to the rate of Hepatitis C co-infection seen in the general HIV-1 infection population (approximately 1/3 of patients with HIV are co-infected with Hepatitis C in the U.S. and Europe<sup>1-4</sup>).*

In terms of on study treatment, the PI of choice, LPV, was pre-selected 61% of the time in RESIST 1 while in RESIST 2 LPV and APV were pre-selected with similar frequency, 38% and 40% respectively. Of note, enfuvirtide (T20) was used much more frequently in RESIST 1 (36%) than it was in RESIST 2 (12%).

In terms of PI resistance patients in RESIST 2 were more likely to be resistant or possibly resistant to their preselected PI (90%) than the RESIST 1 population (82%).

*MO comment: Different assays were used for determining resistance in the RESIST trials (TruGene Assay in RESIST 1 and Virtual Phenotype or TruGene Assay in RESIST 2), which likely lead to the different rates of “not resistant, possibly resistant and resistant” being reported in the two studies. In addition the assays measured the virus’s sensitivity to the unboosted PI and all of the PIs in these trials were boosted by RTV, so the true rate of resistance to the comparator PIs is unknown. However, these are the data that were used in pre-selecting a PI and constructing the best available ARV regimen and therefore the data were analyzed as a part of Dr. Bore’s sensitivity analyses.*

The treatment groups in both studies were balanced with regard to demographics. The majority of patients were male (88%), the mean age was 44 years (range 17 to 80), 73% identified as white, 14% identified as black, 1% identified as Asian. The median baseline plasma HIV-1 RNA was 4.82 (range 2 to 6.8) log<sub>10</sub> copies/mL and median baseline CD4+ cell count was 155 (range 1 to 1893) cells/mm<sup>3</sup>. Forty percent (40%) of the patients had baseline HIV-1 RNA of ≥100,000 copies/mL, 61% had a baseline CD4+ cell count <200 cells/mm<sup>3</sup>, and 57% had experienced an AIDS defining Class C event at baseline.

*MO comment: Twenty-six percent of patients did not identify a race likely due to laws prohibiting the collection of race data in certain countries.*

Table 6.1.4:2 presents the primary efficacy outcome of patients in the Intent to Treat population (ITT).

**Table 6.1.4:2 Treatment Outcomes at Week 24 based on Time to Loss of Virologic Response—RESIST 1 and RESIST 2 trials**

	RESIST 1 Trial (1182.12)		RESIST 2 Trial (1182.48)		Total	
	TPV/r + OBR	CPI/r + OBR	TPV/r + OBR	CPI/r + OBR	TPV/r + OBR	CPI/r + OBR
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<b>Total treated</b>	311 (100)	309 (100)	271 (100)	268 (100)	582 (100)	577 (100)
<b>Treatment response at Week 24</b>	<b>126 (41)</b>	<b>65 (21)</b>	<b>108 (40)</b>	<b>38 (14)</b>	<b>234 (40)</b>	<b>103 (18)</b>
<b>No confirmed 1 log<sub>10</sub> drop from baseline</b>	<b>171 (55)</b>	<b>233 (75)</b>	<b>141 (52)</b>	<b>223 (83)</b>	<b>312 (54)</b>	<b>456 (79)</b>
Initial Lack of Virologic Response by Week 8	108 (35)	164 (53)	95 (35)	176 (66)	203 (35)	340 (59)
Rebound	40 (13)	41 (13)	28 (10)	26 (10)	68 (12)	67 (11)
Never suppressed	23 (7)	28 (9)	18 (7)	21 (8)	41 (7)	49 (8)
Added ARV drug	7 (2)	6 (2)	15 (6)	3 (1)	22 (4)	9 (2)
Death	0	0	0	1 (<1)	0	1 (<1)
Discontinued while suppressed	1 (<1)	2 (1)	4 (1)	1 (<1)	5 (1)	3 (1)
Discontinued due to adverse events	3 (1)	1 (0)	3 (1)	2 (1)	6 (1)	3 (1)
Discontinued due to other reasons	3 (1)	2 (1)	0 (0)	0 (0)	3 (1)	2 (0)
Consent withdrawn	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Lost to follow-up	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)
Non-compliant	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Protocol violation	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)

TPV/r = Tipranavir + Ritonavir

CPI/r = Comparator Protease Inhibitor (one of Lopinavir, Amprenavir, Saquinavir, Indinavir) + Ritonavir

OBR = Optimized Background Regimen

Source: FDA Statistical Reviewer's Analysis

Outcomes for patients in the RESIST trials were largely made up of virologic responders and virologic failures. Other treatment outcomes contributed very little to the overall outcomes.

At Week 24, for the combined RESIST studies the proportion of responders with confirmed 1 log drop in VL was 40% on the TPV/r arm and 18% on the CPI/r arm. This difference in proportions was highly statistically significant with a p-value of < 0.001

*MO comment: The CPI/r group was a suboptimal control with the majority of patients being defined as resistant or possibly resistant to the assigned PI,  $\zeta$*

*] cannot be made based on the data reviewed.*

A sensitivity analysis performed by Dr. Bhore showed that the virologic failures in both treatment groups were largely made up of patients who met the initial criteria for Week 8 definition of lack of virologic response. In a sensitivity analysis Dr. Bhore deemed patients on the CPI/r arm failures as protocol defined, as well as deemed patients on the TPV/r arm who had a lack of virologic response at Week 8 failures.

*MO comment: The Week 8 lack of virologic response was an escape clause that allowed the CPI/r patients to leave the RESIST trials early and roll-over to 1182.17 where they received TPV/r. Given that these studies were open-label this escape clause was a large source of potential bias. Therefore, Dr. Bhore applied the same Week-8-lack-of-virologic-response criteria to both groups and evaluated the outcomes in a sensitivity analysis. The Week 8 lack of virologic response group was an excellent predictor of the 24 week response rate. The response rate at Week 8 was very similar to the response rate at Week 24, indicating that the patients who were responders at Week 24 were also responders at Week 8, and the majority of the non-responders at Week 8 continued to be non-responders at Week 24, whether on the CPI/r arm (most of whom discontinued study) or on the TPV/r arm (most of whom continued on study).*

Secondary efficacy analyses of the ITT population confirmed that TPV/r (N=582) was superior to the suboptimal CPI/r (N=577) arm for the following parameters through 24 Weeks of treatment:

- the median HIV-1 RNA change from baseline in patients receiving TPV/r versus CPI/r was -0.8 and -0.25 log<sub>10</sub> copies/mL, respectively.
- the median change from baseline in CD4+ cell count in patients receiving TPV/r versus CPI/r was +34 and +4 cells/mm<sup>3</sup>, respectively.
- The proportion of patients with HIV-1 RNA < 400 copies/mL was 34% on the TPV/r arm and 16% on the CPI/r arm
- The proportion of patients with HIV-1 RNA < 50 copies/mL was 23% and 9% on the TPV/r and CPI/r arms respectively

Another important efficacy analysis was the evaluation of TPV/r's treatment response with and without T20 (Table 6.1.4:4).

Table 6.1.4:4 Subgroup Analysis by Enfuvirtide (T-20) use of Treatment Response through 24 weeks (confirmed 1 log10 drop in HIV RNA from baseline)—RESIST 1 and RESIST 2 trials

<b>RESIST 1</b>					
Enfuvirtide (T-20) used actually?	TPV/r + OBR	CPI/r + OBR	Difference in proportions (TPV/r – CPI/r)(95% Confidence Interval)†	Test for treatment effect p-value‡	Test for treatment by subgroup interaction p-value§
Yes (36%)	67/119 (56%)	28/105(27%)	30% (17%, 42%)	< 0.0001	0.025*
No (64%)	59/192(31%)	37/204(18%)	13% (4%, 21%)	0.003	
<b>RESIST 2</b>					
Yes (12%)	21/39(54%)	2/23(9%)	45% (26%, 65%)	0.0004	0.036*
No (88%)	87/232(38%)	36/245(15%)	23% (15%, 30%)	< 0.0001	
<b>Both RESIST Trials combined</b>					
Yes (25%)	88/158(56%)	30/128(23%)	32% (22%, 43%)	<0.0001	0.022*
No (75%)	146/424(34%)	73/449(16%)	18% (13%, 24%)	<0.0001	

† Asymptotic confidence intervals based on normal distribution.

‡ p-value is based on the Mantel-Haenszel chi-square test.

§ p-value based on asymptotic normal test.

\* Treatment by subgroup interaction is statistically significant at 0.05 level.

Source: FDA Statistical Reviewer's Analysis.

In the RESIST trials, the treatment difference when T-20 was a part of the background regimen was 32% and when T-20 was not part of the background regimen the treatment difference was 18%. Both of these differences were statistically significant when compared to the CPI/r treatment response with and without T-20, thus TPV/r with or without T-20 is superior over the CPI/r with or without T-20. The difference within the TPV/r group is also statistically significant and supports the practice of using at least two active drugs in an ARV regimen.

As discussed in Section 4.5 over 50% of the patients in the RESIST trials had protocol violations deemed relevant by BIPI with a potential to influence efficacy outcomes. Dr. Bhore performed multiple sensitivity analyses of the primary outcome in which protocol violators were censored. The results are presented in the table below.

Table 6.1.4:5 Sensitivity Analyses of Primary Efficacy Endpoint (Proportion of Patients with confirmed 1 log drop in HIV RNA from Baseline) —RESIST 1 and RESIST 2 Studies Pooled

Potential Source of Open-label Bias addressed		Analysis Type	TPV/r + OBR N = 582	CPI/r + OBR N=577	Difference (TPV/r – CPI/r) (Two-sided Confidence Interval of 99.875% pooled for 2 studies)	p-value
1.	Post-randomization changes in the T-20 randomization strata	ITT analysis adjusting for wrong T-20 stratum	232 (40%)	126 (22%)	18% (9%, 26%)	<0.0001
2a.	Protocol Violations	Per-Protocol analysis excluding Treatment Regimen Violations	215/507 (42%)	98/480 (20%)	22% (13%, 31%)	<0.0001
2b.	Protocol Violations	Per-Protocol analysis excluding Screening Violations	191/465 (41%)	82/457 (18%)	23% (14%, 32%)	<0.0001
3.	Early discontinuations at Week 8 due to initial lack of virologic response	Primary Efficacy ITT analysis by FDA Statistical Reviewer	234 (40%)	103 (18%)	22% (14%, 31%)	<0.0001
4.	Potential Lack of Compliance identified by undetectable blood concentration levels at Weeks 2 and 4	ITT analysis treating all suspected non-compliant patients in the control CPI/r arm as success	234 (40%)	132 (23%)	17% (9%, 26%)	<0.0001

Source: FDA Statistical Reviewer's Analyses.

*MO comment: Although the percentage of protocol violators was very large, multiple sensitivity analyses in which the protocol violators were censored confirmed that the response rate on the TPV/r arm was statistically significantly higher than the response*

rate on the CPI/r arm. In addition to having virtually no impact on efficacy these protocol violations did not appear impact safety either.

### Subgroup Analyses

Dr. Bhore performed a number of subgroup analyses. Below are her analyses by gender, age and race.

Table 6.1.4:6 presents treatment response in the RESIST trials by gender. TPV/r was superior to the CPI/r arm in both the male and female subgroups. Of note, a greater proportion of female patients responded to TPV/r treatment versus male patients while the response rate on the CPI/r arm was similar amongst males and females. In RESIST 2, the subgroup of women was larger than in RESIST 1 and the treatment by subgroup interaction test for treatment difference in male versus female patients had a statistically significant p-value of 0.02.

Table 6.1.4:6 Subgroup Analysis by Gender of Treatment Response through 24 weeks (confirmed 1 log<sub>10</sub> drop in HIV RNA from baseline)—RESIST 1 and RESIST 2 trials

<b>RESIST 1</b>				
Gender	TPV/r + OBR	CPI/r + OBR	Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval) <sup>†</sup>	Test for treatment by subgroup interaction p-value <sup>‡</sup>
Male (91%)	112/278 (40%)	62/287 (22%)	19% (11%, 26%)	0.397
Female (9%)	14/33 (42%)	3/22 (14%)	29% (7%, 51%)	
<b>RESIST 2</b>				
Male (84%)	79/225 (35%)	31/229 (13%)	22% (14%, 29%)	0.021*
Female (16%)	29/46 (63%)	7/39 (18%)	45% (27%, 64%)	

OBR = Optimized Background Regimen of antiretroviral drugs

<sup>†</sup> Asymptotic confidence intervals based on normal distribution.

<sup>‡</sup> p-value based on asymptotic normal test.

\* Treatment by subgroup interaction may be present. However, sample size is low in the female subgroup.

Source: FDA Statistical Reviewer's Analysis.

*MO comment: PK results show that females on TPV/r have increased TPV exposures relative to males. In light of that data and the theory that TPV's efficacy is exposure sensitive the greater treatment response rate in females makes sense. At the same time*

these increased exposures may potentially translate into more AEs and safety issues for women.

In terms of race, analysis of each trial showed a different result. In RESIST 1, where 77% of patients were white and 22% of patients were black, there was a statistically significant difference in treatment response on the TPV/r arm with 46% of white patients responding versus 22% of black patients. However, in RESIST 2 where black only made up 5% of the study population there was no difference between whites and blacks in terms of response rate on the TPV/r or CPI/r arm (Table 6.1.4:7)

Table 6.1.4:7 Subgroup Analysis by Race of Treatment Response through 24 weeks (confirmed 1 log<sub>10</sub> drop in HIV RNA from baseline)—RESIST 1 and RESIST 2 trials

RESIST 1				
Race	TPV/r + OBR	CPI/r + OBR	Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval) <sup>†</sup>	Test for treatment by subgroup interaction (White vs. Non-white) p-value <sup>‡</sup>
White (77%)	110/241 (46%)	50/235 (21%)	24% (16%, 33%)	0.006*
Black (22%)	15/68 (22%)	14/69 (20%)	2% (-12%, 15%)	
Asian (1%)	1/2	1/5	NA	
RESIST 2				
White (68%)	72/189 (38%)	27/179 (15%)	23% (14%, 32%)	0.247
Black (5%)	7/15 (47%)	1/11 (9%)	38% (7%, 68%)	
Asian (1%)	1/2	0/3	NA	
Not reported (France) (26%)	28/65 (43%)	10/75 (13%)	30% (15%, 44%)	

OBR = Optimized Background Regimen of antiretroviral drugs  
<sup>†</sup> Asymptotic confidence intervals based on normal distribution.  
<sup>‡</sup> p-value based on asymptotic normal test.  
\* Treatment by subgroup interaction may be present. However sample size in the non-white subgroups are low.  
NA = Number of patients in subgroup are too small to provide meaningful confidence intervals.  
Source: FDA Statistical Reviewer's Analysis.

MO comment: RESIST 2 data are less reliable for this subgroup analysis because 26% of patients did not report a race. Although this is a subgroup analysis of a relatively small group, it is concerning that there appears to be no difference between a suboptimal

control group and TPV/r in black patients. This finding needs to be further evaluated in a prospective manner.

Subgroup analysis by age did not reveal any significant treatment differences within treatment groups and once again TPV/r maintained its superior treatment response over the CPI/r group (Table 6.1.4:8).

Table 6.1.4:8 Subgroup Analysis by Age of Treatment Response through 24 weeks (confirmed 1 log<sub>10</sub> drop in HIV RNA from baseline)—RESIST 1 and RESIST 2 trials

<b>RESIST 1</b>				
Median Age	TPV/r + OBR	CPI/r + OBR	Treatment Effect, i.e., Difference in proportions (TPV/r – CPI/r)(95% Confidence Interval) <sup>†</sup>	Test for treatment by subgroup interaction p-value <sup>‡</sup>
<=43 years (48%)	53/139 (38%)	36/157(23%)	15% (5%, 26%)	0.260
> 43 years (52%)	73/172(42%)	29/152(19%)	23% (14%, 33%)	
>=65 years	2/5	0/2		
<b>RESIST 2</b>				
<=43 years (59%)	71/161(44%)	22/157(14%)	30% (21%, 39%)	0.141*
> 43 years (41%)	37/110(34%)	16/111(14%)	19% (8%, 30%)	
>=65 years	½	1/7		

OBR = Optimized Background Regimen of antiretroviral drugs

<sup>†</sup> Asymptotic confidence intervals based on normal distribution.

<sup>‡</sup> p-value based on asymptotic normal test.

\* Treatment by subgroup interaction may be present.

Source: FDA Statistical Reviewer's Analysis.

*MO comment: It is important to note that there were only 16 patients in the RESIST trials who were 65 years of age or older, so no conclusions can be made about the geriatric population.*

### 6.1.5 Clinical Microbiology

Please refer to Dr. Lisa Naeger's Microbiology review for detailed analyses of the microbiology data for this NDA. Below is a summary of Dr. Naeger's findings.

Tipranavir (TPV), a protease inhibitor, has 50% inhibitory concentrations (IC<sub>50</sub> value) ranging from 40 to 390 nM against laboratory HIV-1 strains grown *in vitro* in PBMCs and cell lines. The average IC<sub>50</sub> value for multi PI-resistant clinical HIV-1 isolates was 240 nM (range 50 to 380 nM). Human plasma binding resulted in a 4-fold shift in the antiviral activity. Ninety percent (94/105) of HIV-1 isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, or SQV had ≤3-fold decreased susceptibility to TPV.

Because TPV will be administered to HIV-positive patients as part of a combination ARV regimen, the activity of TPV in combination with other ARV drugs was determined in cell culture to assess the impact of potential *in vitro* drug interactions on overall antiviral activity. Additive to antagonistic relationships were seen with combinations of TPV with other PIs. Combinations of TPV with the NRTIs were generally additive, but additive to antagonistic for TPV in combination with ddI and 3TC. Combinations of TPV with DLV and NVP were additive and with EFV were additive to antagonistic. Activity of TPV with enfuvirtide (T20) was synergistic.

#### **In Vitro Selection of TPV-Resistant Viruses**

TPV-resistant viruses were selected *in vitro* when wild-type HIV-1<sub>NL4-3</sub> was serially passaged in the presence of increasing concentrations of TPV in tissue culture. Amino acid substitutions L33F and I84V emerged initially at passage 16 (0.8 μM), producing a 1.7-fold decrease in TPV susceptibility. Viruses with >10-fold decreased TPV susceptibility were selected at drug concentrations of 5 μM with the accumulation of six protease mutations (I13V, V32I, L33F, K45I, V82L, I84V). After 70 serial passages (9 months), HIV-1 variants with 70-fold decreased susceptibility to TPV were selected and had 10 mutations arising in this order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V. Mutations in the CA/P2 protease cleavage site and transframe region were also detected by passage 39. TPV-resistant viruses showed decreased susceptibility to all currently available protease inhibitors except SQV. SQV had a 2.5-fold change in susceptibility to the TPV-resistant virus with 10 protease mutations.

#### **Clinical TPV Resistance**

BIPI submitted genotypes from 1482 isolates and 454 phenotypes from the two pivotal Phase 3 trials, RESIST 1 and RESIST 2, for review.

In the comparator arm (CPI/r), most patients received LPV/RTV (n=358) followed by APV/RTV (n=194), SQV/RTV (n=162) and IDV/RTV (n=23). The patient populations in RESIST 1 and 2 were highly treatment-experienced with a median number of 4 (range 1-7) PIs received prior to study. In the combined RESIST trials 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 treatment arms from both studies were balanced with respect to baseline genotypic and phenotypic resistance. Baseline phenotypic resistance was equivalent between the TPV/r arm (n=745) and the CPI/r arm (n=737) with 30% of the isolates resistant to TPV at baseline and 80-90% of the isolates resistant to the other PIs - APV, ATV, IDV, LPV, NFV, RTV or SQV. The number of PI-resistance mutations was equivalent between the TPV/r and CPI/r arms in RESIST 1 and 2 and the median number of baseline PI, NRTI and NNRTI mutations was equivalent between arms in both studies.

#### **Mutations Developing on TPV Treatment**

TPV/r-resistant isolates were analyzed from treatment-experienced patients in Study 1182.52 (n=32) and RESIST 1 and 2 (n=59) who experienced virologic failure. The most common mutations that developed in greater than 20% of these TPV/r virologic failure isolates were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V. Other mutations that developed in 10 to 20% of the TPV/r virologic failure isolates included E34D/R/Q/H, I47V, I54V/A/M, K55R, A71V/I/L/F, and L89V/M/W. In RESIST 1 and 2, TPV/r resistance developed in the virologic failures (n=59) at an average of 38 weeks with an average decrease of >30-fold in TPV susceptibility from baseline. The resistance profile in treatment-naïve subjects has not yet been characterized.

#### **Baseline Genotype/Phenotype and Virologic Outcome Analyses**

The FDA analyses of virologic outcome by baseline resistance are based on the As-Treated population from studies RESIST 1 and 2. To assess outcome, several endpoints including the primary endpoint (proportion of responders with confirmed 1 log<sub>10</sub> decrease at Week 24), DAVG24, and median change from baseline at weeks 2, 4, 8, 16, and 24 were evaluated. In addition, because patients were stratified based on enfuvirtide (T20) use, we examined virologic outcomes in three separate groups - overall (All), patients not receiving T20 (No T20), and patients receiving T20 (+T20) as part of the optimized background regimen. We focused on the No T20 group in order to assess baseline resistance predictors of virologic success and failure for TPV/r without the additive effect of T20 use on the overall response.

Both the number and type of baseline PI mutations affected response rates in RESIST 1 and 2. Virologic responses were analyzed by the presence at baseline of each of 25 different protease amino acids using both the primary endpoint (>1log<sub>10</sub> decrease from baseline) and DAVG24. Reduced virologic responses were seen in TPV/r-treated patients when isolates had a baseline substitution at position I13, V32, M36, I47, Q58, D60 or I84. The reduction in virologic responses for these baseline substitutions was most prominent in the No T20 subgroup. Virologic responses were similar or greater than the overall responses for each subgroup (All, No T20, +T20) when these amino acid positions were wild-type. In addition, virologic responses to substitutions at position V82 varied depending on the substitution. Interestingly, substitutions V82S or F or I or L, but not V82A or T or C, had reduced virologic responses compared to the overall.

Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. In these analyses, any changes at protease amino acid positions - D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 and L90 were counted if present at baseline. These PI mutations were used based on their association with reduced susceptibility to currently approved PIs, as reported in various publications.

Regardless of the endpoint used for these analyses, the response rates were greater for the TPV/r treatment arm compared to the CPI/r arm. In both the TPV/r and CPI/r arms of RESIST 1 and 2, response rates were similar to or greater than the overall response rates for the respective treatment groups for patients with one to four PI mutations at baseline. Response rates were reduced if five or more PI-associated mutations were present at baseline. For patients who did not use T20, 28% in the TPV/r arm and 11% in the CPI/r arm had a confirmed 1 log<sub>10</sub> decrease at Week 24 if they had five or more PI mutations in their HIV at baseline. The patients with five or more PI mutations in their HIV at baseline and not receiving T20 in their OBT achieved a 0.86 log<sub>10</sub> median DAVG24 decrease in viral load on TPV/r treatment compared to a 0.23 log<sub>10</sub> median DAVG24 decrease in viral load on CPI/r treatment. In general, regardless of the number of baseline PI mutations or T20 use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 log<sub>10</sub> decrease at Week 24) and greater declines in viral load by median DAVG24 than the CPI/r arm.

An examination of the median change from baseline of HIV RNA at weeks 2, 4, 8, 16 and 24 by number of baseline PI mutations (1-4 and 5+) showed the largest decline in viral load by Week 2 for all groups with the greatest decline observed in the TPV/r arms. A 1.5 log<sub>10</sub> decrease in viral load at Week 2 was observed for patients receiving TPV/r regardless of the number of baseline PI mutations (1-4 or 5+). Sustained viral load decreases (1.5 – 2 log<sub>10</sub>) through Week 24 were observed in patients receiving TPV/r and T20. However, patients who received TPV/r without T20 and who had five or more baseline PI mutations group began to lose antiviral activity between Weeks 4 and 8.

#### **Proportion of Responders by Baseline TPV Phenotype**

TPV/r response rates were also assessed by baseline TPV phenotype. Again, focusing on the No T20 group in order to more accurately assess the effect of baseline phenotype on virologic success for TPV/r. With no T20 use, the proportion of responders was 45% if the fold change in IC<sub>50</sub> value from reference of TPV susceptibility was 3-fold or less at baseline. The proportion of responders decreased to 21% when the TPV baseline phenotype values were >3- to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

#### **6.1.5.1 Efficacy Conclusions**

FDA analysis confirmed that a statistically significantly greater proportion of patients on TPV/r achieved at least a 1 log<sub>10</sub> decrease in the surrogate endpoint of viral load at 24 weeks as compared to the suboptimal CPI/r group. Sensitivity analyses adjusting for open-label biases in the RESIST trials also confirmed the superiority of TPV/r over the suboptimal CPI/r arm. Efficacy of TPV/r was demonstrated regardless of T-20 use, but the efficacy was significantly greater when combined with T-20

Additional efficacy information is need in the subgroup of black patients. Based on the limited data in this application this subgroup did not derive any additional benefit from TPV/r over that of the suboptimal control.

TPV is a protease inhibitor with antiviral activity against multi PI-resistant clinical HIV-1 isolates. The most common protease mutations that developed in >20% of isolates from treatment- experience patients who failed on TPV/r treatment were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V. The resistance profile in treatment-naive patients has not yet been characterized. Both the number and type of baseline PI mutations affected response rates to TPV/r in RESIST 1 and 2. Virologic response rates in TPV/RTV-treated patients were reduced when isolates with substitutions at positions I13, V32, M36, I47, Q58, D60 or I84 and substitutions V82S/F/I/L were present at baseline. Virologic responses to TPV/r at week 24 decreased when the number of baseline PI mutation was 5 or more. Patients taking enfuvirtide with TPV/r were able to achieve >1.5 log<sub>10</sub> reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations. Virologic responses to TPV/r decreased in Resist 1 and 2 when the baseline phenotype for TPV was >3.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Studies 1182.12 (RESIST 1) and 1182.48 (RESIST 2) are the two randomized, controlled pivotal Phase 3 studies of TPV. The similarity in study design of these two studies allowed for the direct comparison of results from both trials and an integrated presentation of the FDA safety analysis. FDA safety analysis was done separately for each study. If a potential safety signal was identified in either study then the other study was analyzed for confirmation. For each RESIST 1 and 2, the final study reports, case report forms, and summary of clinical safety were reviewed (SCS) and the data provided in the case report tabulations were analyzed in great detail.

*MO comment: Throughout this Safety Review AEs are presented as straight proportions rather than by duration of exposure.*

Studies 1182.17 (the Rollover study) and 1182.58 (Open Label Safety Study) were also reviewed in detail; however, since neither study was controlled the data were not pooled with the RESIST trials data. Instead the data reviewed for these two studies will be described as further supportive evidence of what was observed in the RESIST trials.

*MO comment: The Open Label Safety Study (OLSS), 1182.58, was designed to only capture SAEs and AEs that lead to discontinuation. Given the study design limitations those data will only be presented in the appropriate sections of the Safety Review.*

The other 35 clinical trials were reviewed in less detail and the results of only significant findings or findings, which significantly strengthened or contradicted conclusions drawn in the RESIST trials are presented below.

For the interim analysis of both studies BI assessed the following primary safety endpoints: the proportion of patients reporting AEs and the proportion of patients reporting SAEs. The secondary safety endpoints assessed were the proportion of patients reporting AEs by severity and action taken with regard to test drug, proportion of patients with laboratory test abnormalities by DAIDS grading, laboratory test value changes over time, and discontinuations due to AEs.

BI used both the “Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences” and the “Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences for Vaccine & Prevention Research Programs” to report AEs and laboratory test abnormalities during the trial.

*MO Comment: The DAIDS Table for Grading Severity of Adult Adverse Experiences for Vaccine & Prevention Research Programs was used in error at the beginning of the trial and was corrected as per Amendment 6 to IND 51,979, June 16, 2004 to use the appropriate DAIDS Table for Grading Severity of Adult Adverse Experiences. As per BI this error resulted in a small number of patients being enrolled into the trials with > Grade 1 ALT or AST value.*

For laboratory test abnormalities not defined in the DAIDS grading scale, the Common Toxicity Criteria was used (namely, for grading total cholesterol, carbon dioxide and creatine phosphokinase). For abnormalities not defined in the DAIDS or CTC grading scales investigators were instructed to list them as mild moderate or severe.

*MO Comment: Two study design flaws were discovered just prior to the submission of the NDA:*

- 1. Clinical adverse events were captured as mild, moderate and severe and not as Grade 1-4. Mild corresponded to Grade 1, moderate corresponded to Grade 2, severe corresponded to Grade 3 and Grade 4. Given that Grade 3 and 4 clinical adverse events were not captured discretely it is unknown what the true frequency of severe events versus life threatening events was.*
- 2. BIPI designed the RESIST trials to capture data for only five half-lives (namely, 3 days) after the subject discontinued study unless that subject had an unresolved AE. Therefore AEs that may have started shortly after study drug discontinuation, but outside of the 3-day window, were not routinely captured. During the Pre-NDA meeting with BIPI this study design flaw was brought to the attention of the FDA, and the FDA instructed BIPI to amend all ongoing studies to include a 30-day follow-up period. This reviewer defined the treatment period” as day 1 of treatment through a 30 day follow-up period post treatment and analyzed all AE data using this criterion.*

### 7.1.1 Deaths

BI reports “a total of 103 death cases representing 102 patients who died” during the entire TPV clinical development program up through the database locking of pivotal studies 1182.12 and 1182.48 on June 11, 2004. One of the 102 deaths, subject 3270 experienced an SAE (progressive multifocal leukoencephalopathy, PML) while he was being treated with CPI/r in Trial 1182.48. This subject later switched into Trial 1182.17 as subject no. 483270 and died as a result of worsening PML while receiving TPV/r. Therefore, this subject's death is counted twice: once in Trial 1182.48 (attributed to CPI/r) and once in Trial 1182.17 (attributed to TPV), hence the 103 death cases.

*MO comment: For the FDA clinical review a subject's death will be considered and counted only one time. In other words subject 483270 is only counted once and attributed to study 1182.17, since the subject was off the comparator drug for approximately 47 days and on TPV/r for that same duration. This decision is based on a set of criteria chosen by this reviewer for analyzing deaths in the TPV development program (see below).*

All of the TPV clinical development program deaths were in HIV-positive, ARV experienced, adult patients. No HIV negative, HIV+ naïve, or HIV+ pediatric patients have died as of June 11, 2004.

A total of 57 of the 103 death cases (55.3%) were reported in the US. The next highest number of death cases were reported in France (n = 15, 14.6%). Proportionally, the number of death cases in the US and France is consistent with the number of patients receiving TPV/r in these 2 countries (42.1% treated in the US, and 12.1% treated in France).

*MO Comment: DAVDP and BI agree on the total number of deaths, however in a few cases the study to which the death was attributed and whether the death was pre-, on- or post-treatment differed. These differences will be highlighted throughout the review as each case is discussed. This reviewer used the same database cutoff date used to create the Summary of Clinical Safety (SCS), June 11, 2004, as the cutoff date for deaths, since this represents all the audited data to date in the drug development program.*

Table # below outlines the number of deaths per trial, treatment period and treatment arm (if applicable).

*MO comment: To ensure that subject deaths were ascribed to the correct study this reviewer performed several analyses and applied the following criteria:*

- 1. Any subject who died prior to taking any study drug was considered a pretreatment death.*
- 2. Any subject who died while on treatment or within 30 days of discontinuing study drug was considered an “on-treatment” death.*
- 3. Any subject who died > 30 days after discontinuing study drug was considered a “post-treatment” death.*

4. All patients who rolled over to study 1182.17 were evaluated to determine how long they were off the original study and on 1182.17. If they were off the original study for greater than 30 day and on study 1182.17 at the time of death then the above criteria were applied. If they were on 1182.17 for less than 30 days at the time of death then the death was attributable to the study of origin.

Table 7.1.1:1 Cummulative TPV Development Program Subject Deaths Through June 11, 2004

Study	Pre-tx	TPV or TPV/r			CPI/r		
		On-tx	Post-tx (>30 days off study drug)	TPV total	On-tx	Post-tx (>30 days off study drug)	CPI/rTotal
1182.12	6	10	4	14	7	1	8
1182.48	4	5	0	5	6	0	6
1182.51	0	2	1	3	n/a	n/a	n/a
1182.52	1	2	2	4	n/a	n/a	n/a
1182.17	0	13	8	21	n/a	n/a	n/a
1182.58	1	19	6	25	n/a	n/a	n/a
1182.1	0	2	0	2	n/a	n/a	n/a
1182.4	0	1	0	1	n/a	n/a	n/a
1182.6	0	1	0	1	n/a	n/a	n/a
Total	12	55	21	76	13	1	14

MO comment: FDA and BI concur on the total number of deaths as 102. However there are a few discrepancies with respect to the study a death was attributed to and whether the death was pre-, on- or post-drug exposure.

BI reports a total of 13 pretreatment deaths, but this reviewer found only 12 pretreatment deaths. Subject 2060 in study 1182.12 was listed by the sponsor as dying in the pretreatment phase; however, all supportive data indicate that the subject was on study drug for 9 days prior to dying, so subject 2060 is listed as an "on-treatment" death in the FDA analysis. Therefore the FDA analysis reports 6 pretreatment deaths and 10 on treatment deaths in 1182.12 and a total of 12 pretreatment deaths in the TPV development program.

Although in the SCS BI reports that subject 3270 is counted as two death cases: once in 1182.48 and once in 1182.17; subject 3270 is only reported once in the datasets as a death for study 1182.48. This reviewer believes that subject 3270 should be considered only once and his death should be attributed to study 1182.17 (as per the aforementioned criteria), since he died more than 30 days off the CPI/r.

*BI reports subject 121543 as a 1182.17 on study death; however, subject 121543 rolled over to 1182.17 one day after discontinuing 1182.12 and died 5 days later as the result of an AE (lymphoma) that started while on 1182.12. Based on the criteria listed above, this reviewer determined that subject 121543's death should be attributed to the CPI/r arm of study 1182.12. This reclassification results in 7 on-study deaths for the CPI/r arm of study 1182.12 and 12 on study deaths for study 1182.17.*

In total 12 patients died during the pretreatment phase and 90 patients died after being exposed to at least one dose of drug, which will be referred to as post-drug exposure. Three of the 90 post-drug exposure subject deaths were considered to be possibly TPV/r treatment related. Subject 521394 from the rollover study 1182.17 died of acute renal failure, but the subject had a history of chronic renal disease and was on a number of potentially nephrotoxic agents. Subject 121025 from the rollover study 1182.17 died of multi-system organ failure including hepatic failure. The subject had a history of fatty liver disease and was taking other potentially hepatotoxic medications at the time of death. Subject 215 in study 1182.6 died from respiratory failure and brain stem infarction subsequent to developing elevated liver enzymes and lactic acidosis.

*MO comment: This reviewer agrees with the assessment of the above patients whose deaths were felt to be potentially related to TPV/r with one exception. BI assessed that subject 215 developed elevated liver enzymes while on TPV/r and developed the lactic acidosis some time after stopping TPV/r and that the two events were unlikely to be related. Based on the evidence provided the subject actually had an anion gap of 20 while his LFTs were still abnormal. So the abnormal LFTs and acidosis did occur simultaneously and the two events cannot be deemed unrelated to each other or TPV/r use.*

The following table presents key characteristics of the patients who died in the pivotal studies, 1182.12 (Resist 1) and 1182.48 (Resist 2).

**Table 7.1.1:2 Characteristics of Patients who Died in Resist 1 and Resist 2 per FDA Analysis**

	Resist 1		Resist 2		Total	
	TPV/r (%) N=311	CPI/r (%) N=309	TPV/r (%) N=435	CPI/r (%) N=428	TPV/r (%) N=746	CPI/r (%) N=737
# of patients who died	14 (4.5)	8 (2.6)	5 (1.1)	6 (1.4)	19 (2.5)	14 (1.9)
Gender						
M	14 (100)	7 (86)	4 (80)	6 (100)	18 (95)	13 (93)
F	0	1 (14)	1 (20)	0	1 (5)	1 (7)
Mean age	47	45.4	48	43.8	46.5	44.7
Median treatment duration [days]	134.5	120	100	65	123	95

	Resist 1		Resist 2		Total	
	TPV/r (%) N=311	CPI/r (%) N=309	TPV/r (%) N=435	CPI/r (%) N=428	TPV/r (%) N=746	CPI/r (%) N=737
Median baseline VL	5.00	4.91	5.09	4.95	5.05	4.95
Median last available VL	4.45	4.16	4.58	4.91	4.48	4.67
Median baseline CD4+ count [cell/mm <sup>3</sup> ]	13.75	157	15	39	15	102.25
Median last CD4+ count [cell/mm <sup>3</sup> ]	13	161	8	28	11	67.5
Causes of death by SOC						
Cardiac d/o	1	0	0	2	1	2
Hepatobiliary d/o	1	0	0	0	1	0
Infections	4	2	1	1	5	3
Neoplasms	4	4	2	2	6	6
Respiratory d/o	2	0	0	0	2	0
Unknown	0	0	1	0	1	0
General disorders and administration	1	1	1	1	2	2

Source: Corporate safety death dataset 12/5/04

Overall there are more deaths in Resist 1 than in Resist 2 (22 versus 11), and there are more deaths on the TPV/r arms compared to the CPI/r arms (19 versus 14). In Resist 1 there are two major differences between the two arms: 1. The number of deaths on the TPV/r arm are nearly double the number of deaths on the CPI/r arm (14 versus 8), and 2. the TPV/r arm has a much lower median baseline and last CD4+ count as compared to the CPI/r arm (baseline 13.75 versus 149; last 13 versus 158). There is also a difference in the baseline and last CD4+ counts of the TPV/r arm versus the CPI/r arm in Resist 2; however, the difference is not nearly as dramatic as in Resist 1. None of the deaths in the Resist trials were considered by the investigator to be potentially drug related.

*MO comment: It is impossible to say whether the difference in the death rate on the TPV/r arm versus the CPI/r arm in RESIST 1 is real or meaningful. What can be said is that at this early time point in a trial not designed to detect a clinical benefit no clinical benefit in terms of mortality was observed in the TPV/r arm as compared to the CPI/r arm.*

*The difference in baseline and last CD4+ cell count between the two treatment groups is driven by a few patients on the CPI/r who had very high CD4+ counts and thus skewed*

*the median. Of note, when considering the entire RESIST 1 and RESIST 2 study population there was no difference between the TPV/r and CPI/r arms with regard to CD4+ count.*

When looking at causes of death by System Organ Class (SOC) there are no striking differences observed between the TPV/r arms and the CPI/r arms. Table # below explores in more detail the causes of death.

Table 7.1.1:3 Causes of Death

Preferred Terms	Resist 1		Resist 2		Total	
	TPV/r (%) N=311	CPI/r (%) N=309	TPV/r (%) N=435	CPI/r (%) N=428	TPV/r (%) N=746	CPI/r (%) N=737
AIDS	3	1	1	0	4	1
Asthenia	1	0	0	0	1	0
Cachexia	0	0	1	0	1	0
Cardiac arrest	0	0	0	1	0	1
COPD	1	0	0	0	1	0
CMV pneumonia	0	1	0	0	0	1
Death	0	1	0	0	0	1
Hepatorenal syndrome	1	0	0	0	1	0
Kaposi's sarcoma	0	0	1	0	1	0
Leukemia	0	1	0	1	0	2
Lymphoma, CNS	1	2	0	0	1	2
Lymphoma, not CNS	1	1	1	1	2	2
Melanoma	1					
MI	1	0	0	0	1	0
Multi-organ failure				1		
PML	0	0	0	2	0	2
Rectal CA	1	0	0	0	1	0
Respiratory distress/failure	2	0	0	0	2	0
Sepsis	1	0	0	0	1	0
Ventricular fibrillation	0	0	0	1	0	1
Not reported	0	0	1	0	1	0

Source: 12/5/04 Corporate Safety Deaths Dataset

AIDS is the leading cause of death in the TPV/r arms (4 cases versus 1 case in the CPI/r arms); however the relevance of this increased rate is questionable since it is not clear to this reviewer from the evidence provided why or how AIDS (and several other causes) was determined as the cause of death (see MO comment below).

*MO Comment: After reading the narratives submitted for each subject death, this reviewer can not concur with several of the reported causes of death.*

*Subject 1029: 43 year old white male on TPV/r (last available CD4+ count = 21, VL = 510,504) was reported as dying of AIDS; however his narrative reports that he was found dead in his apartment. Approximately one week prior to his death the subject had been hospitalized and diagnosed with PCP pneumonia.*

*Subject 1550: a 55 year old white male on TPV/r (last available CD4+ count = 377, VL = 59) with a past medical history of COPD was found dead at home and the immediate cause of death was listed as COPD. There is no indication in the narrative that the subject was experiencing or had recently experienced any acute respiratory problems or that his chronic pulmonary disease was unstable.*

*Subject 1568: a 47 year old black male on TPV/r (last available CD4+ count = 11, VL = 171,001) died three weeks after being hospitalized and recovering from diarrhea, hypophosphotemia, fever and mental status changes died. The cause of death was listed as AIDS.*

*Subject 1878: a 44 year old black male on TPV/r (last available CD4+ count = 11, VL = 255,270) was admitted to the hospital with upper and lower body weakness and diagnosed with a cervical spinal cord mass 'rule out lymphoma'. The subject deteriorated rapidly and died. Cause of death listed as "probable myocardial infarction".*

*Subject 2090: a 43 year old black male on CPI/r (last available CD4+ count = 164, VL = 35,809) was found dead at home and cause of death was listed as "death".*

*Subject 3033: a 51 year old male on TPV/r (last available CD4+ count = 4, VL = 105,925) was hospitalized in the intensive care unit with severe dyspnea, severe anemia, dry cough and fever. He recovered from the acute pulmonary illness and was transferred to the Infectious Diseases ward where he arrested. No mention is made of resolution of the fever or anemia. Cardio-pulmonary arrest is listed as his cause of death.*

*Subject 8032: 46 year old male on CPI/r (last available CD4+ count = 11, VL = 366,437) was hospitalized for "investigations of PCP" and died 8 days later of multiorgan failure and ventricular fibrillation. The cause of death is listed as ventricular fibrillation.*

*Subject 9137: 43 year old female on TPV/r (last available CD4+ count = 4, VL = 12,302) was listed as dying of AIDS, however the subject had ongoing neurotoxoplasmosis and approximately 2 weeks prior to her death she was hospitalized with symptoms of increased intracranial pressure and aspiration pneumonia. On the day of her death she presented with dyspnea, but "treatment was not provided" and she later died at home.*

*Although the above diagnoses cannot be definitively confirmed or refuted, this reviewer believes that the information provided to BI and the FDA does not provide conclusive evidence that the listed cause of death was the actual cause of death. In fact in several instances there is evidence that a more appropriate alternate diagnosis exists.*

The FDA received a Safety Update of the TPV clinical development program from the time of the original NDA database closure, June 11, 2004, through September 30, 2004. In the Safety Update BI reports an additional 29 deaths: 21 on-treatment and 8 post-treatment deaths on the TPV/r arm; there were no additional deaths on the CPI/r arm. The table below presents the breakdown of deaths for individual studies through the Safety Update period.

Table 7.1.1:4 Cummulative TPV Development Program Subject Deaths Through September 30, 2004

Study	TPV or TPV/r				CPI/r		
	Pre-tx	On-tx	Post-tx (>30 days off study drug)	TPV total	On-tx	Post-tx (>30 days off study drug)	CPI/rTotal
1182.12	6	17	2	19	7	1	8
1182.48	4	5	2	7	6	0	6
1182.51	0	2	1	3	n/a	n/a	n/a
1182.52	1	2	2	4	n/a	n/a	n/a
1182.17	0	15	12	27	n/a	n/a	n/a
1182.58	1	30	10	40	n/a	n/a	n/a
1182.1	0	2	0	2	n/a	n/a	n/a
1182.4	0	1	0	1	n/a	n/a	n/a
1182.6	0	1	0	1	n/a	n/a	n/a
1182.16	0	1	0	1	n/a	n/a	n/a
<b>Total</b>	<b>12</b>	<b>76</b>	<b>29</b>	<b>105</b>	<b>13</b>	<b>1</b>	<b>14</b>

Source: NDA 21-814 death\_3 dataset EDR submission 2/22/05

*MO comment: Of note there are two less post-tx deaths in Study 1182.12 as per the Safety Update database as compared to the original NDA submission database. Specifically patients 1050 and 1308 were originally classified as post treatment deaths with deaths occurring 73 and 192 days respectively after stopping treatment. In the Safety Update both subject 1050 and 1308 met the criteria for on-treatment deaths as they died 15 and 1 day respectively after stopping treatment.*

The causes of death in the additional 29 patients in the Safety Update were similar to the causes of death reported for patients in the original NDA submission.

The applicant submitted the following conclusions in their 2 month safety update regarding the details of deaths associated with hepatic events (source: section 4.4 of volume 1.1 of 1.27; submission date 2/22/05).

“There were 131 deaths in all patients in the TPV development program reported through the September 30, 2004 cut-off and an additional 39 deaths reported in the interim of October 1, 2004 to December 31, 2004. All codes within the hepatobiliary organ system level and all codes of hepatic preferred terms regardless of organ system classifications were used to identify fatal cases with hepatic events. Using the December 31 2004 cut-off date, a total of 14 cases that included hepatic event terms were identified. Among these cases, five included only the term “encephalopathy”, but review of the cases did not reveal hepatic components to the fatal outcome of the patients. Among the remaining nine cases, two revealed liver findings that were too mild to have contributed to death (one was associated with hyperbilirubinemia for which the autopsy results revealed *mild macrovesicular steatosis* and mild chronic hepatitis, and one was associated with *acalculous cholecystitis*. Thus, seven cases have been identified in the global safety database up through December 31, 2004, which have potential drug-related hepatotoxicity. In summary, seven male patients who received TPV/r, two of whom initially received CPI/r in RESIST, had a fatal outcome with hepatic events reported. Three of the seven patients had fatal outcomes while on-treatment in one of the RESIST studies (1182.12, 2 cases [patients #2272 and #2052]; 1182.48, 1 case [patient #4168]), three occurred in the rollover study 1182.17 (patients #121025, #482621, and #510361), one occurred in the Expanded Access Program. Each of the seven patients had AIDS with a history of opportunistic infections prior to study entry. Each patient suffered multiple additional medical complications. Each case also had some level of hepatic decompensation prior to death. In two of the cases, the investigator considered the hepatic event to be related to study treatment with TPV/r [patients #121025 and #482621].”

*MO Comment: These narratives were reviewed in detail and it is the opinion of this reviewer that hepatic decompensation was definitely a part of the final clinical event however, attributing the liver dysfunction to TPV/r and attributing the liver dysfunction to the actual death event is difficult. Based on the information provided in the narrative it appears to this reviewer that hepatic decompensation was part of the final pathway to death rather than the initial insulting event. That being said drug relatedness based on the data reviewed cannot be ruled out.*

FDA reviewers conducted 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, to place the mortality rate observed in the RESIST trials into perspective. Fourteen unique studies from 13 registrational drug programs were found to meet our search criteria. Mortality rate per study in 100 subject-years by year of DAVDP approval are shown in Figure 7.1.1:1.

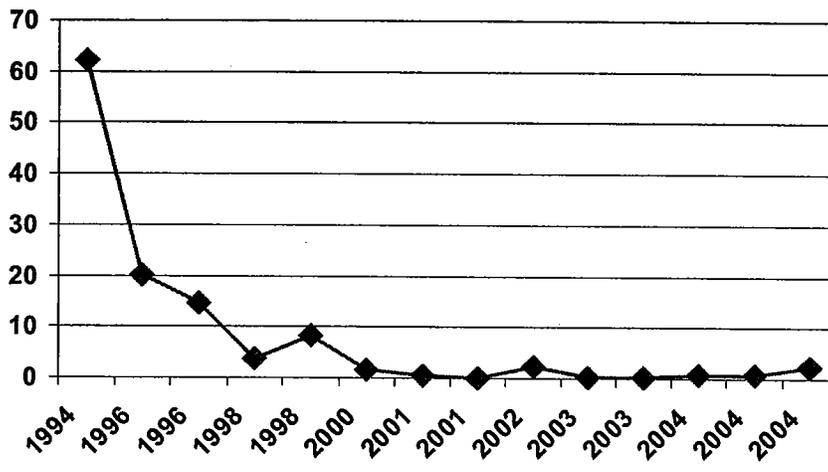


Figure 7.1.1:1

Examination of subject baseline characteristics showed that the population enrolled in the T20 phase 3 studies most closely approximated the population enrolled in the TPV phase 3 studies [http://www.fda.gov/cder/foi/nda/2003/021481\\_fuzeon\\_review.htm](http://www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm).

Each on-treatment TPV death was reviewed and only those deaths which occurred within the window of 24 weeks of treatment + 28 days follow-up were counted as raw numbers (this was how ENF death numbers were counted in ENF's accelerated approval NDA review at 24 weeks). Both NDA death numbers were then used to calculate the mortality rate (#death/100 subject-years) using 24 weeks duration. As shown below, raw numbers of deaths or mortality rates between the test and control arms were similar for both the TPV and ENF NDAs at 24 weeks.

Table 7.1.1: 1 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

*MO comment: The analyses of mortality rates between the TPV/r and CPI/r arms, as well as between two different drug programs (ENF and TPV/r) were similar based upon our comparisons.*

### 7.1.2 Other Serious Adverse Events

In the integrated trials of HIV-positive patients (n = 1854), BIPI reports that 274 (14.8%) of all patients experienced 617 on treatment SAEs, regardless of causality.

In the 12 trials of HIV-negative patients (n = 397), BIPI reports that 2 (0.5%) patients experienced SAEs, regardless of causality. The SAEs experienced consisted of pyelonephritis in 1 subject in the TPV/r 500 mg/100 mg group and joint ligament rupture and ligament sprain in 1 subject in the TPV/r 500 mg/200 mg group.

In the RESIST trials (n = 1483), 188 (13%) of all patients experienced 472 SAEs, regardless of causality: 13% (99 of a total 746) of patients in the TPV/r group and 12% (89 of a total 737) in the CPI/r group. Overall there were more SAEs in RESIST 1 (n = 293) than in RESIST 2 (n = 179).

*MO comment: RESIST 1 patients were enrolled earlier than RESIST 2 patients and therefore had more potential drug exposure at the time of the interim evaluation, which is likely the reason for a greater number of SAEs in RESIST 1. There appeared to be no major differences between the types of SAEs and proportions between study arms when comparing the two trials.*

For both RESIST trials and both treatments combined, the highest percentage of patients with SAEs occurred in the following MedDRA System Organ Classes (MSOCs): Infections and Infestations (8%); Gastrointestinal Disorders (4%); General Disorders and Administration Site Conditions (4%); Nervous System Disorders (2%); Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) (2%); Investigations (2%) Respiratory, Thoracic and Mediastinal Disorders (2%). All others occurred in ≤ 1% of each of the remaining SOCs.

The most frequently observed SAEs by Preferred Term in the TPV/r group were pyrexia (2%); pneumonia, CMV disease (1% each); increased ALT, diarrhea, abscess, lymphoma (0.8% each), and AST increased (0.5%). Overall, the SAE profiles of TPV/r and CPI/r are similar with the exception of ALT and AST increases reported in 0.8 and 0.5% of TPV/r patients respectively, as compared to 0% of CPI/r patients.

*MO comment: This reviewer grouped Preferred Terms (PT) that were related. Please refer to the footnotes beneath Table 7.1.2:1 for details.*

The rate of SAEs by MSOC and Preferred Term occurring in >1 subject is shown below in Table 7.1.2:1.

Table 7.1.2:1 Serious Adverse Events Occurring in > 1% of Patients In Either Arm of RESIST 1 and RESIST 2 by MSOCs and Preferred Term SAEs in > 1 subject by Preferred Term

	TPV/r	CPI/r
	N=746	N=737
<b>Serious Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>
Patients with ANY SAE	99 (13%)	89 (12%)
Total number of SAEs	236	220
<b>Blood and lymphatics</b>	<b>3 (&lt;1%)</b>	<b>11 (1%)</b>

	TPV/r	CPI/r
	N=746	N=737
<b>Serious Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>
Patients with ANY SAE	99 (13%)	89 (12%)
Total number of SAEs	236	220
anemia	0	7
febrile neutropenia	1	2
<b>Gastrointestinal disorders</b>	<b>28 (4%)</b>	<b>24 (3%)</b>
abdominal pain	5	1
diarrhea	6	5
dysphagia	1	3
odynophagia	0	2
pancreatitis	4	1
vomiting	3	3
<b>General disorders and administration site conditions</b>	<b>27 (4%)</b>	<b>26 (4%)</b>
asthenia	3	1
chest pain	1	2
death	2	0
fatigue	0	2
granuloma	0	2
dyrexia	16	12
digors	3	0
vomiting	3	3
<b>Infections and infestations</b>	<b>62 (8%)</b>	<b>57 (8%)</b>
abscess <sup>a</sup>	6	3
bacteremia <sup>b</sup>	1	2
bronchitis	2	1
candidiasis, esophageal	3	6
cellulitis <sup>c</sup>	2	0
CMV disease <sup>d</sup>	10	9
cryptosporidium	0	2
gastroenteritis	3	1
herpes <sup>e</sup>	2	3
PCP pneumonia	2	4
PML	1	4
pneumonia <sup>f</sup>	11	9
sepsis	2	0
staph infection	2	0
UTI	2	0
<b>Injury, poisoning and procedural complications</b>	<b>11 (1%)</b>	<b>3 (&lt;1%)</b>

	TPV/r	CPI/r
	N=746	N=737
<b>Serious Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>
Patients with ANY SAE	99 (13%)	89 (12%)
Total number of SAEs	236	220
fracture <sup>g</sup>	5	0
traffic accident	3	0
<b>Investigations</b>	<b>15 (2%)</b>	<b>8 (1%)</b>
ALT increased	6	0
AST increased	4	0
weight decreased	2	1
<b>Metabolism and nutrition disorders</b>	<b>12 (2%)</b>	<b>8 (1%)</b>
cachexia	2	1
dehydration	4	2
<b>Musculoskeletal</b>	<b>8 (1%)</b>	<b>8 (1%)</b>
<b>Neoplasms</b>	<b>16 (2%)</b>	<b>10 (1%)</b>
lymphoma <sup>h</sup>	6	5
rectal CA	3	1
<b>Nervous system disorders</b>	<b>12 (2%)</b>	<b>20 (3%)</b>
ataxia	1	2
convulsion	1	3
CVA	2	1
encephalopathy	0	2
headache	3	1
<b>Psychiatric</b>	<b>3 (&lt;1%)</b>	<b>9 (1%)</b>
confusional state	0	2
depression <sup>i</sup>	1	5
<b>Renal and Urinary disorders</b>	<b>6 (&lt;1%)</b>	<b>8 (1%)</b>
renal failure	2	2
renal insufficiency	1	2
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>15 (2%)</b>	<b>10 (1%)</b>
cough	2	1
hypoxia	0	2
respiratory failure	3	0
dyspnea	4	4

- a. Includes PT abscess, neck abscess, groin abscess, scrotal abscess
- b. Includes PT bacteremia, pseudomonal bacteremia
- c. Includes PT cellulites, periorbital cellulitis
- d. includes PT CMV chorioretinitis, CMV colitis, CMV gastritis, CMV infection, CMV esophagitis, CMV pneumonia
- e. Includes PT herpes ophthalmic, herpes simplex, herpes meningoencephalitis
- f. Includes PT pneumonia, pneumonia pneumococcal, pneumonia streptococcal, lung infection pseudomonal, aspiration pneumonia
- g. Includes PT humerus fracture, tibia fracture, wrist fracture, hip fracture, lower limb fracture

- h. Includes PT lymphoma, CNS lymphoma, B-cell lymphoma, Hodgkin's disease, Non-hodgkin's lymphoma, Burkett's lymphoma  
includes PT depression, major depression

Source: AECD12 and AECD48 electronic datasets submitted 12/29/04

In Study 1182.17, 111 (14%) patients had 247 SAEs. Infections and infestations accounted for the majority of the SAES (10%) with the MSOCs GI and General Disorders and Administration Site disorders accounting for 3% of SAEs. By preferred term pyrexia and anemia were the most commonly observed SAEs in patients in the Rollover study (1.2% and 1% respectively). In Study 1182.58, 34 patients (13%) experienced 67 SAEs. Diarrhea and pyrexia were the most common preferred terms (1% each).

*MO comment: Once again both the Rollover study and the OLSS provide rates and causes of SAEs similar to that observed in the RESIST trials.*

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

BIPI's assessment of the disposition of all HIV positive patients in the Phase 2 and 3 trials is presented in the Table 7.1.3.1:1 below.

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Table 7.1.3.1:1 Subject disposition in trials of HIV positive patients

	TPV/r <500/200	TPV/r 500/200	Treatment groups/ TPV/r >500/200	No. (%) of patients Total: All TPV/r doses
Screened/enrolled				4515
Randomised/entered	218	1426	240	1884
Not treated	1	29	0	30
Total treated	217 (100.0)	1397 (100.0)	240 (100.0)	1854 (100.0)
Not prematurely discontinued	75 ( 34.6)	38 ( 2.7)	102 ( 42.5)	215 (11.6)
Currently continuing in trials	67 ( 30.9)	1137 ( 81.4)	54 ( 22.5)	1258 (67.9)
Prematurely discontinued	75 ( 34.6)	222 ( 15.9)	84 ( 35.0)	381 (20.6)
Adverse event	25 ( 11.5)	113 ( 8.1)	37 ( 15.4)	175 (9.4)
Unexpected worsening of disease / condition under study	4 ( 1.8)	14 ( 1.0)	4 ( 1.7)	22 (1.2)
Unexpected worsening of other pre-existing disease / condition	4 (1.8)	14 (1.0)	8 (3.3)	26 (1.4)
Other adverse event	17 ( 7.8)	85 ( 6.1)	25 ( 10.4)	127 (6.9)
Non compliant with protocol	10 ( 4.6)	15 ( 1.1)	6 ( 2.5)	31 ( 1.7)
Lost to follow-up	5 ( 2.3)	7 ( 0.5)	14 ( 5.8)	26 ( 1.4)
Consent withdrawn	5 ( 2.3)	8 ( 0.6)	3 ( 1.3)	16 ( 0.9)
Lack of efficacy	9 ( 4.1)	33 ( 2.4)	11 ( 4.6)	53 ( 2.9)
Other <sup>b</sup>	21 ( 9.7)	44 ( 3.1)	13 ( 5.4)	78 ( 4.2)
Missing <sup>c</sup>	0 ( 0.0)	2 ( 0.1)	0 ( 0.0)	2 ( 0.1)

a Includes data from the following trials: 1182.2, 1182.4, 1182.6, 1182.12, 1182.17, 1182.48, 1182.51, 1182.52. All doses in mg and BID. Less than TPV/r 500/200 dose grouping: 250/200, 500/100. Greater than TPV/r 500/200 dose grouping: 750/100, 750/200, 1000/100, 1250/100.

b Other includes: Virological failure and miscellaneous.

c Missing includes: Two patients have terminated the study but did not have drug stop dates and reasons for discontinuation of trial drug.

Source: SCS

Overall for all TPV/r doses approximately 20% of subjects discontinue study drug and the majority of these discontinuations are due to AEs (9.4%).

The disposition of subjects in the RESIST trials differed dramatically between the treatment arms. The majority of subjects on the TPV/r arm (85.7%) continued on-study while the majority of subjects on the CPI/r arm (51.6%) discontinued by Week 24. The main reason for discontinuation on the TPV/r arm was AEs (7.5%) while “lack of efficacy” was the overwhelming reason for discontinuation on the CPI/r arm (33.6%).

*MO comment: As a reminder the CPI/r arm was a suboptimal control arm that allowed subjects to leave the study early if they failed to decrease their VL by 0.5 log<sub>10</sub> and decrease their VL below 100,000 copies/mL. On the CPI/r arm 28.9% of the patients took advantage of this escape clause to leave the RESIST trials and rollover to 1182.17. This 28.9% makes up a large part of that 33.6% “lack of efficacy” category. If the TPV/r arm*

was held to the same criteria, 36% (209/582) of their subjects would have been allowed to discontinue for "lack of efficacy" as well.

Table 7.1.3.1:2 Disposition of subjects on the RESIST trial up to 24 Weeks

	Treatment groups/ No. (%) of patients		Total
	TPV/r	CPI/r	
Screened/enrolled			3275
Randomised/entered	755	754	1509
Not treated	9	17	26
Total treated	746 (100.0)	737 (100.0)	1483 (100.0)
Currently continuing in trials	639 ( 85.7)	357 ( 48.4)	996 ( 67.2)
Prematurely discontinued	107 ( 14.3)	380 ( 51.6)	487 ( 32.8)
Adverse event	56 (7.5)	27 (3.7)	83 (5.6)
Unexpected worsening of disease / condition under study	3 ( 0.4)	2 ( 0.3)	5 (0.3)
Unexpected worsening of other pre-existing disease / condition	3 ( 0.4)	1 (0.1)	4 (0.3)
Other adverse event	50 (6.7)	24 (3.3)	74 (5.0)
Non compliant with protocol	8 (1.1)	15 ( 2.0)	23 ( 1.6)
Lost to follow-up	5 (0.7)	4 (0.5)	9 (0.6)
Consent withdrawn	6 (0.8)	5 (0.7)	11 (0.7)
Lack of efficacy	22 (2.9)	248 ( 33.6)	270 ( 18.2)
Other <sup>b</sup>	7 (0.9)	18 (2.4)	25 (1.7)
Missing <sup>c</sup>	3 (0.4)	63 (8.5)	66 (4.5)

a Doses in mg, BID, and as follows: TPV/r: 500/200; CPI/r includes: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, APV/r 600/100.

b Other includes: virological failure and miscellaneous.

c Missing includes: Twelve patients receiving CPI/r were reported as not having a medication adjustment, not prematurely discontinued, but did have drug stop dates. Fifty-four patients have terminated the study but did not have a drug stop date and a reason for discontinuation. Many of these patients enrolled in Trial 1182.17 and, therefore, are not reflected as missing in Table 7.1.3: 1.

Source: SCS

It is noteworthy to add that AEs were the major cause of study discontinuation in the HIV negative studies with 12.6% of subjects discontinuing due to AEs. The next highest cause of discontinuation was listed as "other" at 11.6%. Of the 46 subjects that stopped medication for the reason "other", 41 (89%) of the subjects are from 2 trials in which the sponsor requested the studies be terminated (Trial 1182.22, n = 32 and 1182.42, n = 9). The sponsor requested termination of Trial 1182.22 due to the high number and unexplained occurrence of rashes. In Trial 1182.42, a large number of subjects were discontinued from the study based on stopping rules in the protocol for abnormal laboratory test results, which led to the termination of the trial by the sponsor. So in essence an additional 10.6% or a total of 23.2% of HIV negative subjects discontinued TPV/r due directly or indirectly to a TPV/r related toxicity.

*MO comment: Throughout the Phase 1,2 and 3 development program healthy, HIV negative subjects and HIV positive subjects alike discontinue TPV/r because of AEs. Overall the drop out rate due to AEs was higher in the HIV negative, healthy normal subjects (12.6%) as compared to the HIV positive subjects (9.4%) directly reflects the intolerability and toxicity associated with TPV itself versus the interaction of the drug and disease or the drug and other drugs.*

7.1.3.2 Adverse events associated with dropouts

In the RESIST trials, more subjects in the TPV/r group, 8.0%, versus 4.9% in the CPI/r group reported AEs leading to discontinuation of study medication. The most common AEs leading to discontinuation on both arms were nausea, diarrhea and vomiting. Increased ALT lead to the discontinuation of six subjects on the TPV/r arm (0.8%) compared to zero subjects on the CPI/r.

Table 7.1.3.2:1 Treatment emergent adverse events leading to discontinuation

MedDRA Preferred Term	TPV/r N=746	CPI/r N=737
# of Subjects who discontinued treatment	60 (8.0%)	36 (4.9%)
# of AEs leading to discontinuation	124	62
Nausea	10 (1.3%)	6 (0.8%)
Diarrhea	7 (0.9%)	7 (0.9%)
Vomiting	7 (0.9%)	5 (0.7%)
ALT increased	6 (0.8%)	0
Pyrexia	4 (0.5%)	1 (0.1%)
Abdominal pain	3 (0.4%)	4 (0.5%)
AST increased	3 (0.4%)	0
Cytolytic hepatitis	3 (0.4%)	0
Staph infection	3 (0.4%)	0
Rash	3 (0.4%)	0
Sepsis	2 (0.3%)	0

*MO comment: Although the proportion of subjects discontinuing for each Preferred Term is small, there is clearly an indication that hepatic and infectious AE terms (if Preferred terms are grouped) are TPV/r related. When combined the Preferred Terms for hepatic disorders (ALT increase, AST increased and cytolytic hepatitis) account for the highest proportion of subjects (1.8%) subjects who discontinued due to an AE on the TPV/r arm as compared to zero subjects who discontinued to a hepatic disorder.*

*Combined infectious Preferred Terms (staph infection and sepsis) account for 0.7% of subjects on the TPV/r arm, who discontinued treatment versus zero subjects on the CPI/r arm.*

*GI AEs (namely, nausea, diarrhea, and vomiting) are the most common AEs leading to discontinuation on both arms.*

The Rollover study and the OLSS had similar rates and causes of AEs leading to discontinuation as those in the RESIST trials. In Study 1182.17, 7% of subjects (N=776) discontinued study drug due to an AE. The leading causes of discontinuations due to AEs were nausea (1%); renal insufficiency and increased ALT (0.6% each); increased AST and abdominal pain (0.5% each).

In Study 1182.58, 5% (13 of 263) subjects discontinued due to an AE. The leading causes of discontinuations due to AEs were nausea (2%), diarrhea (1%), and vomiting (1%).

Similarly in the Phase 1 and 2 studies, GI AEs (predominantly nausea and diarrhea) were the most common AEs leading to discontinuation with proportions ranging from 2.3% to 8.9% of subjects discontinuing due to GI AEs.

#### 7.1.3.3 Other significant adverse events

There were three safety signals identified throughout the TPV development program: hepatotoxicity, rash and hyperlipidemia.

### **Hepatotoxicity**

Please refer to Dr. Baylor's review for a detailed discussion of the Phase 1 data and Dr. Gibbs's review for a detailed discussion of the Phase 2 data on Hepatotoxicity (Section 10.1).

The initial evidence of TPV induced hepatotoxicity comes from 18 Phase 1 studies in which 19% (N=631) of healthy volunteers with normal LFTs at baseline had drug induced ALT elevations: 13% had ALT elevations above the upper limit of normal (ULN), 4% had Grade 3 ALT, and 2% had Grade 4 ALT. The median time to onset of these LFT abnormalities was 16 days (range 6-46 days). Dr. Baylor describes in detail a single subject in a Phase 1 study that had an increase in ALT from normal limits to 3.5 times the ULN after a single dose of TPV.

*MO comment: TPV's ability to induce this degree of hepatotoxicity in healthy, normal volunteers is quite concerning and warrants an extreme amount of consideration and caution when contemplating studying TPV in HIV negative subjects.*

In Phase 2 studies a total of 47 of 619 subjects (7.6%) who received TPV/r developed treatment emergent, clinically asymptomatic grade 3 or 4 ALT elevations.

The definitive dose finding study 1182.52 demonstrated a linear relationship between the dose of TPV/r and the rate of treatment emergent grade 3 and 4 ALT elevations with the rate of hepatotoxicity doubling from 500/100mg to 500/200mg and then doubling again from 500/200mg to 750/200mg.

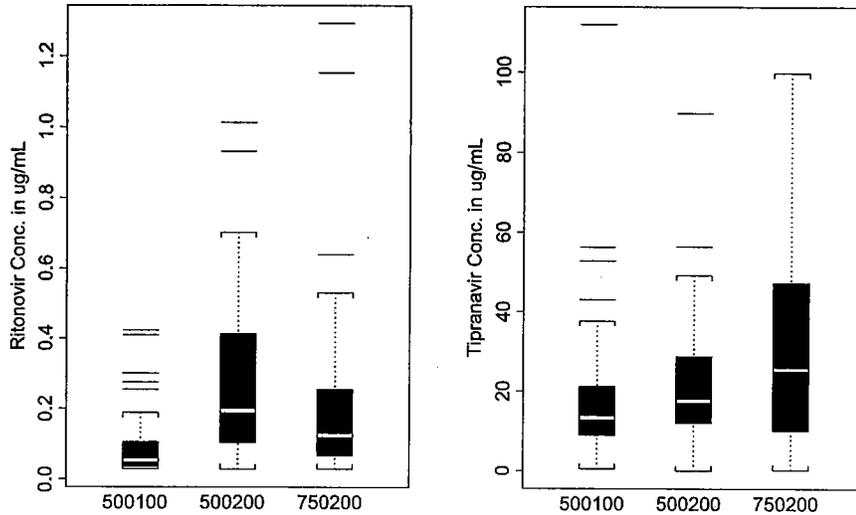
Table 7.1.3.3:2 Proportion of subjects with grade 3 or 4 ALT elevations for each dose group in Study 1182.52

	TPV/r Dose Group		
	500/100 mg BID	500/200 mg BID	750/200 mg BID
Proportion of Subjects w/ Grade 3 or 4 ALT Elevations	4% (3/69)	11% (8/72)	23% (16/69)

*MO comment: Study 1182.52 provided evidence that TPV/r induced hepatotoxicity was dose dependent.*

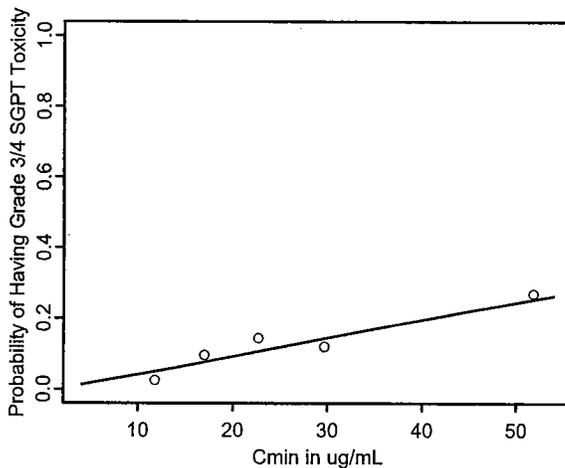
In order to understand whether these ALT elevations were related to TPV or RTV, Dr. Jenny J. Zheng from the Office of Clinical Pharmacometrics determined the exposures of both TPV and RTV across the three doses. The trough concentrations, which are defined in this analysis as the observed concentrations between 9 and 15 hours after the dose at day 14, are shown in Figure 1. The time window was used to account for the fact that not every trough concentration was collected at exactly 12 hours. Day 14 was selected to minimize the induction effect of TPV, assuming that steady state was achieved by day 14. The median RTV concentration is lower (0.281 µg/mL vs. 0.217 µg/mL) and the median 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 and 4 ALT elevations.

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**Figure 1:** Range of trough (Cmin) ritonavir and TPV concentrations at the 3 dose levels. The median ritonavir concentrations are 0.0962  $\mu\text{g/mL}$  (n=40), 0.281  $\mu\text{g/mL}$  (n=56), and 0.217  $\mu\text{g/mL}$  (n=47), respectively for dose level of 500/100 TPV/r, 500/200 TPV/r, and 750/200 TPV/r. The median concentrations of TPV are 17.46  $\mu\text{g/mL}$  (n=60), 21.26  $\mu\text{g/mL}$  (n=63) and 30.75  $\mu\text{g/mL}$  (n=56), respectively.

Dr. Zheng also performed a logistic regression analysis between the incidence of grade 3 or 4 ALT elevations and the logarithm (2 based) of TPV trough concentrations, using the data from 210 subjects with TPV concentrations. One unit change in the log concentration represents 1-fold increase in the drug concentrations. The analysis results showed that the odds ratio associated with log TPV trough concentration is 2.40 (95% CI: 1.43-4.02,  $p=0.00066$ ), suggesting that when TPV trough concentrations double, the odds of having grade 3 and 4 ALT elevations increase by 140% (Figure 2). A similar analysis was conducted for RTV. The results showed that RTV troughs are not significantly correlated to grade 3 or 4 ALT toxicity (results not shown).



**Figure 2:** Probability of subjects having a grade 3 or 4 ALT elevation is higher at higher TPV Cmins. The logistic regression was performed using TPV Cmin as a continuous variable and the incidence of grade 3/4 ALT toxicity as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the

toxicity rates observed 5 concentration groups (0-20 percentile, 20-24 percentile, 40-60 percentile, 60-80 percentile, 80-100 percentile) are presented as symbols to assess the goodness-of-fit.

*MO comment: These exposure plots and the logistic regression analysis are supportive evidence that the dose related hepatotoxicity is an effect of TPV and not RTV.*

In the RESIST trials 6.1% (n=45 of 730) of subjects on the TPV/r arm compared to 2.4% (n=18 of 723) on the CPI/r arm developed treatment emergent grade 3 or 4 ALT/AST elevations.

*MO comment: The number of total subjects included in the laboratory analyses was less 16 subjects on the TPV/r arm and less 14 subjects on the CPI/r due to missing laboratory data.*

*Treatment emergent hyperbilirubinemia was uncommon throughout the TPV development program. In the RESIST trials less than 1% of subjects in either study group experiencing treatment emergent hyperbilirubinemia.*

The maximum range of Grade 3 and 4 ALT and AST values are presented below in Figure 3.

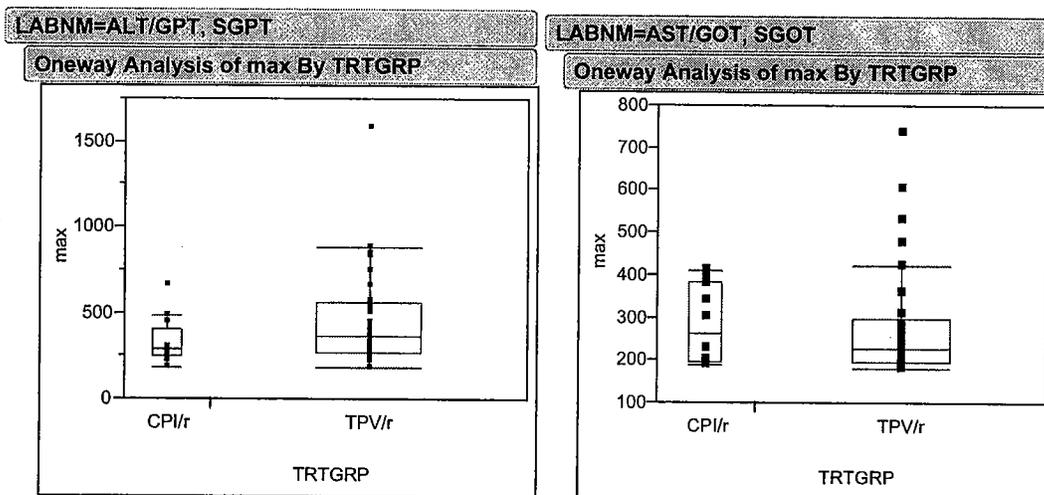
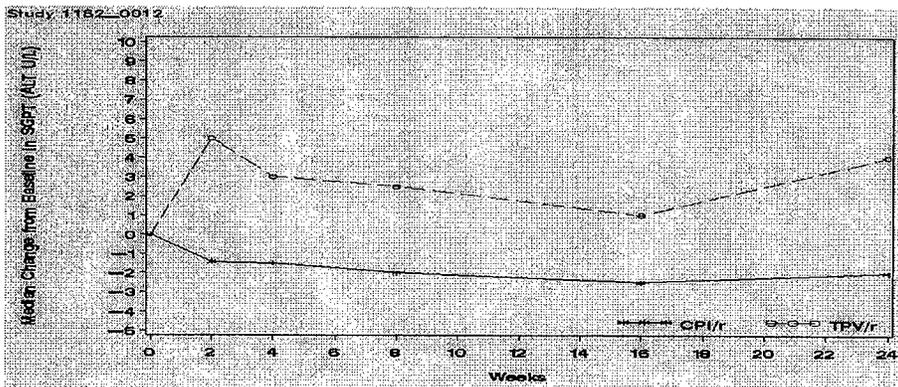


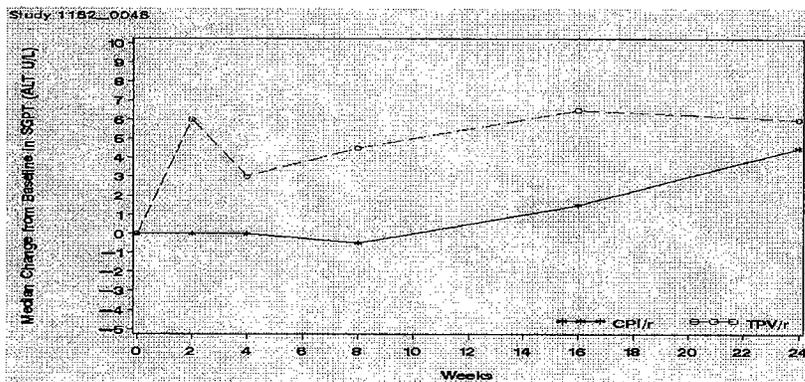
Figure 3: Maximum values of Grade 3 and 4 ALT and AST in the TPV/r group and the CPI/r group with median, confidence intervals and all data points shown.

Figure 4A and 4B show that changes in ALT from baseline were different between the TPV/r arm and the CPI/r arm from Week 2-16 in both RESIST 1 and 2 respectively. These differences were statistically significant at a p-value of 0.0028 and 0.0255 for RESIST 1 and 2 respectively.

**Figure 4A: Median Change from Baseline ALT (U/L) in RESIST 1**



**Figure 4B: Median Change from Baseline ALT (U/L) from RESIST 2**



In the RESIST trials subjects with TPV/r related transaminase elevations presented asymptotically with a median time to onset of 56.5 days (range of days: 8 to 176).

*MO comment: In the RESIST trials the range of days during which hepatotoxicity (defined as a Grade 3 or 4 ALT or AST elevation) occurred on TPV/r encompassed the entire study assessment period of Week 1 to Week 24, so the risk period appears to begin from the time TPV/r is first dosed and remains throughout the treatment period. Additionally, there is evidence that TPV/r has the ability to cause hepatotoxicity after a single dose (one subject in a Phase 1 study developed ALT elevations to 3.5 times the upper limit of normal after a single dose)..*

*Given the asymptomatic presentation clinicians will need to monitor LFTs very closely as there are no other objective or subjective signs or symptoms of TPV related hepatotoxicity known at this time.*

Of the 6.1% of subjects who experienced a treatment emergent grade 3 or 4 ALT or AST, 27% (or 1.6% of the total TPV/r subject population) discontinued treatment as a result of their elevated transaminases whereas none of the subjects on the CPI/r arms with grade 3 or 4 ALT or AST elevations discontinued due to their elevated transaminase.

The majority of the TPV/r subjects with drug-induced hepatotoxicity (64%) resolved their grade 3 or 4 transaminase elevation most of the time while remaining on therapy. Most of the TPV/r subjects with unresolved transaminase elevations were classified as unresolved because their transaminase elevation occurred at the last capture date of the study, namely at study discontinuation or at Week 24. There were no deaths either directly or temporally related to these transaminase elevations at the time of the original NDA submission. (Table 7.1.3.3:3).

Table 7.1.3.3:3 Outcomes of Grade 3 and 4 ALT and AST Elevations in the RESIST Trials

	TPV/r N = 730 <sup>1</sup>	CPI/r N = 723 <sup>2</sup>
Grade 3 or 4 ALT/AST Elevation	45 (6%)	18 (2%)
Discontinued	12 (27%)	0
Resolved	29 (64%)	17 (94%)
On tx	19 (42%)	17 (94%)
Off tx	10 (22%)	0
Unresolved	16 (35%)	1 (6%)
On tx	14 (31%)	1 (6%)
Off tx	2 (4%)	0
Deaths	0	0

1. Sixteen subjects were censored on the TPV/r arm because of multiple missing data points.
2. Fourteen subjects were censored on the CPI/r arm because of multiple missing data points.

*MO comment: DAVDP requested an update on the 35% of subjects, who were unresolved at the time of the original NDA submission. BIPI submitted follow-up information for the 16 subjects on TPV/r who had a Grade 3/4 LFT abnormality on the last observed visit at the time of the original NDA cut-off. As of May 5, 2005 six subjects were still on study and 10 subjects had discontinued study. All six of the subjects who continued on study had improvement in LFTs by  $\geq 1$  grade. Of the 10 subjects who discontinued study*

- 1 subject discontinued due to liver failure with full recovery (Trial 1182.48, subject 1271 on TPV/r, a 37 year old female HIV positive patient was enrolled in Trial 1182.48 and initiated TPV/r on 28 October 2003. Concomitant ARV medications included nevirapine (since 13 December 1999), tenofovir (since 14 November 2002) and abacavir (since 28 January 1999). On [redacted] after TPV/r initiation) the patient presented with jaundice, vaginal bleeding, itching, vomiting and prostration. The patient was diagnosed as having acute liver failure and was hospitalized. All ARVs were stopped [redacted] when an ARV regimen including TPV/r, tenofovir and lamivudine was started. On 1 June 2004, during a routine trial visit, laboratory testing revealed Grade 4 ALT and Grade 2 AST. No concomitant clinical symptoms were reported. The investigator discontinued study therapy permanently on 4 June 2004. A new ARV regimen including

lopinavir/ritonavir, didanosine and lamivudine was initiated on 15 July 2004. Blood sampling performed on [ ] revealed normal LFTs.

- 9 subjects discontinued due to non-hepatic related reasons
  - 6 had improvement in LFTs by  $\geq 1$  grade before discontinuing
  - 3 continued to have Grade 3 or 4 LFT or worsening of their LFTs at the time of discontinuation of treatment
    - Subject 6057 discontinued on January 13, 2004 with a Grade 4 ALT. The subject made a full recovery within 2 weeks.

*Although in the short term subjects appear to be able to tolerate these ALT and AST elevations, as evidenced by their ability to continue treatment, the long term effect of intermittent or persistent transaminase elevations in this population is unknown.*

The RESIST data were analyzed for potential baseline predictors of hepatotoxicity. Based on the results of this reviewer's analyses co-infection with Hepatitis B and C at baseline appears to increase the risk for TPV/r induced hepatotoxicity. Nine of the 76 (12%) subjects co-infected with Hepatitis B or C at baseline developed Grade 3 or 4 ALT/AST while taking TPV/r as compared to less than half that rate (5%) on the CPI/r arm (Table 7.13.3:4)

Table 7.1.3.3:4 Proportion of Subjects Co-infected with Hepatitis B or C who Developed Grade 3 or 4 ALT/AST

% of	TPV/r	CPI/r
Hepatotoxicity among subjects with baseline Hepatitis B or C	9/76 (12%)	6/113 (5%)

However, co-infection with Hepatitis B or C does not appear to be the only risk factor for TPV/r induced Grade 3 or 4 ALT/AST elevations, since only 20% (n=9/45) of subjects who developed Grade 3 or 4 ALT/AST elevations were Hepatitis B or C co-infected at baseline.

BIPI conducted additional analyses which confirmed our analysis that subjects co-infected with Hepatitis B or C at baseline were at increased risk for TPV/r induced Grade 3 or 4 ALT elevations. Additionally, BIPI concluded that the risk of developing Grade 3 or 4 ALT elevations was increased for subjects who had elevated baseline ALT or AST, baseline CD4+ cell count  $>200$  cells/mm<sup>3</sup> or who were taking potentially hepatotoxic drugs.

*MO comment: Through labeling (see Section 9.4 for Labeling Review) healthcare providers will need to be made aware of these potential risk factors, which should be used to guide careful selection of patients to treat with TPV/r and better manage patients who are on TPV/r. These potential risk factors require further exploration in the form of a Phase 4 commitment given the large number of patients co-infected with HIV and HBV or HCV, who are very likely to have elevated ALT or AST at some point during their illness.*

## RASH

The initial signal for “rash” was seen in healthy, female subjects in study 1182.22, which was a drug interaction study of Ortho-Novum 1-35 and TPV/r.

*MO comment: Please see Dr. Baylor’s review of Study 1182.22 for a detailed review and analysis of 1182.22 data.*

*Throughout this review the term “rash” is used to collectively refer to cutaneous reactions that include the following preferred terms: rash, dermatitis, eczema, urticaria, erythema, exanthema, prurigo.*

Thirty-three percent of the women on this study developed rash and an additional 18% of subjects had musculoskeletal symptoms or symptoms consistent with hypersensitivity. BIPi decided to prematurely stop this study because of the concern that these women were experiencing serum sickness.

*MO comment: The role of the immune system is not clear, however, given that the highest rate of rash was observed in women with intact immune systems biological plausibility exists that this represents some sort of immune mediated reaction.*

*TPV is a sulfonamide, however, none of the women in this study had a known sulfa allergy at the time of enrollment.*

In Phase 2 trials of HIV infected patients, 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. 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).

Females had a higher rate of rash as compared to males throughout the entire TPV development program. Females in the Phase 1 (N=265) and 2 (N=114) trials developed rash at a rate of 13% while in comparison 3.6% of males in the Phase 1 trials and 7.9% of males in the Phase 2 trials developed rash. In Phase 1 subjects with rash on rare occasion had associated symptoms like joint pain, tingling, pruritus, slurred speech, tongue swelling and throat tightness. In two subjects these symptoms required treatment: one female subject was treated with benadryl and one male subject was treated with benadryl and steroids.

In the RESIST trials, overall the frequency of rash was similar between the two treatment groups, 11% on the TPV/r arm versus 10% on the CPI/r arm. However, women on the TPV/r arm developed rash at a higher rate of 14% compared to 9% in the women on the CPI/r arm.

*MO comment: Women only comprised 12% of the study population in the TPV development program and therefore all signals observed in this subgroup will need to be confirmed in a study that enrolls a larger proportion of women. However, the consistent rate of 13-14% is convincing that rash is a true safety signal in women. Additionally, we recognize from our PK data that women on average have a higher TPV exposure. We see from our efficacy data that this appears to translate into a better treatment response rate, therefore it makes sense that these higher exposures could also easily translate into a higher safety risk.*

*Women on TPV/r will need further evaluation from an efficacy and safety standpoint.*

In the definitive dose finding study 1182.52 the data suggests that rash may be dose-related 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.

*MO comment: This is more evidence that TPV/r related toxicities may be dose related and that further evaluation of how best to dose TPV/r to get the optimal efficacy while minimizing toxicity is needed.*

## **HYPERLIPIDEMIA**

Overall 46% of TPV/r subjects in the RESIST trials had Grade 2-4 treatment emergent hypertriglyceridemia versus 24% of CPI/r subjects, and 15% of TPV/r subjects had Grade 2-4 treatment emergent hypercholesterolemia versus 5% of CPI/r subjects.

*MO comment: This reviewer chose to include Grade 2 laboratory values because a Grade 2 triglyceride is a risk factor for pancreatitis, and a Grade 2 triglyceride is likely when most clinicians would intervene with triglyceride lowering agents. Similarly, a Grade 2 cholesterol ( $\geq 400$ mg/dL) is the point at which clinicians would likely intervene with a cholesterol lowering agent.*

Tables 7.13.3:5 and 7.13.3:6 present Grade 2-4 treatment emergent hypertriglyceridemia and hypercholesterolemia, respectively, for both treatment groups. In the RESIST trials treatment emergent hypertriglyceridemia occurred on the TPV/r arm at a frequency of 1.75 to 2.34 times greater than the CPI/r arm for each grade. The increased frequency of hypercholesterolemia was the same with the TPV/r arm having Grade 2-4 treatment emergent hypercholesterolemia at a frequency up to 2.7 times greater than that on the control arm.

Table 7.13.3:5 Proportion of Subjects with Treatment Emergent Hypertriglyceridemia Regardless of Causality

# of Subjects with Hypertriglyceridemia (%)	TPV/r N=730 <sup>1</sup>	CPI/r N=723 <sup>2</sup>
Grade 2 (400-750 mg/dL)	195 (26.7%)	111 (15%)
Grade 3 (751-1200 mg/dL)	96 (13.1%)	41 (6%)
Grade 4 (>1200 mg/dL)	45 (6%)	24 (3%)

Source: 12/5/04 1182.12 and 1182.48 LAB dataset and CHEM dataset

3. Sixteen subjects were censored on the TPV/r arm because of multiple missing data points.
4. Fourteen subjects were censored on the CPI/r arm because of multiple missing data points.

*MO comment: At 24 Weeks there were only 5 subjects (3 on the TPV/r arm; 2 on the CPI/r arm) who developed clinical pancreatitis and only 1 of these subjects (on the CPI/r arm) had a documented elevated triglyceride level. One subject discontinued treatment with TPV/r due to hypertriglyceridemia.*

Table 7.1.3.3:6 Proportion of Subjects with Treatment Emergent Hypercholesterolemia Regardless of Causality

# of Subjects with Hypercholesterolemia (%)	TPV/r N=730 <sup>1</sup>	CPI/r N=723 <sup>2</sup>
Grade 2 (>300 - 400 mg/dL)	84 (11.5%)	31 (4%)
Grade 3 (>400 - 500 mg/dL)	18(2%)	2 (0.2%)
Grade 4 (> 500 mg/dL)	6 (0.8%)	0 (0%)

Source: 12/5/04 1182.12 and 1182.48 LAB dataset and CHEM dataset

5. Fourteen subjects were censored on the TPV/r because of multiple missing data points.
6. Fourteen subjects were censored on the CPI/r because of multiple missing data points.

*MO comment: Keeping in mind that all of the PI regimens used in the RESIST trials were boosted by RTV and therefore have the potential to cause hyperlipidemia, the TPV/r arms had a much higher rate of hyperlipidemia as compared to the CPI/r arms. It is not clear whether the extent of the hyperlipidemia is due to the TPV or the RTV or a combination of the two. Regardless, TPV boosted by 200mg of RTV is currently the only way TPV will be marketed, so whether the laboratory abnormalities are due to TPV or RTV they are expected to occur with this boosted PI much more frequently than the boosted PIs studied (namely, LPV/r, SQV/r, IDV/r and APV/r).*

Hypertriglyceridemia was also observed in Phase 1 and 2 studies. Increases in triglyceride levels were reported in 18 of the 20 multi-dose studies and in 2 of the 5 single dose studies. A total of 178 subjects (27%) in the multi-dose studies with normal triglyceride levels at baseline had increases in triglycerides to greater than the upper limit of normal including 27 subjects with Grade 2 increases in triglyceride and one with a Grade 3 increase. Three subjects discontinued study drug due to elevated triglyceride levels. Ritonavir's contribution to the rate of hypertriglyceridemia in healthy volunteers cannot be determined, however, increased triglyceride levels were reported in 24 subjects

in the four studies in which RTV was not used. In the Phase 2 dose finding study 1182.52, 38.4% (83/216) of patients on TPV/r had Grade 2-4 treatment emergent hypertriglyceridemia and 14.8% (32/216) of patients on TPV/r had Grade 2-4 treatment emergent hypercholesterolemia.

#### 7.1.4 Other Search Strategies

Additional searches were performed by BIPI and FDA to evaluate safety signals observed in the preclinical studies including bleeding and renal dysfunction. Neither BIPI nor FDA found evidence increased bleeding or renal dysfunction in the controlled studies.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

Per BIPI the pre-treatment period was defined as the time between the patient signing the informed consent form and his or her first dose of study medication, and the treatment period was defined as the time from the first dose of study medication to three (3) days after the last dose of study medication. The post-treatment period was defined as the time after the treatment period.

*MO comment: BIPI designed the RESIST trials to capture data for only five half-lives (namely, 3 days) after the subject discontinued study unless that subject had an unresolved AE. Therefore AEs that may have started shortly after study drug discontinuation, but outside of the 3-day window, were not routinely captured. During the Pre-NDA meeting with BIPI this error in design was brought to the attention of the FDA and the FDA instructed BIPI to amend all ongoing studies to include a 30-day follow-up period. As stated earlier, this reviewer defined the treatment period" as day 1 of treatment through a 30 day follow-up period post treatment.*

BIPI defined an AE "any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with pharmaceutical product". An SAE was defined as "any AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, is deemed to be serious for any other reason representing a significant hazard, which is comparable to the aforementioned criteria".

Adverse events were monitored throughout the study and reported in the CRF. At every visit the investigator was to ask the question, "How have you felt since your last clinic visit?". Investigators noted the onset, duration, intensity, treatment required, outcome and any action taken with the investigational products. The intensity of each event was recorded as "mild", "moderate" or "severe". Investigators were instructed to record DAIDS graded events as "mild" for DAIDS Grade 1 events, "moderate" for DAIDS

Grade 2 events, and “severe” for both DAIDS Grade 3 and 4 events. To derive Grade 4 clinical AEs for analyses, BI grouped AEs that were recorded as “severe” with those meeting the criteria for SAE.

*MO comment: The FDA disagreed with this post-hoc assessment of “Grade 4” clinical events and decided to analyze the data as presented, which means that there is no way to be certain what portion of the reported AEs are actually due to severe grade 3 AEs versus what portion are due to life-threatening grade 4 AEs and subsequently if there is any difference between the TPV/r group and the CPI/r group with respect to grade 3 and 4 events.*

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

BIPI used the MedDRA dictionary of System Organ Class and Preferred Terms to organize the medical terms for the various AEs provided by the investigator. In general BIPI 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

BIPI’s integrated safety review of HIV positive subjects included data on 1854 subjects. Per BIPI, for all TPV/r doses combined, 83.2% of patients reported any AE, which were severe in 21.5%, considered to be study-drug-related in 47.2%, considered to be drug-related and of moderate and severe intensity in 27.2%, and led to discontinuation of study medication in 9.4%. For all doses combined, the percentage of patients experiencing SAEs, regardless of causality, was 14.8%, and the percentage of patients experiencing drug-related SAEs was 2.2%. According to BIPI “Overall, there appeared to be no direct relationship between TPV/r dose and percentage of patients in the AE categories evaluated.”

*MO comment: The results of multiple FDA analyses for elevated ALT and possibly rash contradict the claim that there is no direct relationship between TPV/r dose and percentages of patients with AEs.*

For the integrated trials of HIV-positive patients the most frequently reported AEs, regardless of causality, were in the system organ class (SOC) gastrointestinal disorders (52.6%), followed by infections and infestations (44.5%), general disorders and administrative site conditions (30.2%), nervous system disorders (24.1%) and skin and subcutaneous tissue disorders (22.4%).

BIPI’s analysis of the RESIST data (n =1483; 746 TPV/r subjects, 737 CPI/r subjects) up to 24 weeks of treatment concludes that overall the percentage of subjects in any of the AE categories evaluated was “consistently numerically higher in the TPV/r group compared with the CPI/r group.” (Table 7.1.5.3:1)

Table 7.1.5.3: 1 BIPI's analysis of subjects reporting any AEs, AEs leading to discontinuation and drug-related AEs up to Week 24

Adverse Events	TPV/r N=746	CPI/r N=737
% of Subjects reporting any AE	82.4%	77.2%
% of Subjects reporting any AE believed to be drug-related	41.7%	27.8%
% of Subjects reporting any severe (Grade 3 or 4) AE	17.6%	14.7%

For both treatments and both trials combined, based on data up to 24 weeks of treatment, the highest percentages of patients (>20%) reported AEs, regardless of causality, in the gastrointestinal disorders SOC (45.0%), followed by infections and infestations (40.5%), general disorders and administrative site conditions (27.4%) and nervous system disorders (21.3%).

*MO comment: In the HIV+ positive trials there appears to be a large difference between all causality AEs and drug related AEs. According to the AE datasets drug relatedness was captured as a "yes" or "no" instead of "unlikely, possibly, probably, or definitely". Therefore investigators who were not positive of the drug's relatedness given the limited option of answering "yes or no" might be more inclined to say "no" and potentially underestimate the drugs' role in causing AEs. Assessing drug causality of AEs in open label trials is complicated and subject to an extreme amount of bias. In this subject population even if the trial was blinded the nature of the disease and the advanced clinical disease of the enrolled subjects makes differentiating disease from drug very difficult at the single investigator level.*

BIPI assessed the AE frequencies in 12 trials of HIV negative subjects (n = 397 subjects) excluding Trials 1182.5 and 1182.45. The percentage of subjects reporting any AE for the 3 TPV/r dose groups (500/100 mg, 500/200 mg, 750/200 mg) combined was 86.6%. The percentages of patients in each of the AE categories were generally lowest in the TPV/r 500 mg/200 mg treatment group and highest in the TPV/r 750 mg/200 mg group. The percentages of subjects for the combined TPV/r dose groups reporting the following types of AEs were as follows:

- 83.1% - AEs considered to be drug-related (lowest percentage of 69.1% in the TPV/r 500 mg/200 mg treatment group);
- 3.8% - severe AEs (lowest percentage of 0.8% in the TPV/r 500 mg/200 mg treatment group)

In the 12 trials of HIV-negative subjects, individual AEs (preferred terms) reported by the highest percentages of subjects (>10%), regardless of causality, were: nausea (50.4%),

diarrhea (30.5%), abdominal pain, total (30.2%), headache (29.5%), loose stools (26.7%), dizziness (21.7%), vomiting (18.4%), fatigue (14.6%), flatulence (10.8%).

*MO comment: This reviewer combined “abdominal pain” at 19.9% and “abdominal pain upper” at 10.3% into “abdominal pain, total” to arrive at a frequency of 30.2%.*

#### 7.1.5.4 Common adverse event tables

*MO comment: The tables that appear in this section are all AE tables derived from FDA analyses of the RESIST data and are without regard to drug causality, which is the most appropriate way to present AE data for this application in this reviewer’s opinion.*

*This reviewer chose to present a higher cutoff for AEs than recommended by the Clinical Reviewer Guide because AEs of all types and severities are much more common in this type of chronically ill, clinically advanced and ARV resistant HIV-1 infected population as compared to the majority of study subjects.*

The most common AEs regardless of perceived relationship to study drug occurring in at least 5% of the RESIST study population were diarrhea, nausea and headache which were all observed slightly more frequently in the TPV/r group (Table 7.1.5.4)

Table 7.1.5.4:1 All Grade (1-4) Adverse Events by MedDRA Preferred Terms Observed in  $\geq$  5% of Subjects in Either Treatment Group at Week 24 Without Regard to Causality (Safety Population – RESIST trials)

All Grade Adverse Events	TPV/r N=746	CPI/r N=737
Diarrhea	173 (23.2%)	149 (20.2%)
Nausea	123 (16.5%)	100 (13.6%)
Headache	78 (10.5%)	54 (7.3%)
Fatigue	70 (9.4%)	66 (9.0%)
Pyrexia	69 (9.2%)	54 (7.3%)
Vomiting	61 (8.2%)	54 (7.3%)
Abdominal pain	44 (5.9%)	39 (5.3%)
Rash	40 (5.4%)	39 (5.3%)
Nasopharyngitis	40 (5.4%)	28 (3.8%)
Cough	37 (5.0%)	37 (5.0%)

In Study 1182.17 the frequency of all grade AEs were as follows: diarrhea 14%; nausea 9%; pyrexia and upper respiratory tract infection at 7% each; fatigue 6%; nasopharyngitis, vomiting, sinusitis, and cough at 5% each.

*MO comment: The rates of diarrhea and nausea are lower in Study 1182.17 as compared to the RESIST trials. Since Study 1182.17 includes subjects who were*

previously on TPV/r in studies 1182.2, 1182.4 and 1182.6, this lower rate may support the applicants theory that the highest rate of diarrhea occurs within the first month of dosing.

The proportion of subjects reporting any Grade 2, 3, or 4 AE at a frequency of at least 2% are presented in Table 7.1.5.4:2 below. Similar to all grade AEs, diarrhea and nausea are the most common Grade 2-4 AEs in both study groups.

Table 7.1.5.4:2 Percentage of Patients with Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in  $\geq 2\%$  of Patients in Either Treatment Group<sup>a</sup>

	TPV/r (n=746)	CPI/r (n=737)
<b>Gastrointestinal Disorders</b>		
Diarrhea	10.9%	9.4%
Nausea	6.7%	4.6%
Vomiting	3.4%	3.0%
Abdominal pain <sup>b</sup>	2.8%	3.7%
<b>General Disorders</b>		
Pyrexia	4.6%	4.3%
Fatigue	4.0%	3.9%
Asthenia	1.5%	2.3%
<b>Infections and Infestations</b>		
Bronchitis	2.9%	1.1%
<b>Nervous System Disorders</b>		
Headache	3.1%	3.1%
<b>Psychiatric Disorders</b>		
Depression	2.0%	3.0%
Insomnia	1.2%	2.6%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	0.8%	2.2%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	2.0%	2.0%

<sup>a</sup>Excludes laboratory abnormalities that were considered Adverse Events

<sup>b</sup>Abdominal pain includes Preferred Terms "Abdominal pain" and "Abdominal pain upper"

*MO comment: Infections and infestations (namely bronchitis) and nausea occurred more frequently on the TPV/r arm while psychiatric disorders (namely depression and insomnia) and cough occurred more frequently on the CPI/r. Otherwise, moderate to severe (Grade 2 – 4) treatment emergent AEs among the two study groups were similar and are expected for this patient population and these ritonavir boosted PI containing regimens.*

Diarrhea (6.3%), nausea (3.3%) and pyrexia (3.2%) were the most common treatment emergent Grade 2-4 AEs in the Rollover study, 1182.17.

*MO comment: Again, the slightly lower rates of diarrhea and nausea in Study 1182.17 as compared to the RESIST trials may be explained by accommodation to the effect of RTV.*

Table 7.1.5.4:3 presents severe adverse events seen in more than one subject on either arm of the RESIST trials. The most common severe adverse events observed on the TPV/r arms that were rarely if ever seen ( $\leq 1$  subject) on the CPI/r arms were nausea, increased ALT, increased AST, pneumonia, asthenia, dehydration, cytolytic hepatitis, herpes virus infection, hyperlipidemia, and pancreatitis. On the other hand the CPI/r arms had more esophageal candidiasis, PCP, and cryptosporidiosis.

Table 7.1.5.4:3 Severe Adverse Events (Grade 3 and 4) by MedDRA Preferred Terms Observed >1 Subject in Either Treatment Group through Week 24 Without Regard to Causality (Safety Population – RESIST trials)

Severe Adverse Events	TPV/r N=746	CPI/r N=737
Diarrhea	10 (1.3%)	13 (1.8%)
Nausea	8 (1.1%)	1 (0.1%)
Hypertriglyceridemia <sup>1</sup>	8(1.1%)	5 (0.7%)
Alanine aminotransferase increased	7 (0.9%)	2 (0.3%)
Aspartate aminotransferase increased	6 (0.8%)	1 (0.1%)
Headache	6 (0.8%)	6 (0.8%)
Pneumonia	6 (0.8%)	1 (0.1%)
Pyrexia	6 (0.8%)	3 (0.4%)
Vomiting	6 (0.8%)	2 (0.3%)
Abdominal pain	4 (0.5%)	3 (0.4%)
Asthenia	4 (0.5%)	1 (0.1%)
Dehydration	4 (0.5%)	1 (0.1%)
Dyspnoea	4 (0.5%)	2 (0.3%)
Fatigue	4 (0.5%)	4 (0.5%)
Cytolytic hepatitis	3 (0.4%)	0
Cytomegalovirus chorioretinitis	3 (0.4%)	1 (0.1%)
Depression	3 (0.4%)	3 (0.4%)
Gamma-glutamyltransferase increased	3 (0.4%)	2 (0.3%)
Herpes virus infection	3 (0.4%)	0
Hyperlipidemia	3 (0.4%)	0
Pancreatitis	3 (0.4%)	0

<b>Severe Adverse Events</b>	<b>TPV/r N=746</b>	<b>CPI/r N=737</b>
Respiratory failure	3 (0.4%)	0
Acquired immunodeficiency syndrome	2 (0.3%)	0
Anemia	2 (0.3%)	4 (0.5%)
Back pain	2 (0.3%)	1 (0.1%)
Cachexia	2 (0.3%)	2 (0.3%)
Death	2 (0.3%)	2 (0.3%)
Dizziness	2 (0.3%)	0
Gastroenteritis	2 (0.3%)	1 (0.1%)
Hodgkin's disease	2 (0.3%)	0
Kaposi's sarcoma	2 (0.3%)	0
Liver disorder	2 (0.3%)	0
Progressive multifocal leukoencephalopathy	2 (0.3%)	4 (0.5%)
Rectal cancer	2 (0.3%)	1 (0.1%)
Renal failure acute	2 (0.3%)	0
Renal insufficiency	2 (0.3%)	1 (0.1%)
Road traffic accident	2 (0.3%)	0
Sciatica	2 (0.3%)	0
Esophageal candidiasis	1 (0.1%)	5 (0.7%)
Pneumocystis carinii pneumonia	1 (0.1%)	4 (0.5%)
Dysphagia	1 (0.1%)	3 (0.4%)
Central nervous system lymphoma	1 (0.1%)	2 (0.3%)
Febrile neutropenia	1 (0.1%)	2 (0.3%)
Neuropathy peripheral	1 (0.1%)	2 (0.3%)
Neutropenia	1 (0.1%)	2 (0.3%)
Gastroenteritis cryptosporidial	0	4 (0.5%)
White blood cell count decreased	0	3 (0.4%)
Aseptic necrosis bone	0	2 (0.3%)
Central nervous system lesion	0	2 (0.3%)
Cytomegalovirus esophagitis	0	2 (0.3%)
Lethargy	0	2 (0.3%)
Pancytopenia	0	2 (0.3%)
Perianal abscess	0	2 (0.3%)

Source: AECD12 and AECD48 datasets

1. Preferred terms "Hypertriglyceridemia and Blood triglycerides increased" were combined.

*MO comment: The most common severe AEs observed on the TPV/r arm are consistent with what was seen for AEs in general and the known toxicities of the drug, namely gastrointestinal toxicity, infections, hepatotoxicity and hyperlipidemia. The severe AEs observed on the CPI/r are consistent with advanced HIV, namely opportunistic infections.*

*The category “death” represents four subjects (two on each arm) whose investigators listed their death as separate AEs rather than as an outcome of an AE.*

The frequency and types of severe AEs in the RESIST trials and the Rollover study were similar with diarrhea and ALT elevations being the most common at 1% each.

#### 7.1.5.5 Identifying common and drug-related adverse events

Based on what is known of the PI class, specifically RTV boosted PIs, TPV can reasonably be considered the cause of the diarrhea, nausea, vomiting, and abdominal pain commonly observed in the Phase 1 through Phase 3 clinical trials. In addition based on the data reviewed elevated ALT, elevated AST, rash in female subjects, hypertriglyceridemia, and hypercholesterolemia appear to be TPV specific above and beyond what is expected in this drug class.

#### 7.1.5.6 Additional analyses and explorations

Please refer to section 7.1.3.3 for additional analyses of the TPV/r drug-related AEs namely, hepatotoxicity, rash and hyperlipidemia.

#### 7.1.6 Less Common Adverse Events

Less common (<1%) AEs were identified in the RESIST database; however, the numbers were so small that it was impossible to discern any trends or differences between the study arms.

In the Phase 1 studies an uncommon adverse event in subjects taking TPV/r was change in cognition or decreased concentration. One study was changed from an outpatient study to an inpatient study after three subjects complained that difficulties concentrating were interfering with their ability to drive. Ten other subjects reported similar adverse events. Although TPV crosses the blood brain barrier, the reason for this adverse event is not known.

#### 7.1.7 Laboratory Findings

##### 7.1.7.1 Overview of laboratory testing in the development program

As per the RESIST protocols blood samples for hematologic and chemistry safety laboratory analyses were collected at all visits; urine samples were collected at screening, Week 48 and at end of treatment (EOT); and pregnancy tests for female subjects were performed at screening and Weeks 16, Week 24, Week 32, Week 48, Week 64, Week 80 and at EOT. In addition, hepatitis serology was performed at screening to determine the patient’s baseline hepatitis status.

Laboratory abnormalities with clinical symptoms were not reported as AEs. Laboratory abnormalities were reported as AEs when the following occurred: 1) temporary or permanent study drug discontinuation, 2) adjustment of concomitant medication or 3) recording of concurrent clinical symptoms.

Investigators were allowed to use their discretion regarding the frequency at which an abnormal laboratory value was followed up and whether an abnormal laboratory value merited discontinuing the study drug. Investigators were encouraged but not mandated to use the central laboratory for following-up laboratory abnormalities.

The Division of AIDS (DAIDS) grading was used to assess the severity of laboratory test abnormalities. Since DAIDS grading was not available for all lab tests performed, some tests were assessed with alternative grading scales. These alternative grading scales included: white blood cell (WBC) increases and decreases, which were based on Eastern Co-operative Oncology Group grading (ECOG ); and total cholesterol, which was based on Common Toxicity Criteria (CTC).

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

Laboratory datasets were available for the TPV Phase 2 and 3 development program. The laboratory data reviewed for this Clinical Review focused on that from the pivotal RESIST trials where the rates of laboratory abnormalities on the TPV/r arm were analyzed and compared to the rates of laboratory abnormalities on the CPI/r arm.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

BIPI and the FDA analyzed laboratory test results for all patients in the RESIST trials who had both a baseline and an on-treatment or final laboratory measurement. The vast majority of subjects (98%) on the combined arms in the RESIST trials met this criterion. The following Table presents treatment emergent laboratory values occurring in  $\geq 2\%$  of patients.

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Table 7.1.7.3:1 Treatment Emergent Laboratory Abnormalities Reported in  $\geq 2\%$  of patients.

				Studies 1182.12 and 1182.48 (24-weeks)	
				APTIVUS/Ritonavir (500/200 mg BID) + OBR N=732	Comparator PI/Ritonavir + OBR* N=726
		Limit			
<b>Hematology</b>					
WBC count decrease					
Grade 3-4		< 2.0x 10 <sup>3</sup> / $\mu$ L		3.6%	5.4%
<b>Chemistry</b>					
Amylase					
Grade 3-4		>2xULN		2.9%	4.8%
ALT					
Grade 2		> 2.5-5 X ULN		10.7%	5.4%
Grade 3		> 5-10 X ULN		3.1%	1.4%
Grade 4		> 10 X ULN		2.7%	0.4%
AST					
Grade 2		> 2.5-5 X ULN		6.0%	5.8%
Grade 3		> 5-10 X ULN		3.3%	1.0%
Grade 4		> 10 X ULN		0.7%	0.4%
ALT and/or AST					
Grade 2-4		> 2.5 X ULN		17.5%	9.9%
Cholesterol					
Grade 2		>300 – 400 mg/dL		11.3%	4.3%
Grade 3		>400 – 500 mg/dL		2.5%	0.3%
Grade 4		>500 mg/dL		0.8%	0%
Triglycerides					
Grade 2		400 – 750 mg/dL		26.2%	14.7%
Grade 3		>750 – 1200 mg/dL		12.8%	5.6%
Grade 4		>1200 mg/dL		6.1%	3.4%

*MO comment: Grade 2 – 4 ALT, cholesterol and triglycerides occurred more commonly on the TPV/r arm versus the CPI/r as presented earlier in Section 7.3.3. On the CPI/r arm there were more grade 3-4 WBC decreases and amylase increases.*

7.1.7.3.1 Analyses focused on measures of central tendency

Table 7.1.7.3:1 Median Baseline and Median Changes from Baseline in Chemistry Laboratory Values

Chemistry Parameters	N	TPV/r		N	CPI/r	
		Median Baseline values	Median Change at Week 24		Median Baseline values	Median Change at Week 24
AL T (U/L)	730	29	5	723	30	0
AST (U/L)	730	30	0	723	31	1
Bilirubin (mg/dL)	730	0.41	-0.06	723	0.41	0
Cholesterol (mg/dL)	730	175	29	723	178	0
Creatinine	730	0.86	0	723	0.84	0
HDL (mg/dL)	726	33.6	0.8	712	33	0
LDL (mg/dL)	589	91	17	608	93.1	1.1
Triglyceride (mg/dL)	730	231.5	46	723	235	-8

*MO comment: When looking at labs in terms of change from baseline once again a difference between study arms is noted in ALT, cholesterol and triglyceride. However, there is also a noticeable difference in LDL with the TPV/r arm having LDLs increase by a median of 17 while the CPI/r arm had a median increase of 1.1. No cardiac events or signals were highlighted in the safety review by either the applicant or the FDA, but 24 weeks may be too short of a time period to capture such outcomes. Hyperlipidemia and cardiac events warrant follow-up at the time of the 48 Week data review. The applicant is also planning to conduct a large database analysis to assess the cardiovascular risk factors associated with TPV/r use.*

Table 7.1.7.3.7:2 Baseline and Median Changes from Baseline in Select Hematology Laboratory Values

Median Hematology Parameters	N	TPV/r		N	CPI/r	
		Baseline values	Change at Week 24		Baseline values	Change at Week 24
Hemoglobin (g/dL)	722	14.0	-0.2	710	14.1	0
Platelets (/mm <sup>3</sup> )	714	203,000	1,500	704	198,500	9,000
RBC 10 <sup>12</sup> /L	722	4.3	0	710	4.4	0.1
WBC 10 <sup>9</sup> /L	720	4.8	0.1	710	4.9	0.1

*MO comment: This reviewer is not certain if the relative thrombocytosis observed on the CPI/r has any clinical relevance. Otherwise median changes in hematologic parameters were similar between the treatment arms.*

#### 7.1.7.4 Additional analyses and explorations

Additional analyses to evaluate for dose dependence were performed for elevated ALTs. Evidence suggests that TPV/r induced elevated transaminases are dose dependent. Please refer to Section 7.1.3.3 for a detailed discussion of dose dependence as it relates to hepatotoxicity.

#### 7.1.7.5 Special assessments

Please refer to Section 7.1.3.3 for a detailed discussion of TPV/r related hepatotoxicity and hyperlipidemia.

### 7.1.8 Vital Signs

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs in the pivotal RESIST trials and supportive trials, 1182.51 and 1182.52 were not collected beyond the baseline visit. Baseline, on study and end of treatment vital signs including blood pressure and heart rate were collected in the supportive trials 1182.2, 1182.4 and 1182.6 only.

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

None of the controlled studies collected vital signs past baseline therefore there are no TPV/r-control analyses for vital signs.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

No applicable (see explanation under Section 7.1.8.2)

#### 7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were conducted by either BIPI or the FDA.

### 7.1.9 Electrocardiograms (ECGs)

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

The potential of TPV to prolong QTc interval was assessed both in vitro and in vivo. TPV had no effect in either the in vitro guinea pig papillary muscle action potential duration study or the in vivo ECG study in dogs, suggesting that TPV has little potential to prolong the QTc interval. Additionally, no ECG changes were observed in beagle dogs in toxicity studies when TPV was administered up to 39 weeks or when TPV was co-administered with RTV for up to 26 weeks.

TPV has an effect in vitro on the hERG-associated potassium channel (I<sub>Kr</sub>) with an IC<sub>50</sub> of 2.9 μM; however, the plasma concentration associated with the IC<sub>50</sub> value is greater than 60-fold the observed maximum concentration (C<sub>max</sub>) associated with the human therapeutic dose of TPV/r 500 mg/200 mg BID.

BIPI reports that in five Phase 1 trials where 12-lead ECGs were performed at baseline and then again post-treatment TPV/r (doses ranging from 500 mg/100 mg to 1250 mg/100 mg, and 250 mg/200 mg to 1000 mg/200 mg) used alone or in combination with other agents (fluconazole, rifabutin and loperamide) showed no evidence for any ECG effects that may raise a cardiac safety concern.

BIPI is currently conducting a formal QT study to further evaluate TPV's potential to prolong QT.

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

#### 7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

#### 7.1.9.4 Additional analyses and explorations

Not applicable.

#### 7.1.10 Immunogenicity

Although TPV 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 suggested that TPV might have immunostimulatory and/or immunosuppressive potential. The T-dependent antigen response to sheep red blood cells was performed and the results of this study indicate that TPV is not an immunosuppressive agent (see Section 3.2). The immunostimulatory effect of TPV is less clear; there are no definitive assays to rule in or rule out TPV's immunostimulatory potential. Additional evidence to support or refute the theory that TPV may have immunostimulatory potential will need to come from clinical studies. The studies reviewed in support of this NDA show that rarely TPV use has been associated with hypersensitivity like reactions, especially in women.

*MO comment: TPV's true immunostimulatory potential is unknown and requires further investigation in a clinical setting.*

#### 7.1.11 Human Carcinogenicity

Human carcinogenicity studies are pending.

### 7.1.12 Special Safety Studies

No special safety studies were submitted with this application.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section is not applicable since TPV/r has no abuse potential.

### 7.1.14 Human Reproduction and Pregnancy Data

Studies in rats demonstrated that TPV and its metabolites are present in low amounts in breast milk (milk: plasma concentration ratio of total radioactivity range 0.0779 to 0.253). TPV was more abundant than metabolites. There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. There have been 5 known cases of pregnancy through the 11 June 2004 cutoff date from trials using TPV. It should be noted that pregnancy was not systematically reported as an AE or SAE. The outcome for these 5 cases includes a normal birth in 2 cases, a planned termination in 2 cases, and a continued pregnancy in 1 case. Below is a summation of these 5 known cases.

1. 2003-BP-09693BP – Trial 1182.12, Pt #2070, a 36-year-old black female, received TPV/r from 14 July 2003 to 13 November 2003. The TPV/r medication was discontinued when the pregnancy test results came back positive on [redacted].  
– The outcome from the pregnancy was reported as induced abortion.
2. 2003-FF-00366FF – Trial 1182.48, Pt #3119, a 34-year-old female, received TPV/r from 07 May 2003 to 08 July 2003. The TPV/r medication was discontinued on 08 July 2003. The date of conception was determined to be [redacted] prior to starting TPV/r. The outcome from this pregnancy was the premature delivery on [redacted] ( [redacted] weeks) of a normal female baby with no malformations observed and an Apgar score of 10/10. The weight of the baby was [redacted] and the body length was [redacted].
3. 2004-BP-02117RA – Trial 1182.48, Pt #1199, a 38-year-old white female, began TPV/r on 12 November 2003. This patient discontinued TPV/r upon learning the results of her pregnancy test [redacted]. As of [redacted] she was in her [redacted] month of pregnancy with adequate fetal growth and no pregnancy-related complications. She is currently receiving Kaletra/ZDV/3TC. BIPI provided an update that the subject delivered via C-section at 35 weeks a normal male baby with no malformations observed. The birth weight was [redacted]. Apgars were not recorded.
4. 2004-DE-02063SI – Trial 1182.48, Pt #2615, a 30-year-old female, began TPV/r on 16 October 2003 with the TPV/r continuing at this time. The estimated date of conception was [redacted]. The pregnancy has been reported to have resulted in a normal delivery in the interim. At birth, the child tested HIV-negative.

5. Trial 1182.5, Pt #4165, a 36-year-old white female, began TPV on 12/1/03. When the patient came in for the next visit after the start of treatment, it was discovered that the patient was pregnant. TPV was discontinued on 12/15/03. The patient subsequently elected to terminate the pregnancy.

#### 7.1.15 Assessment of Effect on Growth

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

#### 7.1.16 Overdose Experience

This section is not applicable since neither this reviewer nor the applicant has any knowledge of any subjects who deliberately or inadvertently overdosed on TPV/r.

#### 7.1.17 Postmarketing Experience

Not applicable since TPV/r is only recently licensed in one other country, Switzerland, and no postmarketing studies or assessments have been conducted.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

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

A total of 3195 patients or subjects (2430 HIV-positive patients and 765 HIVnegative subjects) have been exposed to at least 1 dose of TPV in 39 clinical trials at the time of the June 11, 2004 cutoff. In total, 1397 HIV-positive patients have received TPV/r at the intended market dose of 500 mg/200 mg for a total of 685.1 exposure years; 761 of these patients have been exposed to TPV/r for 24 weeks.

In the RESIST trials, at the time of database cut-off, 746 subjects had received at least one dose of TPV/r.

##### 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 3 studies RESIST 1 and 2 were the primary sources of safety data.

## 7.2.1.2 Demographics

The following table provides demographic data for all subjects in the BIPI's safety database.

*MO comment: Although 39 trials were submitted for review of safety data, BIPI only provided demographic data on 38 trials. The naïve study, 1182.33, was excluded because at the time of submission the data was still blinded to BIPI and had not been entered into the database.*

Table 7.2.1.2:1 Baseline Demographics for All Patients or Subjects on TPV

	Sponsor and No. of Trials or Trial No. Number/Percent of Patients or Subjects															
	BI (8) HIV-positive <sup>a,c</sup>		P&U (2) HIV-positive <sup>b</sup>		BI 1182.14 paediatrics <sup>c</sup>		BI 1182.33 naïve <sup>c,d</sup>		BI 1182.58 EUP <sup>c,e</sup>		BI (14) HIV-negative <sup>f,c</sup>		P&U (12) HIV-negative <sup>g</sup>		Totals from 38 trials <sup>h</sup>	
Total treated	1854	100.0	71	100.0	37	100.0	15	100.0	450	100.0	540	100.0	225	100.0	3175	100.0
Age																
< 18	2	0.1	0	0.0	37	100.0	0	0.0	3	0.1	0	0.0	0	0.0	42	1.3
18-40	732	39.5	51	71.7	0	0.0	0	0.0	91	20.2	322	59.6	172	76.4	1368	43.1
41-55	944	50.9	15	21.1	0	0.0	0	0.0	147	32.7	154	28.5	52	23.1	1312	41.3
56-64	154	8.3	3	4.2	0	0.0	0	0.0	21	4.7	45	8.3	0	0.0	223	7.0
>= 65	22	1.2	1	1.4	0	0.0	0	0.0	1	0.1	19	3.5	1	0.4	44	1.4
Missing	0	0.0	1	1.4	0	0.0	15	100.0	185	41.1	0	0.0	0	0.0	186	5.9
Gender																
Male	1603	86.5	55	77.5	19	51.4	0	0.0	238	52.9	288	53.3	183	81.3	2386	75.1
Female	251	13.5	16	22.5	18	48.6	0	0.0	28	6.2	252	46.7	42	18.7	607	19.1
Missing	0	0.0	0	0.0	0	0	15	100.0	182	40.4	0	0.0	0	0.0	182	5.7
Race																
White	1465	79.0	35	49.3	20	54.1	0	0.0	124	27.5	470	87.0	203	90.2	2317	72.9
Black	244	13.2	34	47.9	15	40.5	0	0.0	33	7.3	63	11.7	16	7.1	405	12.8
Asian	11	0.6	0	0.0	2	5.4	0	0.0	4	0.1	7	1.3	2	0.1	26	0.8
Other	3	0.2	2	2.8	0	0.0	0	0.0	0	0.0	0	0.0	4	1.7	9	0.3
Missing	131	7.1	0	0.0	0	0.0	15	100.0	287	63.8	0	0.0	0	0.0	418	13.2

a BI trials in HIV-positive patients: 1182.2, 1182.4, 1182.6, 1182.12, 1182.17, 1182.48, 1182.51, 1182.52 (Table 1.2.1, Mod 5, Sec 3.5.3,).

b P&U trials in HIV-positive patients: M/3342/4 (BI 1182.1), M/3342/15 (BI 1182.3).

c Trials 1182.14, 1182.12, 1182.17, 1182.32, 1182.33, 1182.48 and 1182.58 are ongoing trials.

d No data from CRFs has been entered at the time of data cutoff. The information shown is currently blinded to the sponsor and is shown for completeness of information and is not included in the Totals from 38 trials because it is not known how many of the patients were receiving TPV/r or LPV/r.

e Systematic collection of CRFs is not done in this trial; therefore, demographic data are available for only a subset of patients. A total of 450 patients have received TPV/r in the trial, with 2 of the 450 patients receiving TPV in prior TPV trials and are excluded in the total treated column. One additional patient was randomised but did not receive TPV and is excluded from the table.

f BI trials in HIV-negative subjects: 1182.5, 1182.10, 1182.11, 1182.21, 1182.22, 1182.24, 1182.32, 1182.37, 1182.41, 1182.42, 1182.44, 1182.45, 1182.46, 1182.55 (Table 1.2.4, Mod 5, Sec 3.5.3,).

g P&U trials in HIV-negative subjects: M/3342/1, M/3342/2, M/3342/3, M/3342/5, M/3342/7, M/3342/8, M/3342/9, M/3342/11, M/3342/12, M/3342/13, M/3342/14, M/3342/19.

h Although there are 39 trials in the submission, data from 1182.33 are not included because data from CRFs have not been entered as of the cutoff date and because the trial is currently blinded to the sponsor.

i A total of 57 patients have been randomised and treated with TPV/r as of the 11 June 2004 cutoff. Safety data from CRFs are available for 37 of the patients.

Sources: Section 1.6.2, Table 1.6.2: 1, Table 1.2.4, Mod 5, Sec 3.5.3, ; Synopsis 2.7.6.33, U04-3258; Synopsis 2.7.6.25, U04-3384; Synopsis 2.7.6.31, U04-0094

The demographics for the RESIST trials are provided in Table 7.2.1.2:2

Table 7.2.1.2:2 Demographics of RESIST safety population

	Treatment groups/		No. (%) of patients Total
	TPV/r	CPI/r	
Total treated	746 (100.0)	737 (100.0)	1483 ( 100.0)
Age [years]			
<18	2 ( 0.3)	0 ( 0.0)	2 ( 0.1)
18 - 40	280 (37.5)	284 (38.5)	564 (38.0)
41 - 55	395 (52.9)	395 (53.6)	790 (53.3)
56 - 64	61 ( 8.2)	49 ( 6.6)	110 ( 7.4)
>= 65	8 ( 1.1)	9 ( 1.2)	17 ( 1.1)
Missing	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Median	43.0	42.0	43.0
Mean	43.8	43.6	43.7
SD	8.3	7.7	8.0
Range	17-80	21-72	17-80
Gender			
Male	629 (84.3)	651 (88.3)	1280 (86.3)
Female	117 (15.7)	86 (11.7)	203 (13.7)
Missing	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Race			
White	571 (76.5)	542 (73.5)	1113 (75.1)
Black	94 (12.6)	98 (13.3)	192 (12.9)
Asian	5 ( 0.7)	9 ( 1.2)	14 ( 0.9)
Other	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Missing <sup>b</sup>	76 (10.2)	88 (11.9)	164 (11.1)

a Doses in mg, BID, and as follows: TPV/r: 500/200. CPI/r includes: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, APV/r 600/100.

b In some countries, it is prohibited to collect race or ethnicity information.

Source: SCS

### 7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3:1 provides the length of exposure to the different TPV/r dose groups in HIV-1 positive patients.

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Table 7.2.1.3:1 Treatment exposure to TPV/r in HIV-positive patients

	<TPV/r 500/200	TPV/r 500/200	Treatment groups/ >TPV/r 500/200	No. (%) of patients Total: All TPV/r doses
Total treated	217 (100.0)	1397 (100.0)	240 (100.0)	1854 (100.0)
≥ 1 day	217 (100.0)	1397 (100.0)	240 (100.0)	1854 (100.0)
≥ 2 days	217 (100.0)	1396 (99.9)	236 (98.3)	1849 (99.7)
≥ 1 week	213 (98.2)	1390 (99.5)	227 (94.6)	1830 (98.7)
≥ 2 weeks	209 (96.3)	1375 (98.4)	221 (92.1)	1805 (97.4)
≥ 4 weeks	151 (69.6)	1342 (96.1)	129 (53.8)	1622 (87.5)
≥ 8 weeks	132 (60.8)	1295 (92.7)	117 (48.8)	1544 (83.3)
≥ 16 weeks	123 (56.7)	1159 (83.0)	107 (44.6)	1389 (74.9)
≥ 24 weeks	105 (48.4)	761 (54.5)	94 (39.2)	960 (51.8)
≥ 48 weeks	85 (39.2)	57 (4.1)	78 (32.5)	220 (11.9)
≥ 96 weeks	29 (13.4)	6 (0.4)	31 (12.9)	66 (3.6)
≥ 144 weeks	17 (7.8)	0 (0.0)	22 (9.2)	39 (2.1)
Mean [days]	358.7	179.1	309.4	217.0
SD [days]	434.1	110.4	436.3	245.4
Median [days]	167.0	169.0	32.5	168.0
Min [days]	2	1	1	1
Max [days]	1769	679	1767	1769
Total exposure years <sup>a</sup> <sup>b</sup>	213.1	685.1	203.3	1101.5

SD = standard deviation

a Includes data from the following trials: 1182.2, 1182.4, 1182.6, 1182.12, 1182.17, 1182.48, 1182.51, 1182.52. All doses in mg and BID. TPV/r <500/200 dose grouping: 250/200, 500/100. TPV/r >500/200 dose grouping: 750/100, 750/200, 1000/100, 1250/100.

b Definition of total exposure years: (sum of total duration across all patients)/365.25.

Source: SCS

Exposure in the RESIST trials are presented in Table 7.2.1.3:2.

*MO comment: BIPI chose to start calculating exposure from the day of randomization to study drug; however 25% (n=185) of control subjects were randomized to the PI they were already taking. These subjects were on their PIs a median of 512 days (range 89 – 2330 days) prior to randomization. In this type of situation the optimal way to calculate exposure is unclear to this reviewer; however, the CPI/r arm's lengthy prior exposure to these drugs cannot be ignored*

Table 7.2.1.3:2 Treatment exposure to trial medication in the RESIST trials

	TPV/r	Treatment groups/ CPI/r	No. (%) of patients Total
Total treated	746 (100.0)	737 (100.0)	1483 (100.0)
>= 1 day	746 (100.0)	737 (100.0)	1483 (100.0)
>= 2 days	745 (99.9)	733 (99.5)	1478 (99.7)
>= 1 week	743 (99.6)	730 (99.1)	1473 (99.3)
>= 2 weeks	738 (98.9)	728 (98.8)	1466 (98.9)
>= 4 weeks	725 (97.2)	717 (97.3)	1442 (97.2)
>= 8 weeks	713 (95.6)	703 (95.4)	1416 (95.5)
>= 16 weeks	665 (89.1)	526 (71.4)	1191 (80.3)
>= 20 weeks	498 (66.8)	330 (44.8)	828 (55.8)
>= 22 weeks	485 (65.0)	301 (40.8)	786 (53.0)
>= 24 weeks	385 (51.6)	245 (33.2)	630 (42.5)
>= 48 weeks	0 (0.0)	0 (0.0)	0 (0.0)
Mean [days]	147.0	131.1	139.1
SD [days]	39.6	44.8	43.0
Median [days]	168.0	124.0	162.0
Min [days]	1	1	1
Max [days]	274	313	313
Total exposure years <sup>b</sup>	300.3	264.6	564.9

a Doses in mg, BID, and as follows: TPV/r: 500/200, CPI/r includes: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, APV/r 600/100.

b Definition of total exposure years: (sum of total duration across all patients)/365.25.

Source: SCS

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety.

### 7.2.2.1 Other studies

The remaining 37 studies were sources of supportive clinical safety data. The safety results from these 37 studies were not intergrated along with the Phase 3 safety results because they either were conducted in HIV negative subjects, were uncontrolled, lacked CRFs or were not adequately monitored as per study design.

### 7.2.2.2 Postmarketing experience

Not applicable.

### 7.2.2.3 Literature

BIPI provided an extensive review of the literature related to treatment of HIV-1 in particular resistant HIV-1. In addition this reviewer reviewed literature regarding HIV and Hepatitis B and C co-infection.

### 7.2.3 Adequacy of Overall Clinical Experience

Overall based on ICH guidance an adequate number of subjects were exposed to TPV/r at the to-be-marketed dose. However, the TPV clinical program lacked a sufficient number of women in whom issues of exposure, efficacy and safety have been raised during this review, non-whites and patients co-infected with Hepatitis B and C in whom an issue of safety has been raised during this review.

The Phase 3 pivotal trials as designed (open-label, suboptimal control) were prone to many types of bias, which made fair and accurate analyses of the data challenging. Additionally, the study design essentially encouraged a loss of the control arm at Week 8. Nonetheless, looking at the totality of the data submitted, it is possible to conclude that TPV/r is safe and effective in a very restricted patient population with limited treatment options.

*MO comment: Unfortunately 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 RESIST trials where patients on the control arm and even on the TPV/r 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 companies 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

Special animal and *in vitro* testing was adequate. Please refer to Section 3.2 and Dr. Anita Bigger's review for details of preclinical program.

### 7.2.5 Adequacy of Routine Clinical Testing

The types of routine clinical and laboratory testing conducted during the pivotal studies were adequate. The timing of the routine clinical testing is probably inadequate given the safety signal of hepatotoxicity. Routine assessments were conducted every 8 weeks after study Week 8.

*MO comment: Given the relatively limited (in terms of time) data we have on TPV/r induced hepatotoxicity and our recommendation in the label to check LFTs "frequently"*

*BIPI should probably be encouraged to increase LFT monitoring in their ongoing studies.*

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to Section 5 and to Dr. Zhang's review for details of TPV's extensive drug-drug interactions.

#### 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 ADEs be determined prospectively by a blinded adjudication committee. BIPI 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, the trial being open-label and having lots of potential for bias, ADEs being very complex diagnoses to make in real time never mind post-hoc.*

#### 7.2.8 Assessment of Quality and Completeness of Data

After working closely with BIPI to rectify many deficiencies in their AE reporting procedures and safety datasets, the safety data provided was adequate with the following exceptions that have been noted previously throughout this review:

1. BIPI collected data for only 3 days post treatment unless the subject had an ongoing AE.
2. BIPI did not collect Grade 3 and 4 clinical adverse events discretely, but instead captured them collectively as "severe" events.
3. BIPI retrospectively re-assigned AEs as ADEs instead of having an independent, blinded adjudication committee prospectively determine ADEs.
4. BIPI allowed investigator discretion in follow-up of AEs, which lead to inconsistent follow-up of AEs.

#### 7.2.9 Additional Submissions, Including Safety Update

BIPI submitted a Safety Update Report on February 22, 2005 that reported additional safety findings through the cut-off date of September 30, 2004. This reviewer was only able to crosscheck and verify the updated data submitted on "deaths" (see Section 7.1.1) because all other information was in the form of a Study Report. For this reason all information in the Safety Update, other than deaths, are reported here and not integrated

into the Safety review. As per the Safety Update Report, no new safety signals were identified between the time of the original database lock in June 2004 and September 30, 2004.

As of September 30, 2004, 524 (70.1%) of 748 patients in the TPV/r arm and 231 (31.3%) of 737 patients in the CPI/r arms were continuing in the RESIST trials. During the update period, premature discontinuations increased 2 fold in the TPV/r group, from 14.3% to 29.9% and 1.3 fold in the CPI/r group, from 51.6% to 68.7%. The most common reason for discontinuation of study medication in th CPI/r group was due to lack of efficacy (316/737 patients; 42.9%), compared with the TPV/r group (68/748 patients; 9.1%).

*MO comment: Two additional subjects were enrolled into RESIST 2. These subjects were never randomized, but took TPV/r and thus are included in this safety update hence the total number of subjects on the TPV/r arm increased from 746 to 748.*

In the RESIST trials, the most common AEs across both treatment arms were gastrointestinal disorders, which increased from 47.1% to 56.6% in TPV/r patients and from 42.9% to 48.2% in CPI/r patients during update period, followed by infections and infestations, which increased from 43.8% to 53.9% in TPV/r patients and from 37.2% to 44.1% in CPI/r patients during the update period. For drug related events of any severity, the most frequently reported AEs for both treatment groups were diarrhea, which increased from 13.4% to 14.6% in TPV/r patients and from 11.1% to 11.4% in CPI/r patients during the update period, and nausea, which increased from 11.7% to 12.4% in TPV/r patients and from 7.9% to 8.4% in CPI/r patients during the update period, however these AE rates have not been adjusted for duration of exposure.

In the update period, the frequency of Grade 3 or 4 ALT and/or AST elevations increased by approximately 50% in the TPV/r group (9.8% Grade 3 or 4 ALT and/or AST) and increased only by 20% in the CPI/r group (3.0%). Subjects were generally asymptomatic and most continued treatment without permanent discontinuation. No additional risk factors for Grade 3 or 4 AST or ALT elevations were identified.

In the safety updated, the frequency of Grade 3 or 4 cholesterol elevations increased to 4% in the TPV/r patients as compared to 0.4% in CPI/r patients and Grade 3 or 4 triglyceride elevations have increased to 23.3% in TPV/r patients as compared to 12.2% in CPI/r patients.

The frequency of cumulative SAEs in the safety update as compared to the original NDA submission increased in the TPV/r group from 13.1% to 18.9% and increased in the CPI/r group from 11.9% to 14.7%. SAEs associated with liver events, were observed in 14 (1.9%) TPV/r patients as compared to 2 (0.3%) CPI/r patients.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Please refer to Section 7.1.3.3 for a detailed discussion of the drug-related adverse events: hepatotoxicity, hyperlipidemia and rash.

### **7.4 General Methodology**

#### **7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

##### **7.4.1.1 Pooled data vs. individual study data**

Please refer to section 7.1 for the safety review methods including which studies were pooled and which studies were reported individually.

##### **7.4.1.2 Combining data**

Please refer to section 7.1.

#### **7.4.2 Explorations for Predictive Factors**

##### **7.4.2.1 Explorations for dose dependency for adverse findings**

Please refer to Section 7.3.3 for details of explorations for dose dependency of drug-related adverse events.

##### **7.4.2.2 Explorations for time dependency for adverse findings**

The applicant performed an analysis for diarrhea, which is the most common AE observed on TPV/r, occurring in the first 28 days of study. Of the 1483 treated RESIST patients in both trials and both treatments combined, 16.7% reported diarrhea during the first 28 days of therapy: 18.4% in the TPV/r group and 15.1% in the CPI/r group. The median time to the first episode was 4 days overall and for each treatment. The median duration of the first diarrhea episode was 21 days (range of 1 - 236 days) and 18 days (range of 1- 174 days) in the TPV/r and CPI/r groups, respectively. In the TPV/r and CPI/r groups, 10.6% and 6.4% of patients received supportive therapy for diarrhea during the first 28 days. Discontinuation of study medication due to diarrhea beginning in the first 28 days of therapy was observed in 0.8% and 0.4% of patients in the TPV/r and CPI/r groups, respectively. Overall, 13 patients in both treatment groups discontinued study medication due to diarrhea: 9 (69.2%) of these discontinued study medication due

to diarrhea in the first 28 days of treatment: 6 (46.2%) TPV/r and 3 (23.1%) CPI/r patients.

#### 7.4.2.3 Explorations for drug-demographic interactions

The applicant analyzed AEs by age, gender, race and geographic location in the RESIST trials.

##### Age

The focus of the comparison was on the 3 age groups 18-40, 41-55 and 56-64 years. There were only 2 patients <18 and 8 patients >64 years old in the TPV/r group. There were 0 patients <18 and 9 patients >64 years old in the CPI/r group. In the 18-40 year age group, there were 280 TPV/r and 284 CPI/r patients. In the 41-55 year old age group, both TPV/r and CPI/r groups had 395 patients, and in the 56-64 year old age group there were 61 TPV/r patients and 49 CPI/r patients. In general, the overall frequency of AEs was similar among the 3 age groups evaluated in the TPV/r group and in the CPI/r group; however, the percentages of patients with AEs were consistently higher in the TPV/r group.

Comparing the 18-40 and 41-55 years of age groups, there were no individual MSOCs within the TPV/r group with a percentage difference of  $\geq 5\%$  of patients. For the CPI/r group, the MSOC nervous system disorder was 25.0% for the 18-40 age group and 19.5% for the 41-55 age group. Comparing the TPV/r group to the CPI/r group, the following age and SOC had a percentage difference of  $\geq 5\%$ .

- Infections and infestations, 18-40 age: TPV/r 45.4%; CPI/r 40.1%;
- Infections and infestations, 41-55 age: TPV/r 43.5%; CPI/r 34.9%;
- Respiratory, thoracic and mediastinal disorders, 18-40 age: TPV/r 15.4%; CPI/r 9.5%;
- Investigations, 41-55 age: TPV/r 10.9%; CPI/r 5.8%;
- Psychiatric disorders, 18-40 age: CPI/r 17.3%; TPV/r 10.7%.

The number of patients treated in the 56-64 years of age group was smaller than number of patients treated in the 18-40 and 41-55 groups. For TPV/r patients, only the MSOC of general disorders and administration site conditions in the 56-64 age group (31.1%), compared with the 41-55 age group (25.6%); and the SOC investigations, 56-64 age group 14.8%; 18-40 age group 7.5%, were higher by a  $\geq 5\%$  difference in frequency. Only the MSOC respiratory, thoracic and mediastinal disorders was observed to have a higher frequency ( $\geq 5\%$  difference) in the 56-64 CPI/r age group (16.3%) compared with the 18-40 CPI/r age group (9.5%).

Additional differences between treatments for the 56-64 age group were observed:

- Percentages of patients with AEs in the general disorders and administration site conditions and nervous system disorders MSOCs were noticeably higher in the 56-64 age group in the TPV/r group (31.1%, 19.7%, respectively) compared with the CPI/r group (20.4%, 8.2%, respectively);
- Percentage of patients with AEs in the musculoskeletal and connective tissue

- disorders MSOC in the 56-64 age group was higher in the TPV/r group (16.4%) compared with the CPI/r group (8.2%);
- Percentage of patients with AEs in the respiratory, thoracic and mediastinal disorders MSOC in the 56-64 age group was higher in the CPI/r group (16.3%) compared with the TPV/r group (6.6%);
  - Percentage of patients with AEs in the hepatobiliary disorders SOC was higher in all age groups in the TPV/r group, particularly in the 56-64 age group: TPV/r group (8.2%) compared with the CPI/r group (0.0%);
  - Percentage of patients reporting diarrhoea was higher in the 56-64 age group in the TPV/r group (18.0%) compared with the CPI/r group (12.2%);
  - Percentage of patients having the Highest Level Term (HLT) of Candida infections was higher in the 56-64 age group in the CPI/r group (12.2%) compared with the TPV/r group (3.3%).

*MO comment: There appeared to be large differences in the rates of AEs between the two treatment arms in the older age group (56-64 years old). PK evaluations from the RESIST trials demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There were an insufficient number of women greater than age 65 years in the two trials to evaluate the elderly, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported. To the knowledge of this reviewer there is no data on maximum TPV levels in geriatric patients, which may be a better indicator of TPV's potential for toxicity in this population.*

### Gender

There were 629 males and 117 females receiving TPV/r and 651 males and 86 females receiving CPI/r in the 2 trials. The overall frequency of AEs was similar within each of the treatment groups, with both male and female patients receiving TPV/r having a higher percentage of AEs compared with the CPI/r patients. The frequency of AEs by treatment and gender for TPV/r were: males 82.5%, females 82.1%; and for CPI/r were: males 77.1%, females 77.9%.

Comparing the TPV/r males and TPV/r females, the following were observed to have a MSOC percentage difference of  $\geq 5\%$ .

- Gastrointestinal disorders: females 55.6%; males 45.5%;
- General disorders and administration site conditions: males 28.8%; females 22.2%;
- Musculoskeletal and connective tissue disorder: males 17.6%; females 12.0%.

*MO comment: Overall males and females on TPV/r had similar rates of AEs by MSOC.*

Comparing the CPI/r males and CPI/r females, the following were observed to have a SOC percentage difference of  $\geq 5\%$ .

- Gastrointestinal disorders: females 52.3%; males 41.6%;
- General disorders and administration site conditions: males 28.1%; females 19.8%;

- Musculoskeletal and connective tissue disorder: females 22.1%; males 12.1%;
- Infections and infestations: females 41.9%; males 36.6%;
- Blood and lymphatic system disorders: females 11.6%; males 5.1%.

Comparing the TPV/r males and CPI/r males, the following were observed to have a SOC percentage difference of  $\geq 5\%$ .

- Infections and infestations: TPV/r 44.0%; CPI/r 36.6%;
- Musculoskeletal and connective tissue disorder: TPV/r 17.6%; CPI/r 12.0%;
- Psychiatric disorders: CPI/r 16.9%; TPV/r 11.6%.

Comparing the TPV/r females and CPI/r females, the following were observed to have a SOC percentage difference of  $\geq 5\%$ .

- Musculoskeletal and connective tissue disorder: CPI/r 22.1%; TPV/r 12.0%;
- Investigations: TPV/r 9.4%; CPI/r 1.2%.

The following additional findings were observed:

- More males (5.2%) than females (2.6%) in the TPV/r group reported AEs in the renal and urinary disorders MSOC; in the CPI/r group the percentages were almost equal between males (3.4%) and females (3.5%);
- In the MSOC hepatobiliary disorders, the frequency of AEs was higher in both male and females treated TPV/r patients compared with CPI/r patients. TPV/r: (males 2.9%, females 2.6%), and CPI/r: (males 0.9%, females 0.0%);
- In the SOC nervous system disorder, the percentage of females (TPV/r, 14.5%; CPI/r, 16.3%) reporting the preferred term headache was higher in both treatment groups compared with males (TPV/r, 9.7%; CPI/r, 6.1%);
- A higher percentage of females (7.7%) reported the preferred term of rash in the TPV/r group compared with males (4.9%); the opposite was observed in the CPI/r group: 5.5% of males and 3.5% of females.

*MO comment: The applicant's and this reviewer's analysis of rash rate differed in that this reviewer included more preferred terms under the "rash" umbrella; however, the trends are similar with there being a 4-5% difference in rash rate in women between the two treatment arms (TPV/r 14%, 7.7% versus CPI/r 9%, 3.5%).*

### Race

In evaluating data by race, it should be noted that there were over 5 times as many whites as blacks in both treatment groups. There was an insufficient number of Asian patients (n=14 combined TPV/r and CPI/r) to analyse. In addition, the race category of other also consisted of patients for whom data were missing, primarily due to local regulations that prohibit the collection of race and ethnicity information. Comparisons below exclude the other group.

Overall, the percentages of patients in each race group were balanced between the TPV/r and CPI/r groups: TPV/r=571 whites (76.5%), 94 blacks (12.6%), and 81 other (10.9%); CPI/r=542 whites (73.5%), 98 blacks (13.3%), and 97 other (13.2%).

Comparing the TPV/r white patients and TPV/r black patients, the following were observed to have a MSOC percentage difference of  $\geq 5\%$ .

- Infections and infestations: blacks 58.5%; whites 40.6%;
- Skin and subcutaneous tissue disorders: whites 21.0%; blacks 16.0%;
- Musculoskeletal and connective tissue disorder: whites 18.9%; blacks 12.8%;

The following HLTs account for some, but not all, of the differences in the frequency observed for infections and infestations between black and white patients receiving TPV/r:

- Upper respiratory tract infection (URTI): blacks 21.3%; whites 13.0%;
- Herpes viral infections: blacks 12.8%; whites 8.2%;
- Candida infections: blacks 8.5%; whites 4.4%.

Comparing the CPI/r white patients and CPI/r black patients, the following were observed to have a MSOC percentage difference of  $\geq 5\%$ .

- Nervous system disorders: whites 22.9%; blacks 15.3%;
- Skin and subcutaneous tissue disorders: whites 20.3%; blacks 14.3%.

Comparing the TPV/r black patients and CPI/r black patients, the following were observed to have a SOC percentage difference of  $\geq 5\%$ .

- Infections and infestations: TPV/r 58.5%; CPI/r 33.7%;
- General disorders and administration site conditions: TPV/r 30.9%; CPI/r 23.5%;
- Metabolism and nutrition disorders: TPV/r 13.8%; CPI/r 8.2%;
- Investigations: TPV/r 11.7%; CPI/r 6.1%.

Comparing the TPV/r white patients and CPI/r white patients, the following were observed to have a MSOC percentage difference of  $\geq 5\%$ : psychiatric disorders: CPI/r 17.7%; TPV/r 12.1%.

There were few MSOCs that had a  $\geq 5\%$  difference in the TPV/r or CPI/r groups. In general, however, across MSOCs and HLTs, in the TPV/r group, a higher percentage of blacks having AEs were observed, compared with whites. Black patients receiving TPV/r had a considerably higher percentage of AEs in the MSOC infections and infestations compared with TPV/r white patients. The observed difference must be viewed in light that there were over 5 times as many white patients to blacks. There was more balance in the number of AEs observed across MSOCs for black and white patients in the CPI/r group.

*MO comment: The increased rate of AEs particularly infections and infestations in blacks may be a result of poorer virologic response rates in blacks on TPV/r or proportionally more blacks having CD4+ counts < 200 cells/mm<sup>3</sup> at baseline or both. Regardless both the efficacy and safety of TPV/r in blacks require further investigation.*

## Geographic

Geographical regions evaluated were Europe (EU), Latin America (LA) (including sites from Mexico from Trial 1182.48) and North America (NA) (including sites from Australia from Trial 1182.12). In evaluating data by geographic region, it should be noted that the percentages of patients in each geographic region were balanced between the TPV/r and CPI/r groups (NA: 311, 309; SA: 132, 128; EU: 303, 300), respectively. The overall frequency of AEs, by geographic region in the TPV/r and CPI/r groups was: (NA: 90.7%, 86.4%; SA: 75.8%, 75.8%; EU: 76.9%, 68.3%), respectively.

In general, for SOCs, there was a trend in both the TPV/r and CPI/r groups for the highest percentage of patients reporting AEs to be in North America and the lowest percentage to be in Europe. However, there was considerable variability.

Comparing the TPV/r North American, European, and Latin American patients, the following were observed to have a MSOC percentage difference of  $\geq 10\%$ .

- Gastrointestinal disorders: NA 51.4%; EU 39.6%; LA 53.8%;
- Infections and infestations: NA 50.2%; EU 36.3%; LA 46.2%;
- General disorders and administration site conditions: NA 37.9%; EU 23.4%; LA 13.6%;
- Musculoskeletal and connective tissue disorder: NA 23.2%; EU 10.9%; LA 15.2%.

Comparing the CPI/r North American, European, and Latin American patients, the following were observed to have a SOC percentage difference of  $\geq 10\%$ .

- Gastrointestinal disorders: NA 49.5%; EU 33.0%; LA 50.0%;
- Infections and infestations: NA 41.1%; EU 29.7%; LA 45.3%;
- General disorders and administration site conditions: NA 39.8%; EU 18.0%; LA 18.0%;
- Skin and subcutaneous tissue disorders: NA 25.6%; EU 14.0%; LA 15.6%.

The following HLTs account for some, but not all, of the differences in the frequency observed for gastrointestinal disorders, infections and infestations, and general disorders and administration site conditions between countries receiving both TPV/r and CPI/r (presented in the order of NA, EU and LA):

- Nausea and vomiting symptoms:
  - TPV/r: 24.4%, 13.2%, 25.8%;
  - CPI/r: 24.3%, 7.0%, 20.3%;
- URTI:
  - TPV/r: 16.4%, 9.6%, 18.9%;
  - CPI/r: 13.9%, 7.7%, 15.6%;
- Asthenic conditions:
  - TPV/r: 17.0%, 9.9%, 4.5%;
  - CPI/r: 20.1%, 9.7%, 7.0%;
- Injection and infusion site reactions:
  - TPV/r: 10.0%, 3.6%, 0.0%;

- CPI/r: 11.3%, 1.3%, 0.0%.

Although there was considerable variability in the frequency of some SOC's by geographical region, within the region there was a consistency of the reporting of the AEs for both TPV/r and CPI/r patients.

#### 7.4.2.4 Explorations for drug-disease interactions

No specific explorations for drug-disease interactions were performed.

#### 7.4.2.5 Explorations for drug-drug interactions

No specific explorations for drug-drug interactions as it pertains to AEs were performed.

*MO comment: TPV/r is known to have multiple drug-drug interactions and unless patients are carefully chosen to be treated with TPV/r and carefully monitored while on treatment with TPV/r these drug-drug interactions could very likely result in an increased rate of AEs in the postmarketing period.*

#### 7.4.3 Causality Determination

Please refer to section 7.3.3

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

Review of the data provided in the NDA supports the approval of TPV at a dose of 500mg boosted by 200mg of RTV.

The exposure response analysis of phase 2 and phase 3 studies consistently demonstrated that the probability of a patient's response to TPV/r treatment is related to inhibitory quotient ( $IQ = C_{min}/\text{corrected } IC_{50}$ ). However, due to the variability in pharmacokinetics of the drug and the variable degree of resistant virus, the range of resulting inhibitory quotient after the fixed doses are wide, which results in unpredictable virological response for individual patients. To maximize the likelihood of a patient's response, individualized dose by monitoring IQ is an alternative to the fixed dose regimen that requires further prospective investigation.

The above analyses were conducted by FDA reviewers post-hoc and so this information was not available during dose selection. BIPI will be asked to further evaluate the exposure-response and exposure-toxicity relationship of TPV/r in a prospective clinical trial.

## 8.2 Drug-Drug Interactions

Please refer to Section 5

## 8.3 Special Populations

*MO comment: Please see Dr. Baylor's review for details of the Naïve and Hepatic insufficiency studies.*

### Naïve Population

Study 1182.33 is an ongoing study comparing TPV/r at 500mg/100mg or 500mg/200mg with lopinavir / ritonavir 400mg/100mg BID in approximately 540 treatment naïve adult subjects. Subjects in all three arms are also receiving tenofovir 300mg and lamivudine 300mg once a day.

Limited safety data were provided for the first 498 subjects enrolled. As in other studies, gastrointestinal adverse events were the most common tipranavir associated toxicity. The frequency of nausea, abdominal pain, and vomiting were higher in the tipranavir arms than in the lopinavir/ritonavir arms, but the frequency of diarrhea was similar in all arms. Hepatotoxicity has been reported as an adverse event in nine subjects receiving tipranavir compared to one receiving lopinavir. The frequency of rash is similar in the tipranavir 500 mg/200 mg arm and the lopinavir arm. Four deaths in the tipranavir arms and one in the lopinavir arm have been reported. Causes of death in tipranavir subjects were PCP, septic shock, interstitial pneumonia, and renal failure; the cause of death of the lopinavir subject was disseminated tuberculosis.

In conclusion, very preliminary data were provided from this study and it is difficult to reach any conclusions about the safety of tipranavir in this study population. It does appear that this study is enrolling subjects with advanced HIV, which may affect the interpretation and applicability of these study results.

### Hepatically Impaired Population

In a study, 1182.32, comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose plasma concentrations of TPV and RTV were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of TPV administered with ritonavir has not been adequately evaluated or evaluated at all respectively.

### Renally Impaired Population

TPV/r pharmacokinetics has not been studied in patients with renal dysfunction. However, since the renal clearance of TPV is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency

### **8.4 Pediatrics**

*MO comment: Please see Dr. Baylor's review for details of the Pediatric study.*

Study 1182.14 is an ongoing phase I/IIa, randomized, 24 week trial of two doses of the TPV/r oral solution in 100 HIV-1 positive, treatment-naïve and treatment experienced pediatric patients between the ages of 2 and 18. Treatment-naïve subjects are receiving two NRTIs plus TPV/RTV; experienced subjects are being treated with a background antiretroviral regimen chosen based on screening genotype plus TPV/r or have substituted TPV/RTV for their existing PI.

The applicant supplied pharmacokinetic results for the first 37 study subjects. There were too few subjects less than six years of age to identify a dose for this age group, and it appears doubtful that an appropriate dose can be identified for children of any age. Only 3 subjects in the low dose group and five in the high dose group had measurable trough levels on day 28.

Because this study is ongoing, the applicant provided baseline and week 4 plasma HIV RNA data for the first 37 subjects. There was a decrease in plasma HIV RNA from baseline to week 4, but this represents about one-third of all subjects to be enrolled in the study and longer term data is needed before efficacy can be determined.

Twelve week safety information was provided for the first 74 subjects. GI Adverse events were the most common AEs (38%) and were dose related. Rash was observed in 10 subjects (7 in the low dose group and 3 in the high dose group). Grade 3 or 4 laboratory values observed in at least 2 subjects included increased GGT (2 subjects in each treatment arm), increased amylase (2 subjects in each treatment arm), and increased ALT (2 subjects in the high dose treatment arm).

Tolerability of the oral solution was poor in this study. Five have discontinued the study due to adverse events; the reasons included vomiting, nausea, retching, and poor palatability of the solution. One subject was discontinued prematurely due to non-compliance and another subject withdrew consent. Both of these subjects complained about the taste of the oral solution. In addition, ten subjects took 75% or less of their study drug including 3 in the high dose group who took 25% or less and 3 in the low dose who took 50% or less of study drug. Comments were available for subjects with poor compliance and included complaints such as "bad taste and smell", "hates taste", and "nausea with oral solution".

In summary, the applicant has not proven that TPV concentrations in pediatric patients are similar to those observed in adults; an appropriate dose of TPV for use in children was not identified. ☐

☑ No new safety signals have been identified in this pediatric study, but the tolerability of the oral solution was poor.

## 8.5 Advisory Committee Meeting

An Antiviral Drug Advisory Committee (ADAC) Meeting was held on May 19, 2005 to discuss the NDA for TPV. Both the applicant and the FDA presented their separate analyses of TPV's efficacy, resistance, drug interaction and safety profile. Additionally, the applicant presented how the potential utility of TPV in current clinical practice and the FDA presented exposure-response data. At the end of the presentations the committee was charged with seven questions. A brief summary of the questions and general responses are below. For further details please refer to the official ADAC Meeting transcript. FDA questions appear in **bold font** and the ADAC committee responses appear in *Italics font*.

### Question 1:

**Do the data demonstrate that tipranavir/ritonavir (TPV/r) is safe and effective for the multi-drug resistant HIV-1 infected population?**

*Yes = 11      No = 3                      Total Votes = 14*

**If no, what additional data are needed to provide evidence of safety and efficacy?**

*Members that voted "no" felt that additional data providing evidence of safety and efficacy were needed. Data including long term efficacy data, drug interaction, liver toxicity data were among the suggestions. Substantial concerns regarding hepatic toxicity in this patient population were raised by committee members. Overall the committee advised the Agency that additional long-term follow-up was needed, specifically, in the female population.*

**If yes, please address the appropriate population for TPV/r use considering the following:**

- **limited inclusion criteria of the RESIST trials**
- **drug-drug interactions**
- **resistance information and patterns associated with optimal use**
- **safety considerations**

*Members who voted "yes" felt that the need for the drug in this patient population was great; however, members expressed concerns with need for long term follow-up and toxicity management by specialists. Members urged the sponsor and the agency to*

*explore drug-drug interactions, including interactions with lipid lowering agents, contraceptives, and cardiac drugs. The committee suggested future studies include women with rash, liver failure patients, and toxicology.*

**Question 2:**

**Given the data on transaminase elevations, please provide your recommendations for:**

- **TPV/r use in patients with underlying liver disease**
- **Monitoring and management of hepatotoxicity during clinical use**
- **Future studies**

*Close followup of patients receiving this therapy and long-term followup in enrolled study patients for hepatic toxicity were suggested. Specific suggestions for future studies included the evaluation of more Hep B/C + patients and those entering treatment with slightly higher LFT's (such as grade 2). The hepatologists on the panel were concerned that no liver biopsy data was available and strongly recommended that such studies be considered in the future. Because the correlation of fibrosis and transaminase elevation is not perfect, concerns were expressed about the increased risk for disease in those patients with fibrosis already present.*

**Question 3:**

**The limited amount of data in females with HIV infection in the TPV program shows an increased incidence of rash in females. Please provide your recommendations for:**

- **Investigation of this safety signal in future studies with TPV.**

*The committee expressed continued concern about lack of data in women in pivotal clinical trials, particularly when the signal of skin rash was noted early. Recommendations for further studies with women and diverse contraceptive methods were recommended. Please see the official ADAC transcript for details*

**Question 4:**

**Current information indicates the net effect of TPV/r on substrates of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 is not known, and there are competing effects of TPV/r on CYP3A (inhibition) and P-glycoprotein (induction). Please comment on additional post-marketing drug interaction studies.**

*The committee suggested post-marketing drug interactions studies using cocktail studies to evaluate mechanisms of inhibition and induction. These studies should evaluate the impact of TPV/r on various transporter systems including PGP as well as MRP's. Specific interactions using digoxin, proton pump inhibitors, dual PI's, calcineurin inhibitors, and statins were recommended. Other panel members recommended studies of phenytoin, midzaoloam, and tenofovir as common agents in use in these patients.*

**Question 5:**

**Given the high inter-patient variability in TPV exposures following fixed doses and exposure (blood levels)-virologic response relationships, could a biomarker such as Cmin/IC50 be used for the individualization of TPV/r therapy? Please discuss the studies that would supplement the data presented today.**

*Although the committee was very interested in the possibility of therapeutic drug monitoring for the individualization of patient care with potentially toxic drugs, the committee as a whole felt there was not enough data to recommend this at the current time.*

**Question 6**

**Please provide your recommendations regarding the display of TPV/r resistance data/analyses in the TPV package insert that would be useful to clinicians.**

*Simple but complete representation of available data was discussed, with several specific designs suggested. Recommendations for serial evaluation of hepatic function were also discussed.*

**Question 7:**

**Please discuss and recommend future study designs /data acquisition for the heavily pretreated population.**

*The Committee suggested incorporating real time phenotypes in future studies and exploring possible mutations in the patient population. Incorporation of at least two novel PI's in treatment studies was recommended, with potential studies evaluating two or more investigational agents (including those from different manufacturers) encouraged. Although collecting better data on clinical endpoints was highly encouraged and such data was felt to be useful, it was acknowledged that studies using surrogate markers will be necessary in evaluating salvage studies in this patient population. Study designs including open label drug and rollover to experimental arms after relatively short periods may be necessary for practical and ethical reasons.*

## **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 BIPI did not submit a postmarketing risk management plan.

## **8.8 Other Relevant Materials**

Not applicable

## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

In the pivotal RESIST trials at 24 weeks TPV/r had superior activity over a suboptimal control group in a 3 class antiretroviral experienced, clinically advanced HIV-1 infected population especially when the resistance profile was favorable (namely when the TPV associated mutations score were less than 3 and there were less than 5 PI mutations) and when TPV/r was used in conjunction with T20.

However, the use of TPV/r is complicated by multiple drug-drug interactions, the high inter-patient variability in TPV exposure with that variable exposure having potential safety and efficacy implications, and lastly there are the safety concerns of hepatotoxicity, rash and hyperlipidemia.

### **9.2 Recommendation on Regulatory Action**

This reviewer cautiously and with reservation recommends the accelerated approval of TPV for use in a highly treatment experienced, multiple PI resistant patient population with very limited treatment options.

The overall relative short term virologic and immunologic benefits of TPV potentially outweigh the risk of TPV in this restricted patient population especially when TPV is combined with another active ARV (for example, T20) and patients are monitored closely for toxicities and other untoward side effects of the drug.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

Although BIPI did not submit a formal risk management plan there are many risk management activities planned for TPV/r post accelerated approval.

- As a requirement of accelerated approval under 21 CFR 314 subpart H the applicant must submit the 48 Week data for their two pivotal Phase 3 trials, which will provide more safety data for analysis of known and unknown TPV/r 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 labeled indication for TPV/r is very restricted in an effort to minimize the risk/benefit ratio associated with the use of this product.
- The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.
- The product has been contraindicated in subjects with moderate to severe (Child-Pugh B and C) liver disease in light of the known hepatotoxicity associated with TPV/r and a lack of data in this patient population.

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 TPV/r's accelerated approval, BIPI agrees to submit 48 Week safety and efficacy data on 1182.12 and 1182.48 by September 30, 2006 to support the traditional approval of TPV/r. Additionally, BIPI 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:

#### **Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and atazanavir.  
Protocol Submission: Study completed  
Final report Submission: Submitted by December 31, 2005
2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and buprenorphine/naloxone.  
Protocol Submission: July 15, 2005.  
Final report Submission: Submitted by June 30, 2006
3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and carbamazepine.  
Protocol Submission: July 15, 2005  
Final report Submission: Submitted by September 30, 2006
4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and tadalafil.  
Protocol Submission: August 31, 2005  
Final report Submission: Submitted by December 31, 2006
5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and ribavirin/pegylated IFN alpha 2a.  
Protocol Submission: August 31, 2005.

Final report Submission: Submitted by June 30, 2007

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and methadone.  
Protocol Submission: Study completed.  
Final report Submission: Submitted by September 30, 2005  
Pharmacology/Toxicology
7. Complete ongoing carcinogenicity study in mice and submit final report.  
Protocol Submission: Completed  
Final report Submission: December 31, 2006
8. Complete ongoing carcinogenicity study in rats and submit final report.  
Protocol Submission: Completed  
Final Report submission: December 31, 2005

### **Special Populations**

9. Assess the long term (48 week) antiviral efficacy and safety of tipranavir/ritonavir in ARV treatment naive patients through the conduct of study 1182.33.  
Protocol Submission: Completed  
Final report Submission: September 30, 2006
  - Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33), please submit data in resistance template.  
Protocol Submission: Completed  
Final report Submission: September 30, 2006
  - Assess metabolic changes being studied in sub-study of 1182.33.  
Protocol Submission: Completed  
Final report Submission: September 30, 2006
10. Conduct a 48-week prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count.  
Protocol Submission: March 30, 2006  
Final report Submission: September 1, 2008
11. Conduct a 48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.  
Protocol Submission: March 30, 2006  
Final report Submission: July 1, 2008
12. Assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.  
Protocol Submission: December 31, 2006

Final report Submission: December 31, 2007

BIPI understands that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. In the original NDA submission, BI requested deferral of submission of their pediatric studies for ages 2 weeks to 2 years until January 31, 2009. BI also requested deferral of submission of their pediatric studies for ages 2 to 18 years until June 30, 2006.

BIPI understands that the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments as per the Written Request for pediatric exclusivity and any proposed changes in the Written Request for pediatric studies. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

13. Assess two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety in ARV naive and experienced children and adolescents between 2 and 18 years of age.

Protocol submission: Completed

Final report submission: June 30, 2006

14. Evaluate dose requirements and safety in pediatric patients age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA).

Protocol submission: September 30, 2006

Final report submission: January 31, 2009

BIPI commits to submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) will be clearly designated "Required Pediatric Study Commitments".

#### **Pharmacokinetics**

15. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

Protocol Submission: September 30, 2005

Final report Submission: December 31, 2006

#### **Clinical**

16. Conduct a formal QT prolongation study.

Protocol Submission: Special Protocol Assessment Complete

Final report Submission: June 30, 2006

#### **9.3.3 Other Phase 4 Requests**

The following are not postmarketing study commitments, but in a letter dated June 7,

2005, BIPI agreed to conduct the studies listed below:

#### **Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and bupropion.
2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
4. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]
6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug [ ]

#### **Pharmacokinetics**

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with tipranavir/ritonavir twice daily.

#### **Clinical**

8. Conduct a long-term cardiovascular safety evaluation of Protease Inhibitor/ritonavir (including tipranavir) from epidemiologic databases.

#### **Microbiology**

9. Evaluate cleavage site mutations in rebound samples on tipranavir.

#### **Therapeutic Drug Monitoring**

10. BIPI will meet with the Division of Antiviral Drug Products (DAVDP) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIV-infected patients receiving tipranavir/ritonavir. The study will be conducted and the results will be used to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for patients taking APTIVUS/ritonavir.

### **9.4 Labeling Review**

The proposed package insert (PI or label) has been reviewed by all disciplines involved in the NDA review of TPV/r. The major recommendations for revisions to the clinical sections of the proposed label are listed below. These changes were discussed with and agreed upon by the applicant.

2 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

10.1.1 Reviews of the Phase 1 single dose and multiple dose, 1182.14 (pediatric) and 1182.33 (naïve) trials by Dr. Melisse Baylor

**NDA 21-814**

**Tipranavir for the treatment of HIV infection**

**Reviewer: Melisse Baylor, MD**

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## SUMMARY

This analysis included reviews of studies of tipranavir in different populations. Twenty-six studies enrolled healthy adult volunteers. Review of these studies in healthy volunteers provides important information on the safety of tipranavir, since the safety analysis is not complicated by signs and symptoms associated with advanced HIV. Phase 1 data in HIV-infected subjects are limited. Two pharmacokinetic studies enrolled HIV-infected subjects. Finally, two ongoing studies enrolling HIV-infected subjects are also included in this review. Study 1182.33 is a 48 week, safety and efficacy study of tipranavir HIV-naïve subjects, and study 1182.14 is safety and efficacy study of tipranavir in pediatric patients. Preliminary results from both studies are included in this review. Safety findings from this review are summarized below.

- The most common toxicity associated with tipranavir use in HIV-infected subjects and in healthy volunteers was gastrointestinal, particularly diarrhea and nausea. Gastrointestinal adverse events were also the most common reason for study discontinuation.
- Increases in ALT and in triglycerides were frequently reported in healthy volunteers and in HIV-infected subjects.
  - ◆ Increases in ALT were reported in healthy volunteers after a single dose and after multiple doses of tipranavir. Eighteen percent of healthy volunteers in multiple dose studies had increases in ALT including 2% of subjects with Grade 4 increases.
  - ◆ Increases in triglyceride levels were also common; 27% of subjects in multi-dose healthy volunteer studies with normal triglyceride levels had increases in triglyceride to greater than the upper limit of normal. In addition, triglyceride increases were observed in the single dose studies of tipranavir.
  - ◆ Increases in ALT and in triglycerides were observed in studies using tipranavir alone and in those using tipranavir boosted with ritonavir.
- Rash was reported in both single and multiple dose studies and in studies of HIV-infected subjects. The description of rash varied from urticaria to tiny papules. Some episodes of rash were accompanied by other signs and symptoms such as joint pain and throat tightness. In Phase 1 multi-dose studies, rash was substantially more common in females than males; rash was reported in 13% of females compared to 3.6% of males. In study 1182.22, the study was terminated due to concerns of serum sickness when 17 of 51 subjects developed a rash, often associated with musculoskeletal signs and symptoms.
- A hypersensitivity-like reaction was observed in subjects receiving tipranavir. A small number of healthy volunteers had rash with associated symptoms like joint pain, tingling, pruritis, and throat tightness. In addition, one woman had generalized pruritis and tightness of her throat, which resolved after treatment with benadryl. Another male subject had slurring of speech and tongue swelling, which resolved after treatment with steroids and benadryl.

- An uncommon adverse event was change in cognition or decreased concentration. One Phase 1 study was changed from an outpatient study to an inpatient study after three subjects complained that difficulties concentrating were interfering with their ability to drive. Twelve other subjects in the Phase 1 studies reported similar adverse events. Although TPV crosses the blood brain barrier, the reason for this adverse event is not known.
- The Phase 1 studies suggest that adverse events are dose related. In the studies in which subjects were randomized to receive tipranavir and ritonavir at 500 mg/100 mg or at 750 mg/200 mg, gastrointestinal adverse events and hepatotoxicity were more frequent and more severe in subjects in the higher dose groups.
- Insufficient data was provided to reach any conclusions about the safety and efficacy of tipranavir in HIV-infected, treatment-naïve subjects and in pediatric patients. These studies are ongoing and the final study reports will be submitted when complete.

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## REVIEW OF PHARMACOKINETIC STUDIES OF TIPRANAVIR IN HEALTHY ADULT VOLUNTEERS

### 10.1.3 Resume

There were 20 multiple dose, Phase 1 studies of tipranavir in more than 600 healthy adult volunteers. The majority of subjects were White and Male. However, 265 females were enrolled allowing for some analyses based on gender. In five of these studies, subjects received tipranavir and in the remaining 15, tipranavir was administered with low dose ritonavir. Several formulations of tipranavir were used in these studies. The majority of studies were done using the formulation to be marketed, the SEDDS formulation, but the hard filled capsules were used in five studies. In addition, there were five single dose Phase 1 studies in healthy volunteers; the safety results were similar in the single and multiple dose studies. This review is limited to the safety data from these studies. Please see Dr. Zheng's review for discussion of the pharmacokinetic data obtained in these trials.

Adverse events were seen in almost all subjects receiving tipranavir in these Phase 1 studies. Safety signals from these trials are described below.

- The most common toxicity was gastrointestinal, particularly diarrhea and nausea; in seven of the 20 multi-dose studies, three-fourths or more of subjects reported diarrhea. Gastrointestinal adverse events often began on the first day of dosing with tipranavir and sometimes continued throughout the study. Gastrointestinal adverse events were the most common reason for study discontinuation; 24 subjects discontinued due to nausea, vomiting, diarrhea, or abdominal pain.
- Increases in ALT and in triglycerides were frequently reported. See the table summarizing these events at the end of this review.
  - Eighteen percent of healthy volunteers in multi-dose studies had increases in ALT to greater than the upper limit of normal. Twelve subjects or 2% of the subjects in the Phase 1 studies had Grade 4 ALT values and 4% (n=24) had Grade 3 increases. Twelve subjects discontinued the study prematurely due to hepatotoxicity. One subject in a Phase 1 study had an increase in ALT from normal limits to 3.5 times the ULN after a single dose of tipranavir. Increases in total bilirubin were uncommon but were reported in three subjects including one subject with ocular jaundice.
  - Increases in triglyceride levels were also common and were reported in 18 of the 20 multi-dose studies and in two of the five single dose studies. A total of 178 subjects (27%) in the multi-dose studies with normal triglyceride levels had increases in triglyceride to greater than the upper limit of normal. This includes 27 subjects with Grade 2 increases in triglyceride and one with a Grade 3

increase. Three subjects discontinued a study due to elevated triglyceride levels. Ritonavir use is associated with lipid abnormalities, however, increased triglyceride levels were reported in 24 subjects in the four studies in which ritonavir was not used.

- Rash was reported in 48 subjects in multiple dose studies and in one subject in a single dose study. Five subjects discontinued due to rash. Rash was substantially more common in females than males; rash was reported in 13% of females in Phase 1 compared to 3.6% of males. The description of rash varied from urticaria to tiny papules. Some episodes of rash were accompanied by other signs and symptoms such as joint pain and throat tightness.
- A few adverse events suggest that a hypersensitivity-like reaction was observed in subjects receiving tipranavir. Subjects had rash with associated symptoms like joint pain, tingling, pruritis, and throat tightness. In addition, one woman had generalized pruritis and tightness of her throat, which resolved after treatment with benadryl. Another male subject had slurring of speech and tongue swelling, which resolved after treatment with steroids and benadryl.
- An uncommon adverse event was change in cognition or decreased concentration. One study was changed from an outpatient study to an inpatient study after three subjects complained that difficulties concentrating were interfering with their ability to drive. Ten other subjects reported similar adverse events. Although TPV crosses the blood brain barrier, the reason for this adverse event is not known.

Finally, these Phase 1 studies also suggest that adverse events are dose related. In the studies in which subjects were randomized to receive tipranavir and ritonavir at 500 mg/100 mg or at 750 mg/200 mg, gastrointestinal adverse events and hepatotoxicity were more frequent and more severe in subjects in the higher dose groups.

In conclusion, several safety signals were observed in healthy volunteer studies of tipranavir. These included gastrointestinal signs and symptoms, rash, increased ALT, and increased triglyceride levels. Less common adverse events such as possible hypersensitivity reactions and changes in concentration or cognition were also reported. The severity of the hepatotoxicity in some subjects and the female predisposition to rash should be explored further in post-marketing commitments.

## **MULTIPLE DOSE PHASE 1 STUDIES OF TIPRANAVIR IN HEALTHY VOLUNTEERS**

### **I. Studies Which Were Prematurely Discontinued**

#### **A. Study 1182.22**