MEMORANDUM

DATE:	April 22, 2005
TO:	FDA Antiviral Advisory Committee Members/Guests
FROM:	Tipranavir Review Team (HFD-530)
THROUGH:	Mark Goldberger, MD, MPH Director, Office of Drug Evaluation IV Debra Birnkrant, MD Director, Division of Antiviral Products
DRUG:	APTIVUS® (tipranavir) 250 mg Capsules
APPLICANT's PROPOSED INDICATION:	APTIVUS (tipranavir), co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are protease inhibitor treatment-experienced.

This briefing document provides background information for the May 19, 2005 Antiviral Drugs Advisory Committee meeting on tipranavir (TPV). On this day, the committee will be asked to consider efficacy and safety data submitted to support the accelerated approval of TPV administered with low dose ritonavir (RTV, r) and provide comments on the risk-benefit analysis of the use of this drug product given the following challenging issues:

1) Design/analyses of efficacy in studies of "heavily pretreated," HIV-infected individuals
2) Impact of resistance on treatment response
3) Management of known and potential TPV/r drug-drug interactions
4) TPV/r safety concerns including liver toxicity, lipid abnormalities, rash (particularly in women) and HIV clinical events and mortality

TPV is a non-peptidic inhibitor of the HIV protease that inhibits viral replication by preventing the maturation of viral particles. The Applicant submitted NDA 21-814 (tipranavir) 250 mg Capsules on December 22, 2005 seeking approval for marketing under accelerated approval regulations: 21 CFR 314.510 Subpart H. Under the current guidance for HIV treatment, the basis for approval will be based upon surrogate endpoint analyses of plasma HIV RNA levels for primary efficacy balanced with safety analyses in controlled studies up to 24 weeks duration.

I. SUMMARY OF EFFICACY AND SAFETY DATA

Efficacy: Two open-label, multi-center Phase 3 trials (RESIST 1 and 2) submitted in support of this NDA provide evidence of the antiviral effect of TPV over currently available antiretroviral regimens in a population which are "heavily pretreated" (3 class antiretroviral experienced with a median number of 12 prior antiretroviral drugs), and infected with a high level of resistant virus at baseline (97% of the isolates were resistant to at least one PI, 95% to at least one NRTI, and

>75% to at least one NNRTI). The Applicant submitted 24-week efficacy data on all 620 subjects in RESIST 1 and 539 out of 863 subjects in the RESIST 2. In both RESIST trials combined, 87% of the subjects were possibly/definitely resistant to the assigned comparator protease inhibitor (CPI). Thus, although these pivotal trials are presented as TPV/r + optimized background regimen (OBR) versus CPI/r + OBR, in actuality, the results should be interpreted more as TPV/r versus a partially active control with both arms utilizing a large variety of OBR (n = 161 different drug combinations as per FDA statistical analysis) necessitating a superiority efficacy anaylsis.

The primary efficacy endpoint was the proportion of subjects with *confirmed 1 log_{10} RNA drop from baseline at week 24 without evidence of treatment failure*. The trial was designed with an escape clause to allow subjects in the comparator arm with a *lack of initial virologic response at week 8* to discontinue the RESIST trials and receive TPV in a rollover safety trial. *Lack of initial virologic response* was defined as *no drop in viral load $\geq$ 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 $\geq$ 0.5 log_{10} drop*. Subjects who discontinued treatment due to lack of initial virologic response in the comparator arm were considered as treatment failures at week 24, which largely accounted for the treatment difference between the two arms in the primary efficacy endpoint. The initial virologic treatment difference (24%) between the two arms at week 8 explains the virologic treatment difference (20%) between the two arms at week 24.

For all-cause mortality the numbers 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. However, these studies were not powered for mortality, the 24 week time-point may be too premature to see any clinical endpoint differences, and the comparator arm's escape option at week 8 may have salvaged subjects prior to prolonged virologic failure. The relationship of plasma HIV RNA as surrogate endpoints to the actual clinical outcomes may be less well understood in studies of heavily pretreated populations. In addition, the open-label design of the RESIST trials as well as the comparator arm's escape clause for lack of initial virologic response by 8 weeks make it somewhat difficult to discern treatment differences in some efficacy and safety parameters beyond 8 weeks of treatment. Lastly, AIDS defining or AIDS progression events were captured in RESIST trials as adverse events only and not specifically abstracted or adjudicated.

Resistance: Genotypes from 1482 isolates and 454 phenotypes from both studies were submitted for review for the combined RESIST 1 and 2 studies. The FDA analyses of virologic outcome by baseline genotype resistance showed consistently greater response rates for the TPV/r arm over CPI/r arm across multiple sensitivity analyses. 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/r-treated subjects 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. Subjects taking TPV/r with ENF 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 most common protease mutations that developed in >20% of isolates from treatment- experienced subjects 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 subjects has not yet been characterized.

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. The known and potential interactions between TPV/r and other HIV medications are listed in Table 12 on Page 21-23. The table also describes the potential for interactions with other classes of drugs.

- 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.

- 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.

- 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.

- 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.

Safety Issues: A safety concern throughout the TPV drug development program has been hepatotoxicity. Initial 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. 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. The higher proportion of ALT abnormalities on the TPV/r 750 /200 mg arm compared to the TPV/r 500/200 mg arm probably resulted from increased TPV concentrations because RTV exposure was actually lower in the TPV/r 750/200 mg arm than in the TPV 750/200 mg arm. In addition, detailed exposure-response analyses on Study 1182.52 indicate that ALT increases are associated with increased TPV exposures.

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 RESIST 1, time to first DAIDS Grade 3 or 4 ALT elevation ($p=0.0028$) 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 RESIST 2, time to first Grade 3 or 4 ALT elevation ($p=0.0255$) was significantly shorter for subjects in the TPV/r arm compared those for subjects in the CPI/r arm. Very few subjects had documented concurrent symptoms; however, at the time of data submission, a substantial number of subjects had not resolved their LFT elevations, and therefore, no conclusions can be made about the acute clinical impact of these laboratory abnormalities. At this time, FDA exploratory analyses examining the possible baseline

risk factors for hepatotoxicity (i.e. baseline CD4 counts, hepatitis co-infection, gender, or race) are ongoing.

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 RESIST 1 and 2 datasets, 21% of subjects developed treatment emergent grade 3 or 4 triglycerides compared to 11% of subjects on the CPI/r arm. Analyses of RESIST 1 laboratory data showed that the time to first Grade 3 or 4 in total cholesterol ($p=0.0007$) or triglycerides ($p=0.0186$) were significantly different between the two arms. Analyses of RESIST 2 laboratory data showed that the time to first Grade 3 or 4 elevation in total cholesterol ($p=0.0255$) or triglycerides ($p<0.0001$) 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 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 immune-mediated rash 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%). 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 RESIST 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.

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 RESIST 1 than in RESIST 2 (22 versus 11), and there were more deaths on the TPV/r arms compared to the CPI/r arms (19 versus 14). The observed virologic benefit of the TPV/r over CPI/r did not translate to better mortality outcome at the 24 week time-point. However, the RESIST trials were not designed to assess clinical endpoints. The escape clause at 8 weeks precluded optimal evaluation of longer term clinical efficacy and safety.

In order to place the numbers of deaths in the TPV program in perspective, mortality rates were examined from the in the NDA databases of all "treatment-experienced" trials which led to approval of an antiretrovirals. The population enrolled in the enfuvirtide (ENF) phase 3 studies most closely approximated the TPV phase 3 studies. Comparison of the frequency of deaths and mortality rates (MR, #death/100 patient years) between the test and control arms were relatively similar for both the TPV and ENF NDAs at 24 weeks as summarized below:

- TPV vs. CPI: 2% (4.5 MR) vs. 1.2% (2.6 MR)
- ENF vs no treatment: 1.5% (3.3 MR) vs.1.5% (3.3 MR)

Based on the information as summarized above summary, we would like the committee's feedback on the issues outlined in section II. The remaining sections of this background document provides greater detail on the efficacy, safety, resistance profile, and clinical pharmacology of TPV/r.

II. ISSUES FOR COMMITTEE DISCUSSION

- The risk/benefit assessment of TPV/r given the data provided for safety and efficacy in the treatment of "heavily pretreated" HIV-infected individuals.

- Appropriate safeguards for the use of TPV/r given the limited inclusion criteria of the RESIST trials, TPV/r drug-drug interactions, the impact of resistance on response and the safety considerations outlined above.

- Display of TPV/r resistance data/analyses in the TPV package insert that would be useful to clinicians.

- Monitoring and management of hepatotoxicity during clinical use of TPV/r given the transaminase elevations data in healthy volunteers and HIV-infected patients in the development program.

- Further investigation and characterization of the safety signal of rash in females in the TPV program given the limited available data in HIV-infected females.

- Lessons learned from the TPV drug development program regarding the study of heavily pretreated HIV-infected individuals including:

    - Need for drug-drug interaction and resistance data
    - Use of open-label study designs
    - Use of escape clauses resulting in a diminishing comparator arm
    - Need for better adjudication of clinical events (i.e. treatment-emergent AIDS progression events) and need for comprehensive data collection for serious adverse events including death
    - Increasing female participation in HIV drug trials

III. DESIGN/ANALYSES OF THE EFFICACY IN STUDIES OF "HEAVILY PRETREATED" POPULATION

A. Study Design of Phase 3 Trials

Please see Appendix I for discussion of dose selection for RESIST trials..

RESIST 1 (1182.12) and RESIST 2 (1182.48), were multi-center, multi-national, randomized and controlled, open-label studies in highly treatment-experienced HIV-infected subjects with triple antiretroviral class (NRTI, NNRTI, and PI) experience and with at least two failed PI-based regimens. The two major differences between the RESIST trials was 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 24 week interim analyses while RESIST 2 performed 16 week interim analyses. For the accelerated approval application, the Applicant submitted 24-week efficacy data on all 620 subjects in RESIST 1 study and 539 out of 863 subjects in the RESIST 2 study who were able to reach 24 weeks. The safety and efficacy of TPV/r 500 mg/200 mg was compared through 24 weeks of treatment against a control group of other protease inhibitors boosted with RTV (comparator PI/r or CPI/r) where the control PIs were genotypically determined. The studies were designed to continue through 96 weeks. Genotypic resistance testing was done at screening, and as protocol defined, subjects were required to have at least one primary PI mutation(s) at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and have no more than two protease mutations at codons 33, 82, 84, or 90.

Subjects were randomized 1:1 to either TPV/r or the comparator PI/r group and stratified with respect to pre-selected protease inhibitor (PI) as well as use of ENF. Both treatment groups (TPV/r versus CPI/r) were designed to receive OBR regimen based on genotypic resistance testing prior to randomization. Due to the complex comparator treatment group containing various protease inhibitors, the studies had to be designed as open-label trials. Furthermore, the FDA review team strongly recommended that the studies be designed to test for superiority of efficacy of TPV/r versus CPI/r, since testing for non-inferiority against multiple control groups in such an experienced population would be uninterpretable. A schematic of the RESIST trials shows the complexity of the study design of these trials (Appendix II). As shown in the schema, the subjects who had a lack of initial virologic response by Week 8 in the control arm of comparator protease inhibitors were allowed to enroll into the roll-over Study 1182.17 where all subjects would receive TPV/r. This escape clause for subjects in the control group has complicated our ability to interpret the efficacy of TPV/r in a controlled fashion beyond 8 weeks of treatment.

B. Baseline demographics and disease characteristics in RESIST trials

Baseline characteristics of subjects enrolled in these studies are summarized below.

Table 1: Baseline Characteristics: Studies 1182.12 and 1182.48

	RESIST 1 (012)	RESIST 2 (048)
# of Subjects Randomized	630	880
# of Subjects Treated	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^3)		
Mean	164	224
Median	123	189
Range	0.5, 1183.5	1.5, 1893
HIV RNA (log_{10} copies/mL)		
Mean	4.7	4.8
Median	4.8	4.8
Range	2.0, 6.3	2.9, 6.8
Proportions w/ HIV RNA (copies/mL)		
< 10,000	16%	15%
>=10,000 to <100,000	43%	49%
≥ 100,000	41%	36%
Stage of HIV Infection (CDC Class)		
Class A	24%	17%
Class B	73%	80%
Class C	3%	3%
Protease Inhibitor Stratum		
APV	14%	40%
IDV	4%	3%
LPV	61%	38%
SQV	21%	20%
Genotypic Resistance to Pre-selected Protease Inhibitor		
Not Resistant	8%	20%
Possible Resistance	35%	6%
Resistant	57%	74%
Actual use of ENF		
Yes	36%	12%
No	64%	88%

C. Primary Efficacy Endpoints

The primary efficacy endpoint in the RESIST trials is the *proportion of subjects with a treatment response at 48 weeks* (≥ 1 log_{10} reduction from baseline HIV RNA in two consecutive measurements without prior evidence of *treatment failure*). The efficacy endpoint for the 24-week data submitted in this application is the *proportion of subjects with a treatment response at 24 weeks*. Multiple secondary analyses were performed for each study.

This efficacy analysis is models the FDA analysis of time to loss of virologic response (TLOVR) analysis which is an intent-to-treat analysis that examines endpoints using the following

definitions of treatment response and treatment failure for subjects who have achieved a confirmed 1 $\log_{10}$ drop in HIV RNA from baseline.

Treatment response is defined by confirmed virologic response (two consecutive viral load measurements ≥1 $\log_{10}$ below baseline) without prior treatment failure, i.e., occurrence of any of the following events: death, permanent discontinuation of the study drug, loss to follow-up, introduction of a new ARV drug to the regimen for reasons other than toxicity or intolerance to a background ARV drug, and confirmed virologic failure (defined as 1) viral load of <1 $\log_{10}$ below baseline confirmed at two consecutive visits >2 weeks apart, following a confirmed virologic response of two consecutive viral load measurements ≥1 $\log_{10}$ below baseline, or 2) one viral load of <1 $\log_{10}$ below baseline followed by permanent discontinuation of the study drug or loss to follow up, following a confirmed virologic response of two consecutive viral loads ≥1 $\log_{10}$ below baseline.)

According to the study design, investigators were allowed to switch subjects in the control arm of boosted CPI/r after 8 weeks of treatment if they had initial lack of virologic response (defined as 1) viral load has not dropped 0.5 $\log_{10}$ during the first 8 weeks of treatment and 2) 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.

D. Study Design Issues

The open-label design of the RESIST trials was unavoidable because of the choice of various CPIs in the control arm (LPV, IDV, SQV, APV—boosted with low-dose ritonavir). Additionally, due to the choice of the control group, the studies must be evaluated for superiority of TPV/r over the CPIs to which the majority of the subjects have documented drug resistance at baseline.

The open-label design poses a number of challenges in evaluation of efficacy. Both RESIST trials were conducted in subjects with very limited treatment options for whom TPV represented a potential and possibly the only option. Therefore subjects who met the same failure criteria or experienced similar toxicity or safety events may act differently depending on the treatments they received: TPV subjects will be more likely to elect to remain in the same treatment group despite problems whereas control group subjects will be more likely to switch to TPV through the roll-over trial 1182.17. This creates a potential bias in efficacy assessments if we regard all switches or discontinuations as failures.

To address this open-label bias issue, we used the protocol-defined failure criteria—of initial lack of virologic response—at Week 8 to supplement the analysis. In other words, all subjects who met the failure criteria at Week 8, regardless of whether they switched treatments, were considered failures for the Week 24 evaluation in the FDA analysis.

Another bias that was introduced by the open-label design of RESIST trials was the ability to change the pre-determined OBR. Subjects were required to have a pre-determined background regimen at the time of randomization based on their genotypic resistance test results and background ARV medication history. In RESIST 1 and RESIST 2 trials, there were a total of 11% and 14%, respectively of subjects whose pre-determined OBR was different from the actual background regimen received. One example of this bias is the number of subjects who had ENF predetermined as part of their OBR (TPV/r 165 versus CPI/r 159) differed from the number of subjects who actually took ENF (TPV/r 166 versus CPI/r 134). The TPV/r arms had a net gain of

1 subject using ENF although it was not predetermined, while the CPI/r arm had a net loss of 25 subjects who did not actually use ENF although it was part of their predetermined background. The Applicant believes, and DAVDP concurs, that the RESIST Investigators likely wanted to save ENF for use with a known active PI, and therefore, once subjects were randomized to the CPI/r the Investigator changed the OBR to exclude ENF. In addition, due to the high total number of combinations of ARVs in the OBRs (161), it was also difficult to examine the treatment effect by ARV regimen. This analysis might have helped determine the clinical effect of TPV drug-drug interactions.

The Applicant had difficulty enrolling the RESIST trials as designed to compare TPV/r to an active CPI/r, so they amended the protocol to allow subjects with no available sensitive PI, as per their genotype, to enroll. This amendment resulted in complete enrollment of the RESIST trials; however, most of the CPI/r subjects entered the trial already genotypically resistant to their assigned PI (92% of subjects in RESIST 1 and 80% of subjects in RESIST 2 had possible or full resistance to the pre-selected PIs). Therefore, the CPI/r arm is not truly an active control arm, but a suboptimal control arm. The results of the RESIST studies should be interpreted as TPV/r versus suboptimal control, and the studies must be evaluated for superiority of TPV/r over the CPIs.

E. HIV RNA Results

Tables 2 and 3 show the primary efficacy results for TPV on the proportion of subjects with treatment response (confirmed 1 $\log_{10}$ reduction in HIV RNA from baseline without prior evidence of treatment failure). This was based on the time-to-loss of virologic response (TLOVR) algorithm as defined in the primary efficacy endpoint.

In each RESIST trial, the proportion of treatment responders were significantly higher in the TPV/r treated group versus the subjects in the CPI/r treated group (RESIST 1: 36% TPV/r versus 16% CPI/r; RESIST 2: 32% TPV/r versus 13% CPI/r.

As explained above, in order to address the bias due to an open-label study design, the FDA analysis treated all subjects who showed an initial lack of virologic response by Week 8 (that is no 0.5 $\log_{10}$ drop in HIV RNA during first 8 weeks of treatment and failure to achieve viral load <100,000 copies/mL) as treatment failures. We believe that the FDA analysis differs from the Applicant's results primarily due to this group of subjects who had initial lack of virologic response during first 8 weeks. These subjects would be most likely to discontinue the study drug later, roll-over to Study 1182.17 to receive TPV, or add additional background ARV drugs.

Table 2: RESIST Outcome at Week 24: FDA Analysis (TLOVR)

	RESIST 1 Trial 1182.12		**RESIST 2 Trial 1182.48**		**Total**	
	TPV/r n (%)	CPI/r n (%)	TPV/r n (%)	CPI/r n (%)	TPV/r n (%)	CPI/r n (%)
Total treated	311 (100)	309 (100)	271 (100)	268 (100)	582 (100)	577 (100)

Treatment response at Week 24	**112 (36)**	**49 (16)**	**86 (32)**	**34 (13)**	**198 (34)**	**83 (14)**
No confirmed 1 log10 drop from baseline	**172 (55)**	**234 (76)**	**143 (53)**	**223 (83)**	**315 (54)**	**457 (79)**
Initial Lack of Virologic Response by Week 8	109 (35)	166 (54)	97 (36)	176 (66)	206 (35)	342 (59)
Rebound	40 (13)	40 (13)	28 (10)	26 (10)	68 (12)	66 (11)
Never suppressed through Week 24	23 (7)	28 (9)	18 (7)	21 (8)	41 (7)	49 (8)
Added ARV drug	**20 (6)**	**21 (7)**	**35 (13)**	**8 (3)**	**55 (9)**	**29 (5)**
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)

Source: FDA Statistical Reviewer's Analysis

Table 3: Proportion of Subjects with Treatment Response

	RESIST 1 – 24 weeks		RESIST 2 – 24 weeks	
HIV RNA	**TPV/r + OBR n/N (%)**	**CPI/r + OBR n/N (%)**	**TPV/r + OBR n/N (%)**	**CPI/r + OBR n/N (%)**
Response Rate (confirmed 1 $\log_{10}$ drop in HIV RNA)	112/311 (36)	49/309 (16)	86/271 (32)	34/268 (13)
Difference in proportions (TPV/r – CPI/r) (95% Confidence Interval)	20.2% (13.4%, 26.9%)		19.0% (12.2%, 25.9%)	
p-value	<0.001		<0.001	

Source: FDA Statistical Reviewer's Analysis

In the RESIST trials, randomizations were stratified according to the pre-selected protease inhibitors (APV, IDV, LPV, SQV) based on genotypic resistance testing and according to the use of ENF or not. FDA conducted subgroup analyses based on these stratification factors which are summarized in the tables 4 and 5 below

Treatment difference between the TPV/r 500 mg/ 200 mg group and the CPI/r group was statistically significant in both subgroups of the ENF-use strata (used ENF or did not use ENF). These results were consistent between RESIST 1 and RESIST 2 studies. In addition, FDA conducted statistical tests to examine interaction between the subgroups on ENF use and treatment group. A statistically significant treatment interaction was observed for the subgroup of subjects who *actually used ENF* versus *did not use ENF* (p-value = 0.02 significant at α=0.15 level).

In other words, in this highly treatment-experienced subject population, the net proportion of subjects with confirmed 1 $\log_{10}$ reduction in HIV-RNA using TPV/r in combination with ENF would be likely to be significantly greater than if TPV/r was used alone without ENF (net treatment effect of 29.4% vs 15.6%, respectively, for ENF users versus non-use of ENF).

Table 4: Proportion of Subjects with Treatment Response through 24 weeks by ENF use

Both RESIST Trials combined (confirmed 1 log10 drop in HIV RNA from baseline)

Enfuvirtide (ENF) used?	TPV/r N=311	CPI/r N=309	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 (25%)	76/158 (48%)	24/128 (19%)	**29.4%** (19.0%, 29.7%)	<0.0001	0.02**
No (75%)	122/424 (29%)	59/449 (13%)	**15.6%** (10.3%, 20.9%)	<0.0001	

† Asymptotic confidence intervals based on normal distribution.
‡ p-value is based on the Mantel-Haenszel chi-square test.
§ p-value based on t-test
** Treatment by subgroup interaction is statistically significant at a 0.15 level.
Source: FDA Statistical Reviewer's Analysis.

With regard to the pre-selected comparator protease inhibitor stratum, FDA also conducted analyses to see the treatment effect of TPV/r in the PI strata if subjects were not-resistant to the PI versus possibly/definitely resistant to the comparator PI. In both RESIST trials combined, only 13% were not resistant to the pre-selected PI stratum, and remaining 87% were possibly/definitely resistant to the comparator PIs. In the subgroup of subjects for whom the pre-selected PI was not resistant to the HIV, the treatment difference between TPV/r and CPI/r was not consistent between RESIST 1 (US, Canada, Australia) study versus RESIST 2 (the non-US study). The treatment difference between TPV/r and CPI/r (-4.8%) among subjects not resistant to PIs was not statistically significant in RESIST 1 (-4.8%) or in RESIST 2, (15.4%). Additionally, in RESIST 1, there was a strong treatment by subgroup interaction (p-value = 0.03) between the non-resistant group versus possibly/definitely resistant group, indicating that the treatment effect in non-resistant group was not significant (-4.8%) and in resistant group was significant (~20%). For both RESIST studies combined, among the subgroup of possibly/definitely resistant comparator PIs, the treatment difference was statistically significant in favor of TPV/r versus CPI/r (treatment effect of ~21%). The result of this subgroup of subjects with possible/definite resistance to PIs was consistent with the overall results on the primary efficacy endpoint (treatment effect of 19% to 20%).

In summary, TPV/r showed significantly greater treatment effect than CPIs/r only when subjects were possibly or definitely resistant to their CPI/r. When ENF was added to TPV/r, the treatment effect was even more significantly greater than if ENF was not used.

Table 5: Proportion with Treatment Response through 24 weeks by resistance CPI stratum

RESIST 1

Resistance in PI stratum	TPV/r N=311	CPI/r N=309	Difference in proportions (TPV/r – CPI/r)	Test for treatment effect	Test for treatment by subgroup interaction p-value§

			(95% Confidence Interval)†	p-value‡	(Not Resistant versus Possibly or Resistant)
Not Resistant	5/21 (24%)	8/28 (29%)	-4.8% (-29.5%, 19.9%)	0.711	0.03**
Possibly Resistant	47/120 (39%)	18/94 (19%)	20% (8.2%, 31.8%)	0.002	
Resistant	60/169 (35%)	23/187 (12%)	23.2% (14.6%, 31.8%)	<0.0001	
RESIST 2					
Not Resistant	18/55 (33%)	9/52 (17%)	15.4% (-0.1%, 31.5%)	0.0677	0.61
Possibly Resistant	9/15 (60%)	5/18 (28%)	32.2% (-.001%, 64.5%)	0.066	
Resistant	59/200 (29%)	20/198 (10%)	19.4% (11.8%, 26.9%)	<0.0001	

† Asymptotic confidence intervals based on normal distribution.
‡ p-value is based on the Mantel-Haenszel chi-square test.
§ p-value based on t-test
** Treatment by subgroup interaction is statistically significant at a 0.15 level.
Source: FDA Statistical Reviewer's Analysis.

F. CD4 Cell Counts

At baseline the mean CD4 cell counts in RESIST 1 and RESIST 2 trials were 164 cells/mm^3 and 224 cells/mm^3, respectively. FDA conducted an on-treatment analysis to compare the change from baseline in CD4 cell counts between TPV/r and CPI/r groups and determine whether the results would be significantly different if subjects in the CPI/r group were to continue beyond Week 8 rather than discontinue in the CPI/r arm at Week 8. In general, the CD4 cell counts increased in the TPV/r group through Weeks 2, 4, 8 and 16, and remained stable at Week 24. The mean increase in CD4 cell counts in the TPV/r group at Weeks 8 and 24 were +50 and +58 cells/mm^3, respectively, for both RESIST studies combined. The mean increases in CD4 cell counts from baseline in the CPI/r group were modest through Week 8 and were around +20 cells/mm^3. Recall that there were greater numbers of subjects with initial lack of virologic response during the first 8 weeks in the CPI/r group who may have influenced the mean increase in CD4 cell counts.

At Weeks 16 and 24, among the subjects who remained in the RESIST 1 trial with the assigned treatment, the differences between TPV/r group and CPI/r group were no longer statistically significant. However, in RESIST 2, the difference in mean increase in CD4 cell count at Week 24 was statististically significant, but this difference may not have clinical significance due to the small magnitude of differences. For both studies combined, the Week 24 mean increase in CD4 cell counts in TPV/r group and CPI/r groups were +58 and +40 cells/mm^3, respectively.

IV. Impact of resistance information

TPV has 50% inhibitory concentrations (IC_{50} value) ranging from 40 to 390 nM against laboratory HIV-1 strains grown *in vitro* in PBMCs and cell lines. The average IC_{50} value for multi PI-resistant clinical HIV-l isolates was 240 nM (range 50 to 380 nM). Human plasma

binding resulted in a 1.6- to 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-1 positive subjects in combination with other antiretroviral agents, the activity of TPV in combination with other antiviral 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 and each of the NRTIs were generally additive, but additive to antagonistic for TPV with ddI or 3TC. Combinations of TPV and DLV or NVP were additive, and TPV with EFV was additive to antagonistic. Activity of TPV with ENF was synergistic.

A. In Vitro Selection of TPV-Resistant Viruses

TPV-resistant viruses were selected *in vitro* when wild-type HIV-l_{NL4-3} 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 reduction in susceptibility to the TPV-resistant virus with 10 protease mutations.

B. Clinical TPV Resistance

The efficacy of TPV/r was examined in treatment-experienced HIV-infected subjects in two pivotal phase III trials, RESIST 1 and 2. Genotypes from 1482 isolates and 454 phenotypes from both studies were submitted for review. In the comparator arm (CPI/r), most subjects received LPV/r (n=358) followed by APV/r (n=194), SQV/r (n=162) and IDV/r (n=23). The subject 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 (Table 6).

Table 6. Median Number of Mutations at Baseline in RESIST 1 and 2

	FDA PI mut	TPV PI mut	Key PI mut	Primary PI mut	IAS PI mut	NRTI mut	NNRTI mut
TPV/r n = 745	4	3	2	3	9	5	1
CPI/r	4	3	2	3	9	5	1

n = 737							

FDA PI mut - Number of substitutions at D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, or L90 at baseline
TPV PI mut - Number of tipranavir-specific protease mutations: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, or 84V at baseline
Key PI mut - Number of protease mutations at 33, 82, 84, or 90 at baseline
Primary PI mut - Number of primary protease mutations at 30, 33, 46, 48, 50, 82, 84, or 90 at baseline
IAS PI mut - Number of protease mutations at 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, or 90 at baseline
NRTI mut - Number of RT mutations at 41, 44, 65, 67, 69, 70, 74, 115, 118, 184, 210, or 215 at baseline
NNRTI mut - Number of RT mutations at 98, 100, 103, 106, 108, 181, 188, 190, 225, 230, or 236 at baseline

C. Mutations Developing on TPV Treatment

TPV/r-resistant isolates were analyzed from treatment-experienced subjects 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-naive subjects has not yet been characterized.

D. 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 $\log_{10}$ decrease at Week 24), DAVG24, and median change from baseline at weeks 2, 4, 8, 16, and 24 were evaluated. In addition, because subjects were stratified based on ENF use, we examined virologic outcomes in three separate groups - overall (All), subjects not receiving ENF (No ENF), and subjects receiving ENF (+ENF) as part of the optimized background regimen. We focused on the No ENF group in order to assess baseline resistance predictors of virologic success and failure for TPV/r without the additive effect of ENF 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 (>1 $\log_{10}$ decrease from baseline) and DAVG24. Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline substitution at position I13, V32, M36, I47, Q58, D60 or I84 (Table 7). The reduction in virologic responses for these baseline substitutions was most prominent in the No ENF subgroup. Virologic responses were similar or greater than the overall responses for each subgroup (All, No ENF, +ENF) 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.

Table 7. Effect of Type of Baseline PI Mutation on the Primary Endpoint in Resist 1 and 2.

	TPV/r Arm (n=513)			CPI/r Arm (n=502)		
Mutation	**All**	**No ENF**	**+ENF**	**All**	**No ENF**	**+ENF**
Overall	47% (240/513)	40% (147/369)	65% (93/144)	22% (109/502)	19% (75/389)	30% (34/113)

I13V/A/L/S	40% (69/171)	27% (32/119)	69% (37/54)	20% (35/178)	15% (20/133)	33% (15/45)
V32I/L	39% (29/74)	26% (12/46)	61% (17/28)	15% (9/59)	14% (6/43)	19% (3/16)
M36I/A/V/L/N	40% (124/310)	29% (60/208)	63% (64/102)	20% (65/318)	18% (45/345)	27% (20/73)
I47V/A	31% (29/93)	18% (11/62)	58% (18/31)	11% (9/82)	10% (6/63)	16% (3/19)
Q58E	38% (28/74)	27% (14/52)	64% (14/22)	18% (17/93)	18% (14/79)	21% (3/14)
D60E/K/A/N	39% (43/110)	30% (24/79)	61% (19/31)	12% (8/66)	11% (6/53)	15% (2/13)
V82 any change	48% (149/311)	41% (90/222)	66% (59/89)	18% (54/202)	14% (33/236)	32% (21/66)
V82A/T/C	50% (133/264)	45% (85/189)	64% (48/75)	18% (46/259)	13% (27/202)	33% (19/57)
V82S/F/I/L	34% (16/47)	15% (5/33)	79% (11/14)	21% (9/43)	21% (7/34)	22% (2/9)
I84V/A	41% (64/155)	31% (32/103)	62% (32/52)	20% (32/162)	20% (23/115)	19% (9/47)

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. The results of these analyses are shown in Tables 8 and 9.

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 subjects with one to four PI mutations at baseline. Response rates were reduced if five or more PI-associated mutations were present at baseline. For subjects who did not use ENF, 28% in the TPV/r arm and 11% in the CPI/r arm had a confirmed 1 $\log_{10}$ decrease at Week 24 if five or more PI mutations were present at baseline (Table 8). The subjects with five or more PI mutations in their HIV at baseline and not receiving ENF in their OBT achieved a 0.86 $\log_{10}$ median DAVG24 decrease in viral load on TPV/r treatment compared to a 0.23 $\log_{10}$ median DAVG24 decrease in viral load on CPI/r treatment (Table 9). In general, regardless of the number of baseline PI mutations or ENF use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 $\log_{10}$ decrease at Week 24) (Table 8) and greater declines in viral load by median DAVG24 (Table 9) than the CPI/r arm.

Table 8. Proportion of Responders (confirmed 1 $\log_{10}$ decrease at Week 24) by Number of Baseline PI Mutations

# Baseline FDA PI Mutations	TPV/r N=531	CPI/r N=502

	All	No ENF	+ ENF	All	No ENF	+ ENF
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)
1-2	70% (30/43)	69% (27/39)	75% (3/4)	44% (19/43)	41% (17/41)	100% (2/2)
3-4	50% (117/236)	44% (78/176)	65% (39/60)	27% (60/221)	23% (39/169)	40% (21/52)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)

Any change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

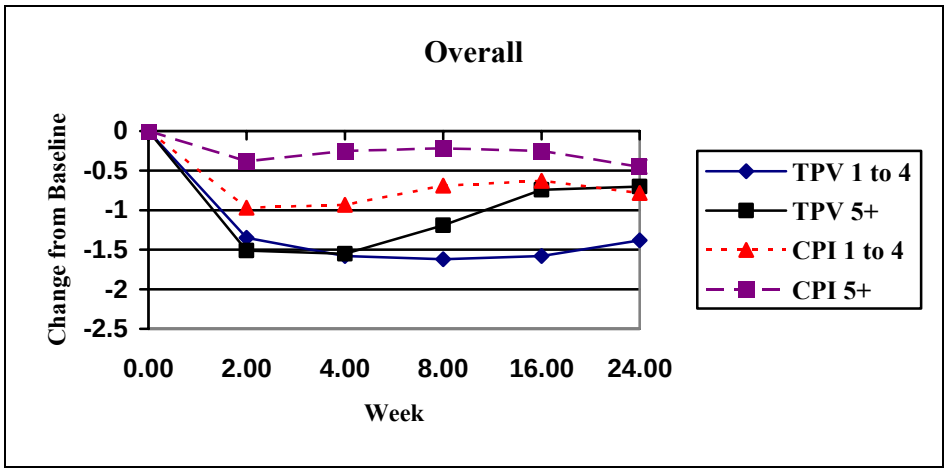
Table 9. Median DAVG24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations	TPV/r N=704			CPI/r N=705		
	All	**No ENF**	**+ ENF**	**All**	**No ENF**	**+ ENF**
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)
1-2	-1.43 (76)	-1.44 (69)	-1.42 (7)	-1.13 (65)	-1.01 (63)	-1.90 (2)
3-4	-1.36 (322)	-1.29 (259)	-1.96 (63)	-0.53 (316)	-0.44 (252)	-0.89 (64)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)

Any change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

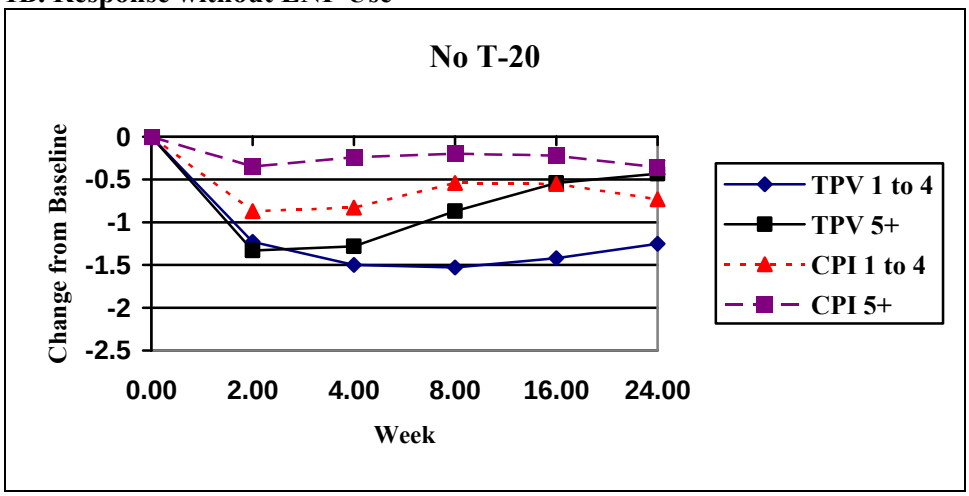
An examination of the median change from baseline of HIV RNA at weeks 2, 4, 8, 16 and 24 by number of baseline PI mutations (1-4 and 5+) showed the largest decline in viral load by Week 2 for all groups with the greatest decline observed in the TPV/r arms (Figure 1). A 1.5 $\log_{10}$ decrease in viral load at Week 2 was observed for subjects receiving TPV/r regardless of the number of baseline PI mutations (1-4 or 5+). Subjects who had five or more baseline PI mutations and who received TPV/r without ENF began to lose antiviral activity between Weeks 4 and 8 with their HIV RNA trending back toward baseline (Figure 1B). However, sustained viral load decreases (1.5 – 2 $\log_{10}$) through Week 24 were observed in subjects receiving TPV/r and ENF (Figure 1C).

Figure 1. Median Change from Baseline by Number of Baseline PI Mutations
1A. Overall Response



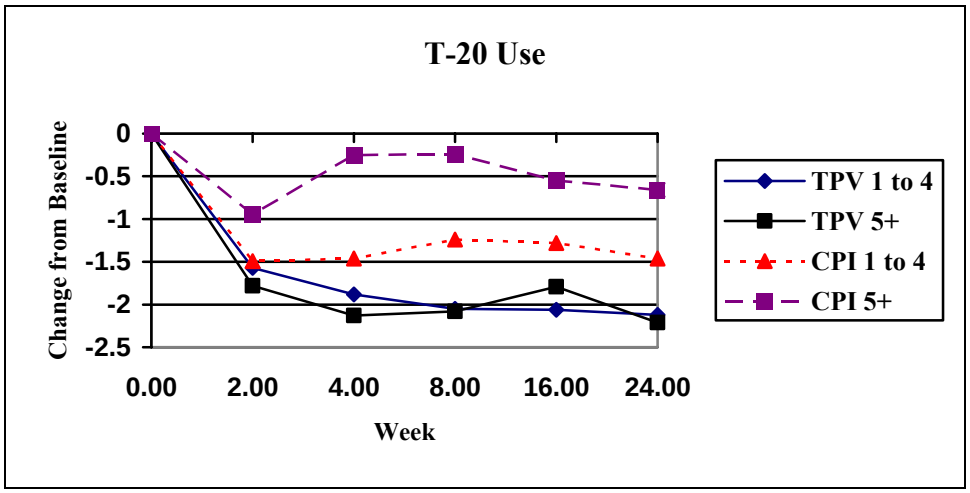
N@ Week:	0	2	4	8	16	24
TPV 1-4	398	378	284	387	365	262
TPV 5+	303	288	289	297	289	211
CPI 1-4	381	352	358	363	308	173
CPI 5+	322	304	312	311	242	110

1B. Response without ENF Use



N@ Week:	0	2	4	8	16	24
TPV 1-4	328	311	315	318	297	199
TPV 5+	215	204	201	211	201	136
CPI 1-4	315	291	294	298	254	131
CPI 5+	258	244	252	249	194	62

1C. Response with ENF Use



N@ Week:	0	2	4	8	16	24
TPV 1-4	70	67	69	69	68	63
TPV 5+	88	84	85	88	83	75
CPI 1-4	66	61	64	65	54	42
CPI 5+	64	60	60	62	48	28

E. Proportion of Responders by Baseline TPV Phenotype

TPV/r response rates were also assessed by baseline TPV phenotype. Again, we focused on the No ENF group in order to more accurately assess the effect of baseline phenotype on virologic response for TPV/r. With no ENF use, the proportion of responders was 45% if the fold change in IC_{50} value from reference of TPV susceptibility was 3-fold or less at baseline (Table 10). 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.

Table 10. Proportion of Responders by Baseline TPV phenotype

Baseline TPV Phenotype	All	No ENF Use	ENF Use
Overall	47% (146/313)	39% (84/218)	65% (62/95)
0-3	54% (120/223)	45% (74/163)	77% (46/60)
>3-10	29% (22/75)	21% (10/47)	43% (12/28)
>10	27% (4/15)	0% (0/8)	57% (4/7)

V. MANAGEMENT OF KNOWN AND POTENTIAL DRUG-DRUG INTERACTIONS

The management of known and potential drug-drug interactions emerged as a challenging issue for TPV administered with ritonavir. The interaction potential for 500 mg TPV in combination with 200 mg ritonavir is summarized below:

A. Potential for TPV/r to affect other drugs

1. TPV is a CYP 3A inhibitor and a CYP3A inducer. TPV, co-administered with low-dose ritonavir 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.

3. TPV is a P-glycoprotein (P-gp) substrate, a weak P-gp inhibitor, and likely a potent P-gp inducer as well. 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 [1, 2].

B. 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. Particular caution should be used when prescribing these drugs with TPV/r.

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 described in the Clinical Pharmacology Appendix to the document.

The following tables highlight drugs that are contraindicated and not recommended for co-administration with tipranavir/ritonavir (Table 11) and some other established or potential drug interactions (Table 12) for discussion. Table 12 also includes HIV drugs that are not expected to interact with TPV/r. 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. The Clinical Pharmacology Appendix includes more details about the design of drug interaction studies.

Table 11 : Drugs that Should Not be Co-administered with TPV/r

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

Table 12: 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
	HIV-Antiviral Agents	
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.
Emtricitabine	Interaction is not expected.	No interaction expected
Lamivudine	↔Lamivudine ↔Tipranavir	No interaction
Stavudine	↔ Stavudine ↔Tipranavir	No interaction
Tenofovir	↔ Tenofovir ↔Tipranavir	No interaction
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.
Non-Nucleoside Reverse Transcriptase Inhibitors: Efavirenz	↔ Efavirenz ↔Tipranavir	No interaction (based on cross-study comparison)
Nevirapine	As with efavirenz, no interaction is expected.	The interaction between nevirapine and TPV SEDDS formulation in combination with low dose ritonavir was not evaluated.
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
Fusion inhibitor: Enfuvirtide	Interaction is not expected.	The interaction was not evaluated.

Table 12: 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
	Other Agents	
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 studied. Patients should be monitored carefully for adverse events.
Antifungals: Fluconazole Itraconazole Ketoconazole Voriconazole	↑Tipranavir, ↔Fluconazole Expected ↑Itraconazole, Expected ↑Ketoconazole Expected ↑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. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction.
Anticoagulant: Warfarin	Cannot predict the effect of TPV/r on warfarin due to conflicting effect of TPV and RTV on CYP2C9	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, ↓14-hydroxy metabolite	No dosage adjustments are needed.
Azithromycin	Interaction is not expected.	The interaction was not evaluated.

Table 12: 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
Calcium Channel Blockers: e.g., felodipine, nifedipine, nicardipine	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. Women using estrogens may have an increased risk of non-serious rash.
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.
Disulfiram/Metronidazole		Tipranavir capsules contain alcohol which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).

References

1. Transporter-enzyme interactions: implications for predicting drug-drug interactions from in vitro data. Benet LZ, Cummins CL and Wu CY. Curr Drug Metab. 2003;4(5):393-8.
2. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Zhang Y and Benet LZ. Clin Pharmacokinet. 2001;40(3):159-68.

V. SAFETY CONSIDERATIONS

A. Adverse events in the RESIST trials

Unless otherwise stated the adverse events (AEs) presented below are treatment emergent, which includes day 1 of treatment through a 30 day follow-up period post treatment. BI 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 captured and thus are not presented here.

BI captured AEs as mild, moderate and severe, which corresponded to grade 1, grade 2, and grade 3 or 4 respectively. Retrospectively BI created a category of "severe and serious" reportedly to represent grade 4 AEs. Since there is no accurate way to establish what is a grade 3 and what is a grade 4 AE post hoc, DAVDP has decided to present the combination grade 3/grade 4 data as captured.

B. Overall Summary of AEs

Eighty-four percent of the subjects on the TPV/r arm and 78% of the subjects on the control arm reported at least 1 AE. The most common treatment-emergent AEs regardless of causality on the TPV/r arm were diarrhea (23%), nausea (14%), pyrexia (9%), headache (9%), and vomiting (7%); the rates on the CPI/r arm were 18%, 7%, 7%, 6%, and 7% respectively. More subjects on the TPV/r arm compared to the CPI/r arm had AEs in the following MeDRA System Organ Classes (MSOC): Gastrointestinal disorders (48% versus 44%), Infections and infestations (46% versus 38%), Metabolism and nutrition (14% versus 9%), Investigations (10% versus 7%).

C. AEs leading to Discontinuation

Eight percent of subjects on the TPV/r arm compared to six percent of subjects on the CPI/r arm discontinued study treatment due to AEs. 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 compared to zero subjects on the CPI/r.

D. Severe AEs

Eighteen percent of TPV/r subjects had at least one severe AE compared to 15% of the subjects on the CPI/r arm. Grade 3/4 AEs reported by at least 1% of the subjects included: diarrhea (1.3% TPV/r versus 1.8% CPI/r) and nausea (1.1% TPV/r versus 0.1%).

E. Serious Adverse Events (SAEs)

In the RESIST trials (n = 1483), 188 (13%) of all subjects experienced 456 SAEs, regardless of causality: 13% (99 of a total 746) of subjects in the TPV/r arm and 12% (89 of a total 737) in the CPI/r arm. The most common MSOCs affected were infections and infestations (26%), general disorders and administration sites (12%), gastrointestinal disorders (11%), nervous system disorders (7%).

F. Summary of AEs Observed in the RESIST Trials

Overall the TPV/r arm had more subjects with AEs and more subjects who discontinued due to AEs. The leading causes of discontinuations due to AEs (namely, diarrhea, nausea, and vomiting) were also amongst the leading causes of AEs in general (in addition to headache and pyrexia). Diarrhea, nausea and vomiting are well known, Investigator Brochure listed, TPV/r associated treatment limiting toxicities.

Although the TPV/r arm had more AEs and more discontinuations due to AEs, the number of subjects with severe AEs (grade 3/ 4 combined) was only slightly higher on the TPV/r arm and SAEs were similar across the two arms. Of note, DAVDP was not able to discriminate grade 4 AEs from grade 3 AEs, so it is possible that a difference might exist between the two arms that was not captured and therefore can not be conveyed.

G. AEs of Special Interest in the TPV development Program

Rash

The initial evidence that TPV/r might cause rash and more specifically rash in female subjects came from Study 1182.22. Study 1182.22 was a randomized, open-label, parallel group drug interaction study comparing plasma concentrations of ethinyl estradiol (EE) and norethindrone (NET) after administration of Ortho-1/35, an oral contraceptive pill, when given alone versus concentrations of EE and NET after co-administration with TPV/r. The study enrolled healthy females between the age of 18 and 50 years with no history of an allergies or illnesses that might interfere with the study results or place the subject at increased risk. Study subjects could not have participated in any other investigational trials within 30 days of the start of this trial. Healthy female volunteers were randomized to receive single doses of Ortho 1/35 on days 1 and 15 of the study plus *either* TPV/r 500/100 mg *or* TPV/r 750/200 mg twice daily from study day 4 to 16. The to-be-marketed SEDDS formulation of TPV was used in this study. Pharmacokinetic measurements were planned for days 1-3 and days 14-17. A total of 52 healthy, predominately white (n=47) female volunteers at a single study center were randomized 1:1 to either Ortho-1/35 plus TPV/r 500/100 mg (n=26) or to Ortho-1/35 plus TPV/r 750 mg/200 mg (n=26). There were a total of 501 AEs in the study; all study participants reported at least one AE. Gastrointestinal AEs were most commonly reported (n=47). However, rash (n=11) and musculoskeletal pain (n=5) were more common reasons for premature study discontinuation, and the study was stopped early due to the possibility of serum sickness.

Seventeen subjects (33%) developed a rash while receiving TPV and 20% had musculoskeletal pain. Three subjects had both skin and musculoskeletal findings. An additional three subjects reported symptoms that can be associated with drug hypersensitivity while receiving TPV; one had generalized pruritis and conjunctivitis on day 11, one had conjunctivitis on day 11, and the other had intermittent numbness and tingling in the leg on day 11. Therefore, the most conservative analysis, defined as all subjects with a *possible* drug hypersensitivity, would include 26 subjects (51%). Based on the signal observed in healthy female volunteers in this one Phase 1 study, DAVDP analyzed the rash data from the remainder of the TPV/r development program.

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 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. The 5 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 RESIST trials overall, the incidence of rash was similar on both arms (11% TPV/r versus 10% CPI/r). The severity and need for treatment were also similar between the two arms, and only a small number of subjects (three) on the TPV/r arm compared to zero on the CPI/r arm ended up discontinuing study treatment due to their rash.

The exploratory analysis of the females in the RESIST trials (n=118 TPV/r; n=90 CPI/r) revealed 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%). Baseline CD4 counts for females with rash were similar between the two arms (TPV/r 222 cells/mm^3; CPI/r 207.5 cells/mm^3).

In conclusion, there was a high and unexplained incidence of rash in healthy, female volunteers on Study 1182.22 raising the possibility that gender and immune status may have an impact on the frequency and types of AEs observed with TPV/r use. The higher incidence of rash in females on TPV/r was supported by data from the RESIST trials; however, the small number of women in these trials and the relatively low CD4+ counts of the women with rash made it impossible to draw any definitive conclusions. Although BI is currently conducting a study in ARV naïve subjects, the study is already fully enrolled and women make up only approximately 20% of the population (similar to the RESIST trials) and based on baseline CD4+ count, viral load and AIDS defining illnesses, these naïve subjects have very advanced disease. Therefore the current naïve trial is unlikely to provide the definitive answer to whether or not TPV/r affects women, or immunocompetent patients differently than the remainder of the HIV+ population.

Transaminase Elevation

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 the best evidence that TPV independent of, but in the presence of, ritonavir causes grade 3/4 ALT elevations in a dose dependent manner.

Table 13: 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)

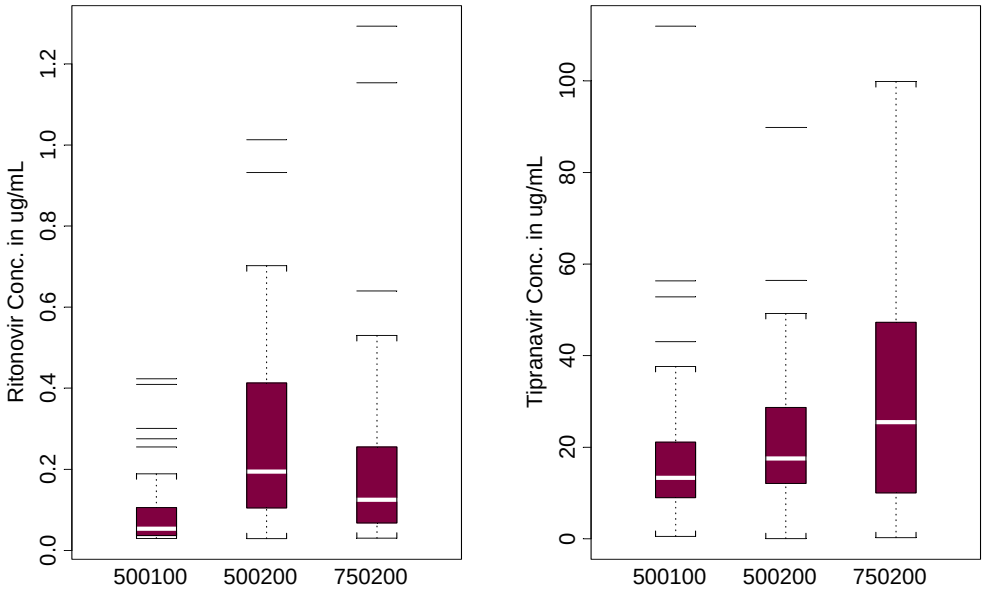


Figure 2: Range of trough (Cmin) ritonavir and tipranavir concentrations at the 3 dose levels. The median ritonavir concentrations are 0.0962 μg/mL (n=40), 0.281 μg/mL (n=56), and 0.217 μg/mL (n=47), respectively for dose level of 500/100 TPV/r, 500/200 TPV/r, and 750/200 TPV/r. The median concentrations of tipranavir are 17.46 μg/mL (n=60), 21.26 μg/mL (n=63) and 30.75 μg/mL (n=56), respectively.

In order to understand whether ALT elevation is related to TPV or ritonavir, the exposures of both TPV and ritonavir were compared across treatments. 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 2. 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 tipranavir, assuming that steady state was achieved by day 14. The median ritonavir concentration is lower (0.281 μg/mL vs. 0.217 μg/mL) and tipranavir 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 (Figure 3). In spite of this, the 750/200 mg dose group had a higher proportion of subjects with grade 3/4 ALT elevations.

The logistic regression analysis was conducted between the incidence of grade 3/4 ALT and 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 3/4 ALT elevations increase by 140% (Figure 3). A similar analysis was conducted for ritonavir. The results showed that ritonavir Cmins are not significantly correlated to grade 3/4 ALT toxicity.

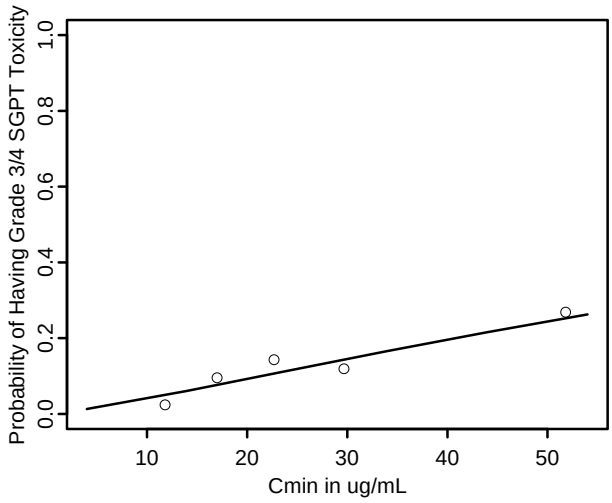


Figure 3: Probability of subjects having a grade 3/4 ALT elevation is higher at higher TPV Cmins. The logistic regression was performed using TPV Cmin as a continuous variable and the incidence of grade 3/4 ALT toxicity as a binary variable (yes or no). The solid line represents the regression fit. Subsequent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

In the RESIST trials 6% (n=45) of subjects on the TPV/r arm compared to 3% (n=22) on the CPI/r arm developed treatment emergent grade 3 or 4 ALT/AST elevations. Twenty percent (n = 9/45) of the TPV/r subjects with Grade 3 or 4 ALT/AST elevation had a baseline diagnosis of viral Hepatitis B or C as compared to 30% (n = 7/22) of the CPI/r subjects with Grade 3 or 4 ALT/AST elevation. Very few subjects had documented concurrent symptoms (defined as 7 days prior and 14 days post laboratory abnormalities); however, at the time of data submission, a substantial number of subjects had not resolved their LFT elevations, and therefore, no conclusions can be made about the acute clinical impact of these laboratory abnormalities. Approximately 27% of subjects (n=12) with elevated AST/ALT discontinued treatment on the TPV/r arm versus 5% on the CPI/r arm (n=1). At this time, FDA exploratory analyses examining the possible baseline risk factors for hepatotoxicity (i.e. baseline CD4 counts, hepatitis co-infection, gender, or race) are ongoing. Figure 4A and 4B show that changes in ALT from baseline were statistically significantly different between the TPV/r arm and the CPI/r arm from Week 2-16 in both Resist 1 and 2 respectively.

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

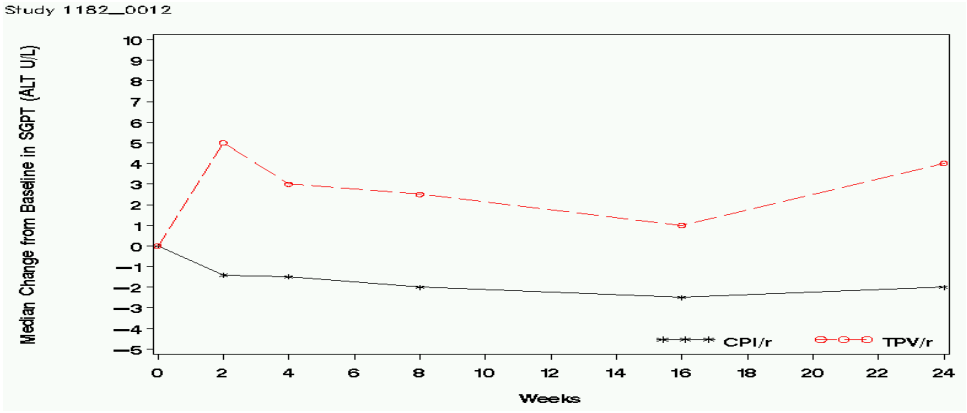
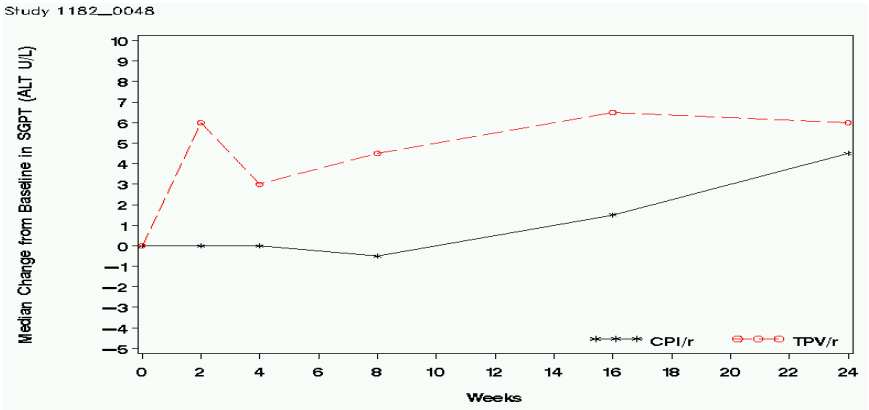


Figure 4B: Median Change from Baseline ALT (U/L) form RESIST 2



In summary, increases in ALT were seen throughout Phase 1, 2 and 3 TPV studies. In general ALT elevations appear to be the most common, clinically relevant LFT abnormality associated with TPV/r use. The majority of the time these ALT elevations are clinically asymptomatic. Resolution data are incomplete at this time; however, it appears that at least 50% of the time these ALT elevations resolve without discontinuing study drug.

Hyperlipidemia

Forty-six percent of subjects (n=335) on the TPV/r arms developed treatment emergent Grade 2 - 4 triglycerides (Grade 2: 400-750, Grade 3: 751-1200, Grade 4: >1200) compared to 24% of subjects on the CPI/r arms (n=176). The TPV/r arms had more subjects with treatment emergent hypertriglyceridemia at each grade compared to the CPI/r arms: 195 versus 111 subjects with Grade 2 elevations; 96 versus 41 subjects with Grade 3 elevations; and 45 versus 24 subjects with Grade 4 elevations respectively. Only one subject on the CPI/r arm had documented clinical pancreatitis and hypertriglyceridemia. The other four cases of clinical pancreatitis (2 on the TPV/r arm and 2 on the CPI/r arm) either had normal triglyceride values or none recorded.

Figure 5A: Median Change from Baseline Triglycerides (mg/dL) in RESIST 1

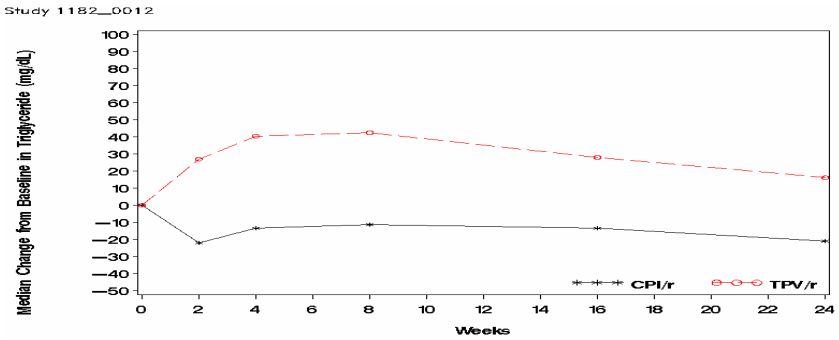
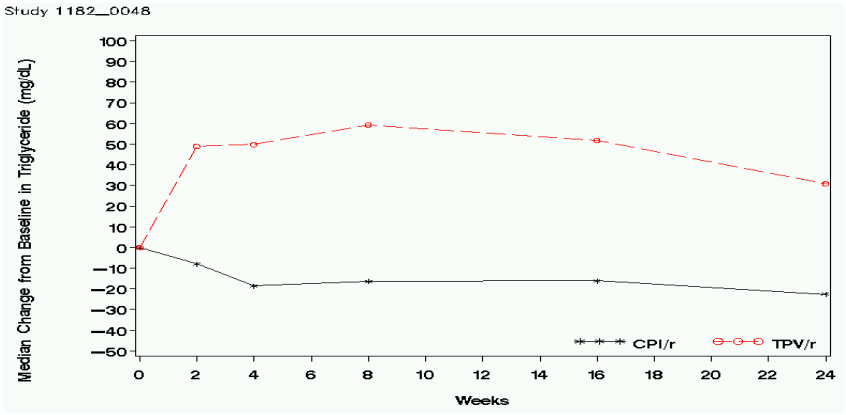


Figure 5B: Median Change from Baseline Triglycerides (mg/dL) in RESIST 2



Fifteen percent (n=108) of TPV/r subjects had treatment emergent Grade 2-4 (values >300 mg/dL) cholesterol elevations as compared to 5% (n=33) of subjects on the CPI/r arms. The TPV/r arms had 84 subjects with emerging grade 2 cholesterol (>300-400 mg/dL), 18 subjects with grade 3 cholesterol (>400-500 mg/dL), and 6 subjects with grade 4 cholesterol (> 500 mg/dL) compared to 31 subjects with grade 2 cholesterol, 2 subjects with grade 3 cholesterol and 0 subjects with grade 4 cholesterol.

AIDS progression and Deaths

Treatment emergent new AIDS progression events were observed in slightly fewer TPV/r subjects (3%) as compared to CPI/r subjects (5%). The major differences observed were in the number of subjects with treatment emergent esophageal candidiasis (5 versus 13), CMV disease (0 versus 4) and cryptosporidiosis (0 versus 4). It is important to point out that the AIDS progression data from the RESIST trials were only deduced from adverse events data. AIDS progression clinical events were not separately captured or adjudicated and thus robustness of the following data is limited.

Table 14: FDA analysis of AIDS defining events (ADEs) abstracted from AE datasets

	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
Subjects w/ a tx emergent ADEs	11	16	11	20	22	36
# of tx emergent ADEs	12	18	13	24	25	42

Source: AECD12 dataset

One hundred and two (102) subjects 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.

All of the TPV clinical development program deaths were in HIV-positive, ARV experienced, adult subjects. No HIV negative, HIV+ naïve, or HIV+ pediatric subjects had died as of June 11, 2004. (However, four treatment naïve subjects with advanced HIV disease at the time of starting TPV have died since the June 2004 cut-off date). A total of 57 of the 102 death cases (55%) 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 subjects receiving TPV/r in these 2 countries (42% treated in the US, and 12% treated in France. Table 15 below outlines the number of deaths per trial, treatment period and treatment arm (if applicable).

Table 15: FDA Analysis of Cumulative 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	5	n/a	n/a	n/a
1182.17	0	13	8	20	n/a	n/a	n/a
1182.58	1	19	6	26	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	75	13	2	14

In total 12 subjects died during the pretreatment phase and 90 subjects 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. This subject had a history of fatty live 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.

The following table presents key characteristics of the subjects who died in the pivotal studies, RESIST 1 and RESIST 2. 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, p-value = 0.19), and 2. the TPV/r arm has a much lower median baseline and last CD4+ count as compared to the CPI/r arm (baseline13.75 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.

Table 16: Characteristics of Subjects who died in RESIST 1&2 as 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 subjects 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
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^3]	13.75	157	15	39	15	102.25
Median last CD4+ count [cell/mm^3]	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

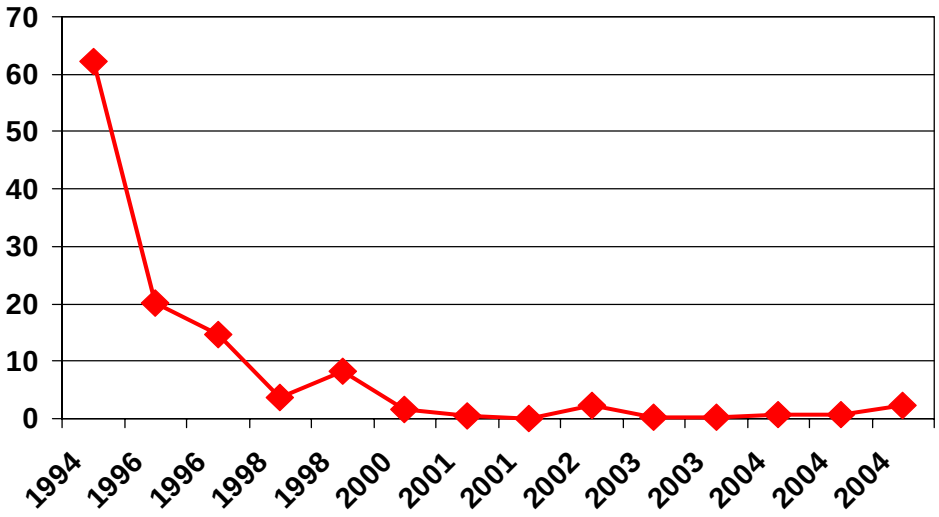
Source: Corporate safety death dataset 12/5/04

For all-cause mortality the numbers of *on-treatment* deaths (15 TPV/r versus 13 CPI/r) were similar between the two arms. AIDS defining or AIDS progression events were captured in RESIST trials as adverse events only and not specifically abstracted or adjudicated. 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, the 24 week time-point is too premature to see any clinical endpoint differences, and/or the comparator arm's escape clause option at week 8 may have salvaged subjects prior to prolonged virologic failure. The relationship of plasma HIV RNA as surrogate endpoints to the actual clinical outcomes may be less well understood in studies of heavily pretreated populations. In addition, due to the open-label nature of these RESIST trials with 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 efficacy data (both virologic and clinical) beyond 8 weeks of treatment.

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 showed that the population enrolled in ENF phase 3 studies most closely approximated the TPV phase 3 studies. Each 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. This was how ENF death numbers were counted (www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm) in ENF's accelerated approval NDA review at 24 weeks. Both NDA deaths numbers were then used to calculate the mortality rate (#death/100 subject-years) using 24 weeks duration. As shown below, absolute numbers of deaths or mortality rates between the test and control arms were similar for both the TPV and ENF NDAs at 24 weeks.

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 RESIST mortality 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 Figure 6.

FIGURE 6: Mortaltiy Rates (100 subject-years) per NDA study in "treatment-experienced" population shown by year of approval by DAVDP



Examination of subject baseline characteristics showed that the population enrolled in T20 phase 3 studies which most closely approximated the TPV phase 3 studies was the ENF trials population (http://www.fda.gov/cder/foi/nda/2003/021481_fuzeon_review.htm). Each 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 ENF death numbers were counted in ENF's accelerated approval NDA review at 24 weeks Both NDA deaths 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 17: 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

We are reassured at this point in the review (24 week analyses) that the 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 above.

APPENDIX I : Discussion of Dose-finding study 1182.52

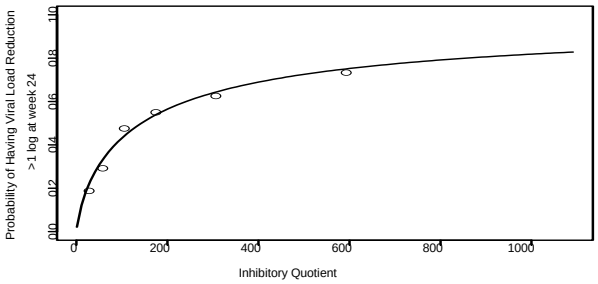
The sponsor selected the dose for phase 3 studies based on Study 1182.52 and other phase 2 studies. Three doses were studied in Study 1182.52: 500/100 TPV/RTV, 500/200 TPV/RTV, and 750/200 TPV/RTV. The median $\log_{10}$ changes from baseline viral load were -0.85, -0.93, and -1.18, respectively, following 2 weeks of treatment with 500/100 TPV/RTV, 500/200 TPV/RTV, and 750/200 TPV/RTV, indicating anti-viral activity was dose-dependent. The safety analysis also demonstrated a dose related relationship

Percent of subjects with safety/tolerability events:

	500/100 TPV/RTV	**500/200 TPV/RTV**	**750/200 TPV/RTV**
Severe AE	17.8%	23.6%	39.4%
Discontinuation due to AE	5.5%	9.7%	15.5%
Grade 3 ALT	5.5%	11.1%	21.2%

Because the Phase 3 dose was selected based on tolerability, it is important to determine the proportion of subjects who may not benefit from treatment at this dose. An analysis of Study 1182.52 data can help determine the proportion of subjects who may be underdosed at the 500/200 TPV/RTV dose level. Due to the large between-subject variability in trough concentrations of TPV (range: 0.885 to 2850 ng/mL) observed from phase 3 studies, some subjects who receive 500/200 TPV/RTV will have low TPV concentrations that are not likely to provide benefit if their virus has a high IC_{50}. Based on the logistic regression analysis of data from Study 1182.52 (Figure 1), an inhibitory quotient ($Cmin/IC_{50}$) of 100 would result in 1 log reduction at week 24 in 43% of the subjects. Of the 293 subjects with tipranavir Cmin and IC_{50} data in two phase 3 studies, only 53% have an inhibitory quotient of 100 or greater at the 500/200 TPV/RTV regimen, due to the high between-subject variability in Cmin and IC_{50}.

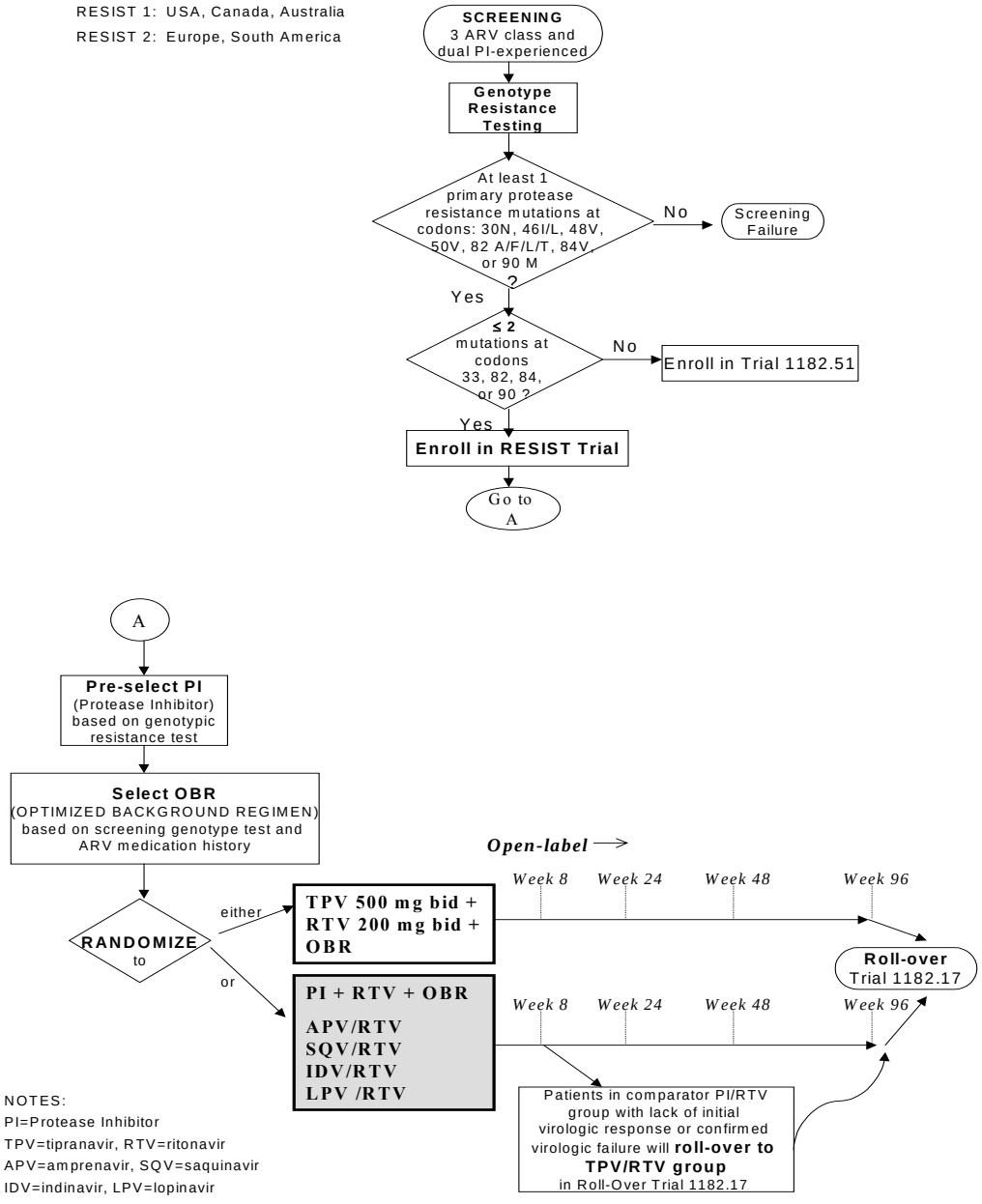
Figure: Probability of subjects achieving at least 1 $_{log}$ VL reduction ↑ with higher IC.



APPENDIX II: Schematic of RESIST Trials—Study Design

STUDIES 1182.12 (RESIST 1) and 1182.48 (RESIST 2)

Open-label, Controlled, Highly ARV-experienced patients



APPENDIX III

Clinical Pharmacology Findings

Absorption of TPV in humans is limited, although no absolute quantification of absorption is available. TPV is a substrate for CYP3A and P-gp, so the limited absorption may be due to the effect of the intestinal CYP3A 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. TPV is a potent CYP3A4 inducer. Repeated dosing with TPV resulted in levels much lower at steady-state than those after a single dose. Ritonavir is a potent CYP3A inhibitor. The proposed dose of TPV 500 mg with RTV 200 mg bid at steady-state resulted in the increase of the mean plasma TPV C_{min}, C_{max} and $AUC_{0\text{-}12h}$ by 45-fold, 4-fold, and 11-fold respectively, compared to TPV 500 mg bid given alone. The effective mean elimination half-life of TPV in healthy volunteers (n=67) and HIV-infected adult subjects (n=120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a TPV/r dose of 500 mg/200 mg twice daily with a light meal.

TPV protein binding is very high (ca. 99.9% at 20 μM) in human plasma. The degree of binding is similar over a wide concentration range from 10 to 100 μM. TPV binds to both human serum albumin and α-1-acid glycoprotein. In clinical samples from healthy volunteers and HIV-positive subjects who received TPV without ritonavir, the mean fraction of TPV unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV-positive subjects 0.019% ± 0.076%). Total plasma TPV concentrations for these samples ranged from 9 to 82 μM.

A mass-balance study in healthy male subjects demonstrated that, at steady-state, a median of 82.3% of the radioactivity from the ^{14}C-TPV dose (TPV 500 mg/RTV 200 mg) was recovered in feces. Renal elimination appeared to be a minor route of excretion for TPV, as only a median of 4.4% radioactivity of the dose was recovered in urine and unchanged TPV was about 0.5% of total urine radioactivity. The main route of excretion of TPV was via the feces, which could be due to a combination of unabsorbed drug as well as the biliary excretion of absorbed drugs and its metabolites. Furthermore, based on the observation that most fecal radioactivity was present as unchanged TPV, and the data from an in vitro study that indicated that TPV is a P-gp substrate, part of the radioactivity could be due to "excretion" into the gastrointestinal tract mediated by this efflux transporter.

Daily trough level monitoring in the mass balance study confirmed that the steady-state of TPV/r was reached following about 7 days of dosing. TPV trough concentrations at the steady-state are about 30% of those on Day 1. At state-steady, unchanged TPV accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of plasma radioactivity). 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 TPV 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.

Following a single dose of TPV/r 500mg/200mg in 9 subjects with mild hepatic insufficiency, the mean systemic exposure of TPV was comparable to that of 9 matched controls. After 7 days of twice daily dosing, the mean systemic exposure of TPV was higher for subjects with mild hepatic insufficiency compared to that of 9 matched controls, and the of 90% confidence intervals (CIs) were quite large. The geometric mean ratios with 90% CIs for AUC, C_{max} and C_{min} 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 ritonavir exposure was also observed. Dosage adjustment may not be warranted for this group of subjects based on the moderate change in TPV and ritonavir systemic exposure and safety profiles observed in this study. There were insufficient data (lack of data at steady-state) from the moderate hepatic insufficiency group to reach any conclusion. The use of TPV/r in subjects with moderate hepatic insufficiency is a current review issue. The liver is the major organ that eliminates TPV from systemic circulation; thus, TPV/r should be contraindicated for subjects with severe hepatic insufficiency due to safety concerns and the lack of data. in this population.

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

In vitro metabolism/transport findings

In vitro metabolism studies with human liver microsomes indicated CYP3A is the predominant CYP enzyme involved in TPV metabolism. Ketoconazole at concentrations of 1 μM or 5 μM inhibited the metabolism of TPV (50 μM) by 90% and 95%, respectively. Correlation analysis confirmed the strong involvement of CYP3A. Incubations of TPV with cDNA-expressed human CYP2D6 confirmed that CYP2D6 is not involved in the metabolism of TPV.

In vitro metabolism studies with human liver microsomes indicated that TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 and CYP3A4. The CYP activity markers used were phenacetin (CYP1A2), diclofenac (CYP2C9), (S)-mephenytoin (CYP2C19), bufuralol (CYP2D6), testosterone (CYP3A4) and midazolam (CYP3A4). The [I]/Ki ratio allows an assessment of the likelihood of in vivo inhibition. For the calculation of [I]/Ki, in vivo C_{max} (bound plus unbound) was used to represent inhibitor concentrations [I]. Because [I]/Ki ratios are greater than 1, drug interactions involving above-mentioned major human CYPs are considered likely. The in vivo effect of TPV/r on enzymes other than CYP3A has not been evaluated. The net in vivo effect of TPV/r on CYP3A is inhibition.

Table 113: Tipranavir K_i and proposed [I]/K_i values for the major CYPs

CYP	K_i (μM)	[I]/Ki*
CYP1A2	24.2	3.9
CYP2C9	0.23	414.8
CYP2C19	5.3	18.0
CYP2D6	6.7	14.2
CYP3A4 (Midazolam)	0.88	108.4
CYP3A4 (Testosterone)	1.3	73.4

* [I] is based on C_{max} of 95.4 μM at steady-state of tipranavir/ritonavir 500 mg/200 mg bid.

An in vitro study in human hepatocytes demonstrated that TPV is a potent CYP3A4 inducer.

In vitro data indicated TPV is a P-gp substrate and a weak P-gp inhibitor. As discussed later, in vivo data indicated TPV is a P-gp inducer as well. Data from Caco-2 cells indicated that TPV's basolateral to apical permeability (secretory direction) was greater than its apical to basolateral permeability (absorptive direction), suggesting that TPV is a substrate of apically located efflux pumps (e.g., P-gp). Data also demonstrated that known P-gp inhibitors such as quinidine, verapamil and LY335979 inhibited the efflux of TPV and increased TPV absorption from the apical side of cells. Cremophor EL, which is currently used in the SEDDS formulation, markedly increased the TPV apical absorption, suggesting it may have a similar effect in vivo. Data from MDCK wild type and MDR1-transfected MDCK cell lines confirmed that TPV is a substrate for P-gp. The Applicant also mentioned that TPV is a weak P-gp inhibitor, using digoxin as a P-gp marker substrate in Caco-2 cells.

Drug interaction findings

TPV/r (500 mg/200 mg) is a net inhibitor of the P450 CYP3A. The Erythromycin Breath Test results showed that the hepatic CYP3A activity was increased following 11 days repeated dosing of TPV alone and was inhibited by co-administration of TPV/r. These results suggest that TPV alone is a hepatic CYP3A inducer and the net effect of TPV/r is inhibition of hepatic CYP3A activity. This conclusion is further supported by the levels of TPV major oxidative metabolite (M1) formation with and without ritonavir. The Erythromycin Breath Test result also demonstrated that a single dose of TPV/r 500/200 mg almost completed inhibited the hepatic CYP3A4 activity. However, CYP3A activity returned to baseline levels as TPV/r was eliminated from the body.

The following data suggest that TPV is also a P-gp inducer and the net effect of TPV/r (500 mg/200 mg) on P-gp at state-steady is induction:

1. Loperamide (LOP) is a known substrate of P-gp and P-gp plays a significant role in LOP's elimination. Co-administration of LOP with steady-state TPV or TPV/r resulted in 63% and 51% decrease in LOP AUC, respectively, and 58% and 61% decrease in LOP Cmax, respectively. However, co-administration of LOP with steady-state ritonavir resulted in increases in LOP AUC (121%) and Cmax (83%).

2. Clarithromycin (CLR) is a P-gp and CYP3A substrate. Steady-state TPV/r administration (500/200 mg bid) increased CLR $AUC_{0\text{-}12h}$ and Cp_{12h} by 19% and 68%, respectively, with no substantial change in the Cmax. However, the formation of the major metabolite, 14-OH-CLR, was almost fully inhibited at the steady-state of TPV/r administration. The degree of CLR exposure increase is less than expected based on the degree of reduction of 14-OH-CLR formation. A possible explanation is that TPV is a P-gp inducer and the low dose of ritonavir can not compensate for the P-gp induction effect caused by TPV. Because CLR is a P-gp substrate, CLR is pumped back to intestinal lumen as unabsorbed drug by increased activity of intestinal P-gp. The net interplay between intestinal CYP3A and P-gp led to similar systemic exposure of CLR when co-administered with TPV/r at steady-state compared to that of CLR alone.

3. In the human mass balance study, daily trough level monitoring confirmed that the steady-state of TPV/r (500 mg/200 mg bid) is reached after about 7 days of dosing. TPV trough concentrations at steady-state are about 70% lower than those on Day 1.

However, in plasma, unchanged TPV was predominant and accounted for 98.4% or greater of the total plasma radioactivity at steady-state. If the lower TPV concentrations at steady-state were due to CYP3A induction, metabolites would contribute to more of the plasma radioactivity. A possible explanation is that TPV is a potent P-gp inducer and the low dose of ritonavir cannot compensate for the P-gp induction effect caused by TPVr. Because TPV is a P-gp substrate, at steady-state more TPV is pumped back to intestinal lumen as unabsorbed drug by increased activity of intestinal P-gp.

4. Co-administration of TPV/r at 500 mg/200 mg twice daily decreased amprenavir, lopinavir and saquinavir steady-state trough plasma concentrations by 52%, 80% and 56%, respectively, when these protease inhibitors were administered with 200 mg ritonavir. A possible explanation is that TPV is a potent P-gp inducer and the low dose of ritonavir can not compensate for the P-gp induction effect caused by TPV. All the PIs studied in this trial are known dual substrates of CYP3A and P-gp and are subject to high intestinal first-pass effect. Thus, the net interplay between intestinal CYP3A and P-pg caused lower systemic exposure of these PIs when co-administered with TPV/r at steady-state.

The Applicant conducted numerous drug-drug interaction studies using proposed to be marketed TPV capsule formulation (SEDDS) in combination with low dose (100 or 200 mg) ritonavir, as described below (also see Tables 11 and 12 in the main text).

<u>Antiretroviral agents: Nucleoside reverse transcriptase inhibitors (NRTIs):</u> abacavir, didanosine (ddI), lamivudine (3TC), stavudine (d4T), tenofovir and zidovudine (ZDV)

Abacavir AUC values were reduced by 35% to 44% following co-administration with three TPV/r dose levels (TPV/r 250 mg/200 mg, 750 mg/100 mg and 1250 mg/100 mg). The extent of the interaction was not dose dependent. Appropriate doses of abacavir when given with TPV/r have not been established.

The interaction of TPV/r with enteric coated-ddI was initially studied in Study 1182.6 where ddI AUC values were reduced by 33% at the TPV/r 250 mg/200 mg dose level, but there were no changes at the 1250 mg/100 mg and 750 mg/100 mg dose levels. In Study 1182.42, the interaction of ddI with co-administered TPV/r could not be evaluated for the group of subjects that received TPV/r 750 mg/200 mg because early discontinuations provided only a single subject on study Day 15. For the group of subjects that received ddI in the presence of TPV/r 500 mg/100 mg, early discontinuation reduced the number of subjects on study Day 15 from 11 to 5. Results from the five completed subjects showed that AUC and C_{max} of ddI were not significantly changed with the co-administration of TPV/r, however the 90% confidence intervals were quite large indicating a high degree of variability. While TPV AUC was not changed when co-administered with ddI, C_{max} increased about 30% and C_{p12h} decreased about 30%, with wide 90% CIs.

There were no significant PK interactions between TPV/r and lamivudine, stavudine and tenofovir.

The interaction of TPV/r with zidovudine was initially studied in Study 1182.6, where TPV/r decreased ZDV AUC and C_{max} by 47% and 68%, respectively. Study 1182.37 confirmed that co-administration of TPV/r with ZDV markedly decreased ZDV exposure, i.e., AUC decreased 43% at the TPV/r 500/100 mg dose and AUC decreased 33% at the TPV/r 750/200 mg dose.

However, zidovudine glucuronide exposure (C_{max} and AUC) was not affected by the co-administration of TPV/r. TPV exposure decreased about 13-23% when co-administered with ZDV at the TPV/r 500/100 mg dose, while TPV exposure was not significantly affected when ZDV was co-administered with TPV/r 750/200 mg. When 300 mg ZDV is co-administered with the proposed clinical dose of TPV/r 500/200 mg, ZDV plasma exposure is expected to decrease 30-40% based on the data from this study. The PK of TPV and ritonavir are not likely to change when co-administered with ZDV. Appropriate doses for the combination of ZDV administered with TPV/r have not been established.

Antiretroviral agents: Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz (EFV) and nevirapine

In Study 1182.41, steady-state efavirenz decreased steady-state TPV AUC 31%, C_{max} 21% and C_{p12h} 42% in the TPV/r 500/100 mg regimen, based on a cross study comparison. However, steady-state efavirenz had little effect on steady-state TPV AUC, C_{max} and C_{p12h} in the TPV/r 750/200 mg regimen, based on a cross study comparison. The change in TPV exposure was less pronounced in the RTV 200 mg group, suggesting that inhibition of CYP3A by the 200 mg RTV partially counteracted the effects of CYP3A induction by EFV. It is anticipated the effect of EFV on TPV/r 500/200 mg would be less than or similar to that of EFV on TPV/r 750/200 mg. A dose adjustment of TPV/r may not be needed in the presence of efavirenz. The effect of nevirapine on TPV SEDDS formulation in combination with low dose ritonavir was not evaluated. However, similar degree of interaction should be expected as that of efavirenz.

Antiretroviral agents: Protease inhibitors (PIs): amprenavir/RTV, lopinavir/RTV (Kaletra) and saquinavir/RTV

Study 1182.51 was a preliminary PK study to investigate the potential drug interactions between TPV/r and other ritonavir boosted-PIs and to provide initial clinical data for this dual PI approach. All four arms received the same total dose of RTV after Week 4, i.e., 200 mg bid.

The dual RTV-boosted PI treatments were:

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 twice daily decreased LPV, SQV, or APV steady-state trough plasma concentrations by 52%, 80% and 56%, respectively. These data were consistent with the results of the intensive PK sub-study where co-administration of TPV/r decreased LPV, SQV, or APV steady-state trough plasma concentrations by 70%, 82% and 55%, respectively, AUC by 55%, 76% and 44%, respectively, and C_{max} by 47%, 70% and 39%, respectively. TPV exposure increased slightly in the dual-boosted groups co-administered with APV/r and LPV/r, but decreased slightly when co-administered with SQV/r. Ritonavir 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. Appropriate doses for the combination of tipranavir, co-administered with low-dose ritonavir, with other PIs have not been established.

Some other commonly co-administered drugs in HIV-infected patients: antacid, atorvastatin, clarithromycin, ethinyl estradiol/norethindrone, fluconazole, loperamide and rifabutin

Simultaneous ingestion of antacid and TPV/r reduced the plasma TPV concentrations by about 25-29%. The exact mechanism of the interaction between antacid and TPV/RTV is not known. TPV/r dosing should be separated from antacid administration to prevent reduced absorption of TPV.

Atorvastatin (ATV) is extensively metabolized by CYP3A4. Co-administration of steady-state TPV/r increased single dose ATV's AUC by 9.4-fold, C_{max} by 8.6-fold and C_{p12} by 5.2-fold. No effect of single-dose ATV on the steady-state PK of TPV/r was observed. Similar findings have been reported for lopinavir/ritonavir 400/100, which increased ATV AUC and C_{max} by 6- and 5-fold, respectively. When co-administered with TPV/r, 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.

Clarithromycin (CLR) is used extensively in HIV/AIDS patients. CLR is metabolized extensively in the liver by CYP3A. One of two major metabolites, 14-hydroxy-R-clarithromycin (14-OH-CLR), is active against some bacteria. CLR is also an inhibitor of CYP3A and can increase the concentrations of drugs that primarily depend upon CYP3A metabolism. Study 1182.11 demonstrated that single-dose TPV/r (500/200 mg) did not affect steady-state AUC_{0-12h} of CLR, but decreased the C_{max} by 12% and increased Cp_{12h} by 50% and that steady-state TPV/r administration (500/200) increased CLR AUC_{0-12h} and C_{p12h} by 19% and 68%, respectively, with no substantial change in the C_{max}. However, the formation of 14-OH-CLR was almost fully inhibited at the steady-state of TPV/r administration. No dosage reductions of TPV/r or clarithromycin are necessary.

The addition of TPV/r at doses of either 500/100 mg bid or 750/200 mg bid to norethindrone/ ethinyl estradiol (NET/EE) (1/0.035 mg) therapy reduced the total EE exposure (AUC_{0-24h}) by 43-48%, and the maximal EE concentrations (C_{max}) by approximately 50%. This reduction of > 40% in the exposure to EE may significantly compromise the efficacy of this oral contraceptive. Therefore oral contraceptives should not be the primary method of birth control in HIV-infected women of child-bearing potential using TPV/r. The 13-27% increase in the exposure (AUC_{0-24h}) to NET after co-administration of TPV/r is not expected to be clinically relevant.

Fluconazole (FCZ) is routinely indicated for oropharyngeal and esophageal candidiasis, and for the treatment of other serious systemic fungal infections in HIV positive patients. FCZ was demonstrated to inhibit midazolam metabolism, a known substrate for CYP3A, administered both intravenously and orally. Co-administration of TPV/r 500/200 mg bid at steady-state caused small decreases in FCZ exposures (-11% in C_{p24h}, -6% in C_{max} and -8% in AUC_{0-24h}). In contrast, steady-state FCZ appeared to have a significant effect on the steady-state PK of TPV, when compared to the results from a cross study comparison. The steady-state TPV C_{p12h}, C_{max} and AUC_{0-12h} were increased by 104%, 56% and 46%, respectively, during co-administration of steady-state FCZ. This is likely due to the inhibition effect of FCZ on P-gp.

Co-administration of loperamide (LOP) with steady-state TPV or TPV/r resulted in 63% and 51% decrease in LOP AUC, respectively, and 58% and 61% decrease in LOP C_{max}, respectively. However, co-administration of LOP with steady-state ritonavir resulted in increases in LOP AUC (121%) and C_{max} (83%). The effect of single-dose LOP on the steady-state pharmacokinetics of TPV/r was less substantial but the clinical relevance is unknown. For TPV, trough concentration was decreased 26% while C_{max} and AUC_{0-12h} remained unchanged. For ritonavir, trough concentration, C_{max} and AUC_{0-12h} were decreased by 30%, 28% and 22%, respectively.

A single 150 mg dose of rifabutin (RFB) increased TPV C_{p12} at steady-state by 16%, with no effect on AUC and C_{max}. However, the steady-state TPV/r increased a single dose RFB's AUC, C_{max} and C_{p12} by 2.9-fold, 1.7-fold and 2.1-fold, respectively. This change may be due to inhibition of CYP3A mediated metabolism of RFB. Modification of the RFB dosing in combination with TPV/r is required. However, the effect of multiple dose of RFB on the steady-state PK of TPV/r was not studied. T he concern is that RFB is also a CYP3A and P-gp inducer and the multiple dose of RFB might shift the balance of induction and inhibition towards more induction; thus, reducing the TPV exposure.