BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

TIPRANAVIR

ANTI-VIRAL DRUGS ADVISORY COMMITTEE (AVDAC) BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
APV	Amprenavir
ARV	Antiretroviral (agent)
BI	Boehringer Ingelheim
BID	Twice a day
BLQ	Below limit of quantitation
CD4+	Cluster of differentiation 4 (antigen marker on T-lymphocytes)
CI	Confidence interval
CPI/r	Comparator protease inhibitor with ritonavir
C_{12h}	Plasma concentration of drug at 12 hours
EFV	Efavirenz
ENF	Enfuvirtide, also referred to as T-20
EAP	Expanded Access Program
EUP	Emergency Use Program (BI Trial 1182.58)
FAS	Full analysis set
FC	Fold-change
GSS	Genotypic sensitivity score
HAART	Highly active antiretroviral therapy
HFC	Hard filled capsule
HIV	Human immunodeficiency virus
IC_{50}	Concentration of drug required to produce 50% inhibition
IDV	Indinavir
ITT	Intent-to-treat (population)
IQR	Interquartile range; 25^{th} percentile and 75^{th} percentile around median
KM	Kaplan Meier probability
LOCF	Last observation carried forward
LPV	Lopinavir
mg	Milligram
mL	Milliliter
mm^3	Cubic millimeter
N	Number of patients
NCC	Non-completer considered censored
NCF	Non-completer considered failure
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OBR	Optimized background regimen
OLSS	Open-Label Safety Study
OR	Odds ratio
OT	On treatment
p	Probability
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction

PEY	Person exposure years
PI	Protease inhibitor
PK	Pharmacokinetics
PPS	Per protocol set
P&U	Pharmacia and Upjohn
RESIST-1	Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir [BI Trial 1182.12]
RESIST-2	Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir [BI Trial 1182.48]
RNA	Ribonucleic acid
RR	Relative risk
RTV	Ritonavir
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SEC	Soft elastic capsule
SEDDS	Self-emulsifying drug delivery system
SQV	Saquinavir
SQV/r	Saquinavir with ritonavir
SOC	System organ class
TPV	Tipranavir
TPV/r	Tipranavir co-administered with ritonavir
TR	Treatment response
µM	Micromole
VL	Viral load
WT	Wild type

SUMMARY

Highly Active Antiretroviral Therapy (HAART) has had a marked impact on the course of the HIV epidemic in the developed world. These potent antiretroviral combination therapies are able to effectively suppress viral replication and are associated with reconstitution of the immune system. However, non-adherence to HAART regimens and increased transmission of drug-resistant HIV-1 are common problems in the clinic, and this has led to the development of a large patient population with multi-drug resistant HIV-1 infection. Each of the major classes of antiretroviral agents (ARVs) is affected by resistance, including protease inhibitors (PI). As a result, novel therapeutic agents are needed to construct active regimens for PI-experienced patients to reduce viral replication and decrease HIV-related morbidity and mortality. Tipranavir (TPV) is a non-peptidic protease inhibitor active against the majority of protease inhibitor resistant HIV-1 seen in clinical practice. Both a soft gelatin capsule and a liquid formulation have been developed to meet the clinical needs of HIV-positive patients. The subject of this document is the capsule formulation only (NDA 21-814). Tipranavir helps to address a continued unmet clinical need for new drugs to treat patients with multidrug resistant HIV-1.

Patients in the tipranavir clinical development program demonstrated multi-drug resistance with varying degrees of cross-resistance to the currently available PIs. In this briefing document, we present 2- and 24-week data demonstrating the antiviral activity of tipranavir, co-administered with low-dose ritonavir (TPV/r), in PI-experienced patients with established PI-resistant viruses.

As of 30 September 2004, the cut-off date for the Safety Update, a total of 3,367 HIV-positive patients have been treated with TPV/r. In the clinical trial database, 1,870 of these patients have been treated with TPV/r representing 1,760 patient-years of exposure. Nearly half of the patients (47%) have been treated for =48 weeks with a maximum exposure of 5 years. 1,411 patients have been treated with the TPV/r 500/200 mg dose with 1,206 having received this to-be-marketed dose for at least 24 weeks.

The ongoing RESIST[1] trial program, which compares TPV/r to a ritonavir-boosted comparator PI (CPI/r) on an optimized background regimen (OBR), is one of the largest programs undertaken in a PI-experienced population. Comparator PIs in the RESIST trials include ritonavir-boosted lopinavir, indinavir, saquinavir, and amprenavir. The intrinsic activity of TPV/r is demonstrated by the = 1 $\log_{10}$ reduction observed at 2 weeks after the initiation of TPV/r therapy. After 24 weeks of treatment (interim analysis), TPV/r had superior antiviral activity compared to CPI/r as shown below:

Overview of Week 24 efficacy endpoints - combined RESIST trials

	TPV/r + OBR N=582	CPI/r + OBR N=577	p-value
Median baseline viral load	4.83	4.82	
Median baseline CD4+ count	155	158	
Treatment Response (confirmed $\geq$ 1 $\log_{10}$ VL decrease)	41%	19%	<0.0001
Median HIV VL change from baseline ($\log_{10}$ copies/mL)	-0.80	-0.25	<0.0001
HIV VL < 400 copies/mL	34%	15%	<0.0001
HIV VL < 50 copies/mL	24%	9%	<0.0001
Median increase in CD4+ cell count (cells/mm^3)	34	4	<0.0001

At 24 weeks, TPV/r had superior virological and immunological responses which were associated with a non-significant decrease in AIDS progression events in patients with PI-resistant HIV-1. The 24-week responses were of greater magnitude when TPV/r is combined with other active antiretroviral agents, for example enfuvirtide.

It has been shown that TPV must be co-administered with low-dose ritonavir to achieve adequate drug levels. Patients taking TPV/r generally achieve plasma concentrations that are many-fold above the protein-adjusted IC_{90} for the majority of PI-resistant HIV-1 strains in the clinic. Despite being an inducer of the cytochrome P450 isoenzyme 3A (CYP3A) when given alone, TPV when combined with 200 mg of ritonavir produces a net inhibition of

[1] RESIST: **R**andomized **E**valuation of **S**trategic **I**ntervention in multi-drug re**S**istant patients with **T**ipranavir; Two randomized, controlled trials with RESIST-1 conducted at North American and Australian sites and RESIST-2 conducted in European and Latin American sites.

CYP3A. The pharmacokinetic drug interactions for most non-antiretroviral concomitant medications are similar to other ritonavir-boosted PIs.

Drug levels for ritonavir-boosted lopinavir, saquinavir, and amprenavir were significantly reduced when combined with TPV/r, therefore these combinations are not recommended. Protease inhibitor levels for novel dual PI regimens containing TPV/r cannot be predicted without formal drug interaction studies possibly due to the mixed patterns of inhibition and induction of CYP pathways seen with these drug combinations.

While reductions in plasma concentrations of abacavir and zidovudine have been observed when they are combined with TPV/r, the clinical relevance of these changes has not been established and no dose adjustment can be recommended at this time.

We have undertaken an extensive evaluation of the resistance profile of TPV/r and have defined the genotypic and phenotypic correlates associated with treatment response. The best correlations of the antiviral activity of TPV/r with a genotypic score were obtained with (1) the key mutations in the HIV-1 protease at positions 33, 82, 84, and 90, and (2) a tipranavir score derived from correlation of mutations in HIV-1 protease to viral phenotype and viral load responses seen in the Phase II and III programs. Based on these analyses, it takes 3 key mutations and > 4 TPV-score mutations to produce decreased TPV susceptibility ($\geq$ 3-fold wild-type) *in vitro* or decreased antiviral responses in the clinic. High level resistance ($\geq$ 10-fold wild type) usually requires all 4 key mutations or > 7 TPV-score mutations which are uncommon in clinical HIV-1 isolates from treatment-experienced patients. These *in vitro* and clinical data confirm that there is a high genetic barrier to resistance with TPV.

Many of the mutations which are associated with decreased susceptibility to TPV have not been associated with drug resistance to currently available PIs. While one or more mutations at protease codons 33, 82, 84, 90 can produce high level resistance to currently available PIs, it takes at least three of these mutations produce reduced susceptibility to TPV/r. The predominant emerging mutations with virologic failure in PI-experienced patients receiving

TPV/r are 33F/I/V, 82T/L, and 84V; the drug resistance pattern which will result from treatment of drug naïve patients is not yet established.

The types and rates of adverse events (AEs) and serious AEs reported for TPV/r in the RESIST trials are similar to CPI/r and are consistent with AEs associated with the use of other ritonavir-boosted PIs except for increased rates of Grade 3/4 elevations in ALT/AST, cholesterol and triglycerides which were more common with TPV/r than with CPI/r. The hepatic events were generally asymptomatic and most patients were successfully continued on treatment. These laboratory abnormalities can be managed with routine monitoring except in patients with chronic Hepatitis B or C co-infection or elevated baseline LFTs where increased monitoring of LFTs is recommended.

There was a nonsignificant difference in fatalities between the TPV/r and CPI/r arms of the RESIST trials at 24 weeks (p=0.64). The types and rate of fatalities in the TPV/r development program are consistent with what has been described for patients with advanced HIV disease. There have been a limited number of cases of clinical hepatitis or death due to hepatic failure in the TPV development program, primarily in patients with advanced HIV disease taking multiple concomitant medications. A causal relationship to TPV/r could not be established.

In summary, tipranavir, co-administered with low-dose ritonavir, is a novel HIV protease inhibitor which retains significant antiviral activity in the face of multiple PI mutations. Regimens containing TPV/r in the RESIST population of patients with highly PI-resistant viruses had superior virologic and immunologic activity at 24 weeks compared with the CPI/r-based regimens. Genotypic resistance testing can assist in the selection of drugs to combine with TPV/r and in determination of which patients are most likely to benefit from a TPV/r-based regimen. Similar to other ritonavir-boosted PIs, pharmacokinetic interactions between TPV/r and other drugs metabolized by CYP3A should be expected. The net effect of TPV/r is CYP3A inhibition. Finally, the safety profile of TPV/r is similar to other ritonavir-boosted PIs in a PI-experienced population, except for increased rates of ALT/AST,

cholesterol and triglyceride elevations which were seen for the TPV/r arms in the RESIST trials.

The use of TPV/r-based regimens in treatment-experienced patients with PI-resistant HIV-1 helps to meet a large unmet clinical need. The balance of the benefits and risks of drug regimens containing tipranavir co-administered with low-dose ritonavir supports the indication for use in PI treatment-experienced patients with HIV-1 infection.

1. INTRODUCTION

With the introduction of the new class of HIV protease inhibitors (PI) in the mid-1990s, the Highly Active Antiretroviral Therapy (HAART) era began. This was associated with dramatic decreases in HIV-related morbidity and mortality and subsequent prolongation of the course of HIV infection.[2] However, the first PIs were associated with poor bioavailability, complex dosing demands, and/or significant GI intolerability. These factors led to development of PI resistance, treatment failure, and an understanding of the importance of treatment adherence.

The second wave of protease inhibitor development focused on making agents that were easier to tolerate, had an improved and more forgiving pharmacokinetic profile, and could overcome established PI drug resistance. These newer agents to varying degrees have fulfilled this need. However, concurrent resistance to reverse transcriptase inhibitors developed during this period to the point where many antiretroviral-experienced patients have evolved significant three-class HIV drug resistance. This population of patients harbouring multi-drug resistant HIV represents a growing difficult to treat group.[3]

Tipranavir is a novel non-peptidic HIV protease inhibitor that was developed with the specific goal of being able to overcome broad PI cross-resistance. It belongs to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. The chemical name of tipranavir is 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl). Its molecular formula is $C_{31}H_{33}F_3N_2O_5S$ with a corresponding molecular weight of 602.7 (Figure 1: 1).

[2] Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD, HIV Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338(13):853-860.

[3] Richman DD, Morton SC, Wrin T, Hellmann N, Berry S, Shapiro MF, Bozzette SA. The prevalence of antiretroviral drug resistance in the United States. AIDS (Phila) 2004;18(10):1393-1401.

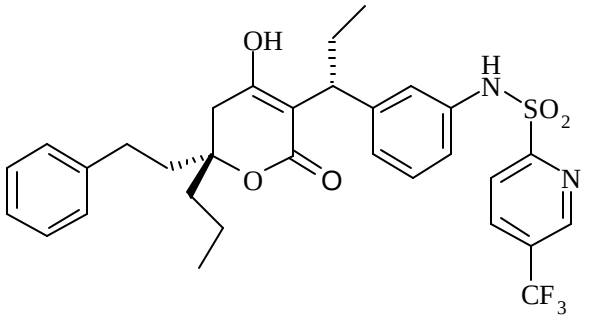

Figure 1: 1 Structural formula of tipranavir

Early *in vitro* studies showed that viral isolates cross-resistant to most of the commercially available PIs retained susceptibility to tipranavir.[4] The IC_{90} for multi-drug resistant clinical HIV isolates ranged from 0.31-0.86 µM, and most clinical HIV isolates had a serum-adjusted IC_{90} of = 2 µM. This is in contrast to an IC_{90} of 0.18 µM for WT HIV-1 in PBMC.

Although the number of new AIDS diagnoses and deaths has fallen since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990's, many HIV-positive patients have not had adequate responses to the regimens, cannot tolerate the toxic effects, or have difficulty complying with treatment regimens that involve large numbers of pills. Up to 50% of patients fail their initial regimens, and there is an increasing population of patients infected with drug-resistant HIV-1 strains who need new agents with improved resistance profiles compared to those of existing ARVs.[5] Thus, the initial tipranavir clinical development program focused on the study of PI-experienced patients in need of new therapy.

Phase II and III clinical trials in patients with a PI-resistant HIV-1 have confirmed that tipranavir has potent antiviral activity. Thus, tipranavir represents a significant advance in the treatment armamentarium for clinicians treating drug-resistant HIV-1 infection.

[4] Larder BA, Hertogs K, Bloor S, Eyne C van den, DeCian W, Yenyun W, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS (Phila) 2000;14(13):1943-48.

[5] Bartlett JA. Addressing the challenges of Adherence. J Acq Immune Defic Syndr 2002; 29(Suppl 1):S2-S10.

2. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

General/Safety pharmacology studies were performed with TPV to assess effects on the cardiovascular, central nervous, pulmonary, renal, and gastrointestinal (GI) systems. These studies indicated that the drug was well-tolerated, with some effects noted in the renal and GI systems. Studies to investigate effects on the cardiovascular system showed an inhibitory effect *in vitro* on the HERG-associated potassium channel (IC_{50} = 2.9 µM; U02-1175), but no changes were noted in the guinea pig papillary muscle assay at similar concentrations, nor were any effects noted on QTc prolongation in the ECGs of conscious dogs following single administration of up to 160 mg/kg. Overall, these results suggest that TPV has little potential to prolong the QTc interval. No evidence of cardiovascular effects was noted in toxicity studies of up to 26 weeks in dogs with TPV/r or up to 39 weeks in dogs with TPV, and no prolongation of the QTc interval has been observed in multiple clinical studies.

Pharmacokinetic studies in humans have demonstrated the requirement for RTV co-administration with TPV treatment in order to achieve and maintain required plasma levels of TPV for anti-viral activity. In humans, TPV is primarily metabolized by CYP3A and is a substrate for Pgp. The boosting effect of RTV on TPV plasma levels noted in humans is also observed in animals. However, the boosting effect seen in nonclinical species does not fully reflect that observed in humans, as there can be distinct species differences in CYP450 and Pgp selectivities. RTV co-administration resulted in an increase in TPV systemic exposure in all nonclinical species: mice (12- to 22-fold), rats (6-to 7-fold), dogs (3-to 13-fold), and monkeys (2-fold). In rats and dogs, co-administration of RTV resulted in a 4- to 5-fold decrease in clearance of TPV, consistent with inhibition of drug-metabolizing enzymes by RTV. In toxicity studies in animals at higher dose levels the boosting effect of RTV is lower in magnitude, perhaps due to a saturation of the boosting mechanism. In humans, in contrast, the boosting effect is more pronounced with co-administration of RTV (200 mg) with TPV (500 mg) at the proposed human dose level resulting in a 45-fold increase in C_{min}, a 4-fold increase in C_{max}, and an 11-fold increase in overall systemic exposure (AUC^{ss}_{0-t}). RTV is clearly increasing plasma concentrations of TPV by inhibiting

metabolism, as the levels of metabolites in rats and humans are negligible following RTV co-administration.

It has been noted in toxicity studies that TPV exposure in animals, even at the highest dose levels tested, is approximately equivalent to or only slightly above that achieved at the human dose level of 500 mg/200 mg TPV/r BID. Toxicity testing on TPV commenced with TPV administered as a singular entity. Once it was recognized that TPV was to be co-administered with RTV in humans to achieve therapeutic plasma levels, co-administration studies in animals were initiated to investigate the toxicity of the two compounds given concurrently and to increase plasma levels of TPV in animals. Co-administration of TPV with RTV does increase plasma levels of TPV in animals, notably at lower dose levels. However, this effect diminishes at higher dose levels, and does not reach the magnitude of the boosting effect that is achieved in humans. Rats in a 26-week TPV study administered 400 mg/kg/day TPV were exposed to maximum plasma concentrations of 90/209 µM in males/females and plasma exposure levels of 910/2320 µM·h (M/F). No total exposure was calculated in the 26-week TPV/r study, but plasma levels measured 8 hours after TPV administration ranged from 180 to 334 µM at the highest dose level tested of 1200/320 mg/kg/day TPV/r. Highest exposure in dogs was achieved in a 39-week study at a dose level of 320 mg/kg/day TPV where C_{max} and AUC values of 114 µM and 1155 µM·h (sexes combined), respectively, were achieved. These are in contrast to plasma levels reached at the human therapeutic dose level of 500/200 mg BID TPV/r, where a C_{max} of 103 µM and an AUC_{0-24} of 1542 µM·h were achieved.

Toxicities seen in repeat-dose studies in rats and dogs are not considered to preclude chronic administration of TPV to the intended patient population, even in view of their observance at plasma levels equivalent to or below human exposure. The reasons for this are primarily their reversibility, manageability, species specificity, and correlation with species-specific hepatic enzyme-inducing effects of TPV in the rodent. Primary target organs identified in rats and dogs included the liver and GI tract. Co-administration of TPV and RTV in rats and dogs revealed only signs of toxicity or target organ effects evident when each compound was

administered alone. More importantly, co-administration did not exacerbate the toxicity of either drug.

Changes in the GI tract in nonclinical studies have included emesis, soft stools, diarrhea, and/or excessive salivation post-dosing. Excessive salivation after TPV administration was attributed to the bitter taste of TPV, which animals were exposed to during gavage administration.

In rats and dogs, TPV plasma levels declined with repeated dosing relative to Day 1, indicative of enzyme induction. This was supported by increases in CYP450 isoforms CYP3A and CYP2B in both species, increases in smooth endoplasmic reticulum, increased liver weights, and hepatocellular hypertrophy. These increases in enzyme levels in animals are considered an adaptive response to exposure to a xenobiotic and not evidence of toxicity. Hepatic effects of TPV were dose-related, and reversible with discontinuation of treatment, or transient and of no clinical relevance.

Hepatic microsomal enzyme induction has resulted in secondary changes during toxicity studies in rodents. These include increased clearance of thyroid hormones with resultant increased thyroid weight and thyroid follicular hypertrophy/hyperplasia, slight increases in plasma proteins, and increases in coagulation parameters. All of these effects were found to be reversible with termination of treatment. Increases in plasma proteins are considered to reflect their increased synthesis in the liver due to enzyme induction. Thyroid effects in rats due to hepatic microsomal enzyme induction are not considered relevant to humans. Reversible increases in coagulation indices (PT and APTT), observed only in rodents administered TPV or TPV/r, were judged secondary to hepatic enzyme induction rather than a direct effect of the drug. Some increases in PT and fibrinogen were observed in mice, but not consistently, and no increases in coagulation parameters have been observed in beagle dogs. In response to these findings in rodents, monitoring of PT was performed in early clinical trials, but no increases in PT have been observed in humans.

Other hepatic changes in rodents included degeneration, vacuolation, necrosis, mineral deposition, and karyomegaly. Karyomegaly was noted at a low incidence in rats treated with

TPV/r over 26-weeks. In these animals, the incidence of karyomegaly was not related to TPV dose. A much higher incidence was noted in RTV-treated animals, and has been previously observed in rat studies on RTV performed by Abbott Laboratories. This finding is therefore an effect of RTV administration and not considered to be of concern for humans administered TPV/r, as in the combination therapy, RTV plasma levels are low. The other hepatic findings, along with elevations of ALT and AST, appeared predominantly in the mouse and were possibly related to tissue anoxia from circulatory derangements caused by hepatocellular hypertrophy. These changes were not observed in rats and dogs and may reflect a species-specific effect. Based on the disparity between species, the implications for humans are not clear. As liver function may be readily monitored, the appearance of increased ALT and AST in one species should not preclude the use of TPV in humans.

In beagle dogs, mild elevations in alkaline phosphatase in TPV or TPV/r treated groups may be related to enzyme induction, but may also be caused by an effect on the biliary system. The alkaline phosphatase increases in dogs were shown in the 26-week SEDDS safety study to be due to the hepatic isoform. Based on a lack of other findings indicating cholestasis, this change raises no concern for humans.

Testicular degeneration and/or atrophy were observed in long-term studies in rats and dogs at high dose levels. Re-evaluation of these data by an expert panel indicated that the findings in the beagle dog were within normal limits of variation. The testicular changes in rats, seen in only three animals at a high dose level, were morphologically and pathogenically unrelated and therefore not related to drug treatment. Consequently, testes are not considered to be a target organ of toxicity.

Genotoxicity studies with TPV have shown no potential for mutagenicity or clastogenicity in standard assays both *in vitro* and *in vivo.* Carcinogenicity studies are ongoing; therefore no definitive statements may be made regarding the potential for TPV to induce tumors. A lack of genotoxicity suggests that TPV would not induce tumors by a mutagenic or clastogenic mechanism. The potential effects of TPV on hepatic enzyme induction with consequent

hepatic and/or thyroid tumors in rodent carcinogenicity has already been discussed and at this time are not considered to be a risk to humans taking TPV chronically.

Reproductive toxicity of TPV was assessed in standard studies in rats and rabbits. At a maximum plasma concentration in rats of 258 µM (2-fold human C_{max}), no effects on spermatogenesis, estrous cycles, copulation, fertility, implantation, or early embryonic development were observed. In studies investigating exposure at the time of organogenesis, the no observed adverse effect levels (NOAEL) in rats and rabbits corresponding to exposures (AUC_{0-24}) of 340 µM·h and 66 µM·h were determined. Maternal toxicity, embryotoxicity, and/or developmental toxicity were observed at greater exposure levels. Human exposure levels, at the recommended dose level, are above these NOAEL exposure levels in animals. Consequently, TPV should be given during pregnancy only if the benefit to the mother and the fetus outweighs the risk to the fetus. The definitive study in rabbits resulted in gross malformations at a maternally toxic dose level. These findings were judged to be due to a litter effect and not a drug effect, as marked maternal toxicity was observed at this dose level, and in a previous study at the same and higher dose levels there were no similar findings. Consequently, TPV was judged not to be a selective developmental toxicant and consequently is not teratogenic. TPV retarded pup growth in rats when administered during gestation and into the postpartum period. Distribution studies in rats administered ^{14}C-TPV have demonstrated that radioactivity is excreted into the milk of rats. Consequently, women should be cautioned to avoid breastfeeding while taking TPV.

The immunotoxic potential of TPV was assessed in a standard assay testing the functioning of the humoral component of the immune system, the T-dependent antigen response to sheep red blood cells (sRBC). Treatment with TPV co-administered with RTV or TPV alone did not adversely affect the functional ability of the humoral component of the immune system in female CD-1 mice, as evaluated in the IgM antibody-forming cell response to the T-dependent antigen, sRBC.

Toxicity of impurities in TPV drug substance and degradation products of TPV in drug product have been evaluated in general toxicity and genotoxicity studies, as recommended by

ICH guidances Q3A(R) and Q3B(R). Impurities in TPV drug substance and drug product have been qualified at levels equal to or greater than the proposed acceptance criteria.

TPV is administered in self-emulsifying drug delivery system (SEDDS) formulations, with both the bulk fill solution and the oral solution each containing a special mixture of excipients. A 26-week safety study was designed in dogs to evaluate the toxicity of the bulk fill solution, with special attention given to the dose levels of one excipient, Cremophor EL (CrEL). CrEL is also present in the co-administered RTV capsule formulation, as it is an excipient included in Norvir® capsules at 60 mg/mL (communication from Abbott Laboratories). Assessment of the bulk fill solution formulation in rats and dogs in toxicity studies of 13 and 26 weeks, respectively, confirm its safety at the human dose level of 500/200 mg BID TPV/r.

Literature assessment of components of the TPV oral solution indicate no toxicity concerns when used as instructed. Levels of propylene glycol (PG) in the TPV oral solution co-administered with RTV oral solution are considered safe when administered to adults and children greater than 2 years of age. Due to the low levels of the PG-metabolizing enzyme alcohol dehydrogenase expressed by young livers, caution must be exercised when administering this combination to infants or children less than 2 years of age when administering TPV oral and RTV oral solutions along with other prescription and/or non-prescription medications containing propylene glycol and/or ethanol. Due to the presence of Vitamin E TPGS in the TPV oral solution, Vitamin E supplementation should not be taken along with the oral solution since the Vitamin E content of this product exceeds the Recommended Daily Intake. Due to anticoagulant effects of high dose levels of Vitamin E, the possibility exists that this excipient could exacerbate coagulation defects in individuals who are deficient in Vitamin K or are receiving anticoagulant therapy and suggests that caution is warranted.

The nonclinical evaluation of TPV/r has confirmed the safety, efficacy, and bioavailability of TPV for its use in man for the treatment of HIV.

3. MICROBIOLOGY

In the course of the development of tipranavir, numerous *in vitro* and *in vivo* studies have been conducted to examine its antiviral activity. Particular focus has been on viral isolates containing mutations (and the patients who harbor these) that confer protease inhibitor resistance. These studies have shown that susceptibility to tipranavir is often maintained despite the development of broad cross-resistance to currently available PIs. In addition, *in vitro* passage experiments have shown that selection of mutations that confer resistance is slow; ongoing studies in antiretroviral naïve patients should help define whether or not there is a signature mutation that confers resistance to tipranavir.

3.1 MECHANISM OF ACTION

Tipranavir is a non-peptidic protease inhibitor (NPPI) of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. In enzymatic assays, TPV demonstrates potent inhibition of the cleavage of a peptidic substrate by the HIV-1 protease with an inhibition constant (Ki) of 8.9 ± 6.8 pM. Using the same assay, TPV also inhibits the activities of HIV-2 protease (Ki < 1 µM) and of mutant HIV-1 proteases carrying the mutations V82A (Ki = 3 nM) or V82F/I84V (Ki = 0.25 µM). Selectivity for the HIV protease was demonstrated by high Ki values against the human aspartyl proteases pepsin (Ki = 2 µM), cathepsin D (Ki = 15 µM), and cathepsin E (Ki = 9 µM). Therefore, TPV is both a potent and a selective inhibitor of the HIV protease.

3.2 ANTIVIRAL ACTIVITY *IN VITRO*

Tipranavir inhibits the replication of laboratory strains and clinical isolates in acute models of T-cell infection, with 50% effective concentrations (EC_{50}) ranging from 0.03 to 0.07 µM (18-42 ng/mL). Tipranavir is also effective at inhibiting the replication of M-tropic strains of HIV ($EC_{90\ ADA}$ = 0.75 uM, 452 ng/mL and $EC_{90\ DGV}$ = 0.3 µM, 180 ng/mL) and at inhibiting the extracellular accumulation of the p24 capsid protein from H-9 cells chronically infected with HIV-1 IIIB (EC_{50} of 0.39 µM, 235 ng/mL). Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present. When used in combination with other antiretrovirals, tipranavir shows

synergy to additivity with the NRTI zidovudine, the NNRTI delavirdine and the PI ritonavir. Activities ranging from synergy to slight antagonism were reported when tipranavir was used in combination with other currently available ARV drugs. No evidence of strong antagonism was seen in any of the drugs combined with TPV, and these data have been recently confirmed by additional analyses of mixed drug cell cultures for all currently available PIs.

A large subset of isolates from PI-experienced patients entering the pivotal Phase III RESIST trials were evaluated for the presence of phenotypic susceptibility to commercially available PIs and TPV. Analyses using these samples are presented in Section 7 on TPV resistance.

4. OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

4.1 EARLY DEVELOPMENT

Tipranavir was discovered by Pharmacia and Upjohn (P&U) and licensed for development by Boehringer Ingelheim (BI) in 2000. The initial development of tipranavir conducted by P&U involved optimizing the soft gelatin capsule SEDDS formulation and characterizing the ritonavir-boosting effect, so as to address issues of bioavailability and plasma exposure typical for PIs.

At BI, the TPV clinical development program was initially focused on PI-experienced patients, as this group has the greatest unmet medical needs. To provide additional data on the possible use of TPV/r in other populations, studies in pediatric and treatment naïve adult patients are ongoing.

Overall, through 30 September 2004[6], 3,367 HIV-positive patients and 769 HIV-negative volunteer subjects have been exposed to TPV/r.

Early open-label, dose ranging studies (BI 1182.3, 1182.2 and 1182.4) demonstrated that tipranavir reduces viral load in HIV-positive patients with variable levels of treatment experience (naïve, single- and multiple-PI-experienced). However, these trials failed to determine the optimal TPV/r dose, thus a Phase II dose-defining study was designed (BI 1182.52).

4.2 DOSE-FINDING TRIAL

BI 1182.52 was the definitive dose-finding study that evaluated three TPV/r doses (TPV/r 500/100, 500/200, and 750/200 given twice daily). The doses chosen for testing in this study were based on data from the Phase I and II trial program and were considered the three best doses for possible further study in the Phase III program.

[6] This date represents the cut-off for the Safety Update, for which comprehensive data have been collected and analyzed.

The study was conducted in patients very similar to those studied in the Phase III RESIST trials. All patients were triple ARV class, two PI-based regimen-experienced and had baseline viral isolates with at least one primary protease mutation (30N, 46I/L, 48V, 50V, 82A/L/F/T, 84V and 90M), with not more than 2 mutations among 82L/T, 84V or 90M. The presence of a primary protease mutation was required to support adherence to the previous treatment regimen. The specific primary protease mutations selected were drawn from a mutation list that had been used in a number of prior clinical trials including the Genotypic Antiretroviral Resistance Testing (GART) and Multiple Drug Resistance (MDR-HIV) studies.[7] The requirement to have no more than 2 mutations among 82L/T, 84V and 90M was based on *in vitro* TPV resistance selection studies, HIV-1 isolates from early Phase II TPV/r trials and a large panel of highly PI-resistant clinical isolates.[8]

BI 1182.52 was a double-blind study with three TPV/r doses: TPV/r 500/100 mg, TPV/r 500/200 mg and TPV/r 750/200 mg, all given twice daily with a genotypically optimized background regimen (OBR) that was individually chosen by investigators. The first 2 weeks of the study were the functional monotherapy phase, in which patients changed the PI they were taking at entry to one of the three TPV/r doses, but maintained the same OBR. The antiviral effect observed in the first 2 weeks was likely due to TPV/r, thereby allowing critical analyses of the activity of the three doses. The study also tested the PK and safety of the three doses.

Based on a composite of optimal safety, PK and antiviral activity against PI-resistant viruses, the TPV/r 500/200 mg dose group was selected for study in Phase III trials. In addition, BI 1182.52 confirmed that patients with virus containing three or more mutations at HIV protease positions 33, 82, 84 or 90 were unlikely to obtain a durable response to TPV/r or the

[7] Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA, Mannheimer SB, Thompson MA, Abrams DI, Brizz BJ, Ioannidis JPA, Merigan TC, CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. AIDS (Phila) 2000; 14(9):F83-F93.

[8] Larder BA, Hertogs K, Bloor S, Eyne C van den, DeCian W, Yenyun W, Freimuth WW, Tarpley G. Tipranavir inhibits broadly PI-resistant HIV-1 clinical samples. AIDS (Phila) 2000;14(13):1943-1948

alternative boosted PIs available. These data were discussed with the FDA at an End-of-Phase II meeting prior to the initiation of the Phase III trial program.

4.3 PHASE III PIVOTAL TRIAL PROGRAM

4.3.1 Trial design

The Phase III Trials (BI 1182.12 [RESIST-1] and BI 1182.48 [RESIST-2]) are ongoing, large, randomized, open-label, multicenter trials designed to evaluate the efficacy and safety of TPV/r in comparison to ritonavir-boosted comparator PIs (CPI/r). Similar to the Phase IIB dose-finding study, patients in the RESIST trials were triple ARV class, two PI-based regimen experienced with HIV RNA ≥1,000 copies/mL at baseline. The study was originally designed for 48 weeks, but has now been extended for up to five years of follow up.

Genotyping was conducted at screening for the study and patients had to demonstrate at least one primary protease mutation (30N, 46I/L, 48V, 50V, 82A/L/F/T, 84V or 90M), with not more than 2 mutations at codons 33, 82, 84 or 90. Patients screening for the RESIST studies with 3 or more of these key mutations were eligible for the companion dual-booted PI study, BI 1182.51.

Both the general design of the tipranavir development program and the protocols in the Phase III program (BI 1182.12, 1182.48, and 1182.51) were reviewed with the FDA and important design elements were agreed upon. The RESIST studies also received a Special Protocol Assessment prior to initiation.

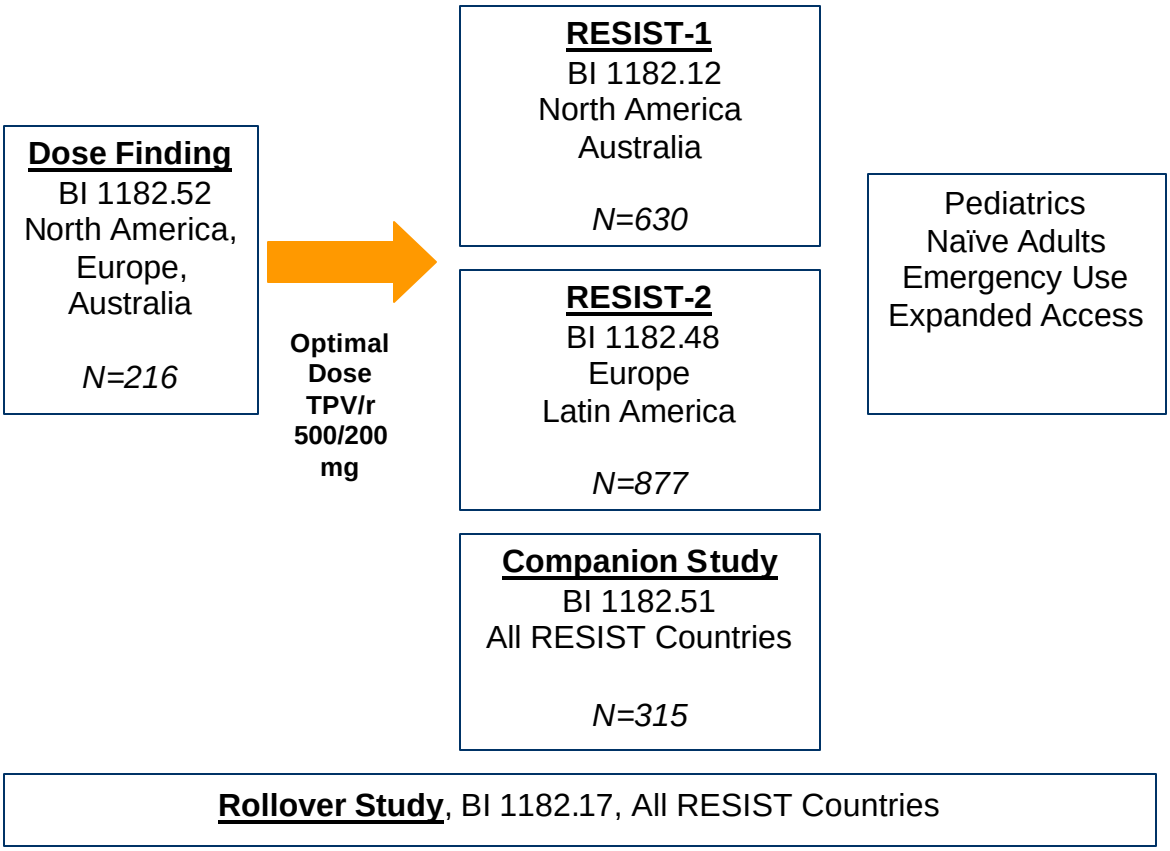

Figure 4.3.1: 1 General design of the tipranavir Phase II—III development program

The genotypic inclusion requirement in both BI 1182.52 and in the RESIST trials was based on the need to test a documented PI-experienced patient population for proof of the efficacy of TPV/r in these treatment-experienced patients. Patients were required to have at least one primary mutation to demonstrate that they had taken and failed a PI-containing regimen with sufficient adherence to select for a mutation. Importantly, any one of the mutations on the list would have been insufficient to develop resistance to all of the 4 comparator PIs used in RESIST.

In earlier *in vitro* and clinical data (BI 1182.52), the presence of multiple mutations at protease codons 33[9], 82, 84, or 90 had been associated with reduced VL responses to TPV/r

[9] The 33 mutation was not included in the eligibility criteria for BI 1182.52. It was added to the list to determine eligibility for the RESIST studies after being found to be heavily selected both *in vitro* and in clinical HIV-1 isolates from patients failing TPV/r in other Phase II clinical studies.

and shown to produce high level resistance to currently available PIs (specifically LPV, IDV, SQV, and APV). By allowing a maximum of two mutations at positions 33, 82, 84, or 90, patients who had clear evidence of PI resistance but still had a sufficient chance to respond to either study arm were selected for the RESIST trials.

Since it was anticipated that patients with three or more mutations at codons 33, 82, 84, or 90 would be unlikely to achieve a durable 1 $\log_{10}$ response with either TPV/r or any of the CPI/r treatments, a dual boosted PI companion study (BI 1182.51) was designed. The objective of this study was to evaluate the PK, safety and preliminary efficacy of a dual-boosted PI regimen containing TPV in patients with 3 or 4 mutations at codons 33, 82, 84, or 90.

To ensure that both arms of the RESIST trials had a balanced number of patients with similar characteristics, the OBR had to be pre-selected prior to randomization. Specifically, using baseline genotyping results and patient treatment history, investigators had to pre-select the PI their patients would receive if they were randomized to the CPI/r arm. In addition, investigators had to pre-select the OBR and decide whether they would choose enfuvirtide as part of the OBR.

Following the selection of the preferred PI and the OBR, patients in the RESIST trials were then randomized 1:1 to either TPV/r or to the comparator arm (CPI/r) Patients in the CPI/r would receive the PI that had been pre-selected (lopinavir [LPV], indinavir [IDV], saquinavir [SQV] or amprenavir [APV]). Importantly, the randomizations were stratified according to both the pre-selected PI and on whether or not they intended to use enfuvirtide.

It was intended that all patients receive the best possible treatment available. If the patient's treatment history and genotype indicated that the PI that was part of the screening regimen was the best option for the patient (an 'ongoing PI'), this could be the pre-selected PI chosen by the investigator for the RESIST trial.

In general, the designs of the two RESIST trials are similar except for the timing of the interim trial endpoints, the statistical hypotheses, and the resistance testing methods used.

The primary endpoint for both trials is treatment response after 48 weeks. As defined in the protocol, the analysis for accelerated approval submission was to be performed at Week 24.

In the two RESIST studies, the key efficacy endpoint for the 24-week analysis was 'treatment response,' a composite endpoint of the proportion of patients with two consecutive viral load measurements ≥1 $\log_{10}$ below baseline without evidence of: confirmed virological failure to < 1 $\log_{10}$ reduction, introduction of a new ARV (for reasons other than toxicity or intolerance to a background drug), permanent discontinuation of study drug, loss to follow-up, or death.

It is the 24-week interim analyses of the RESIST studies that form the foundation of the data provided in the TPV NDA package submitted for accelerated approval.

4.3.2 Trial design issues

4.3.2.1 Choice of comparator PI

The comparator arm treatments in the RESIST studies were selected as an "optimized standard of care." Following the 1:1 randomization, patients could be treated with any of four RTV-boosted comparator PIs along with an OBR. The choice of both the comparator PI and the OBR was made prior to randomization by each investigator and was based on individual treatment history and the screening genotype data provided. As noted above, the objective of the pre-randomization selection of all medications was to ensure balance between the two treatment arms, to provide the optimal treatment response for patients who were randomized to the comparator arm, and to eliminate a potential source of bias.

If needed, investigators were offered the use of an external panel of resistance experts to assist with drug selection (as needed) and to optimize the PI treatments chosen for use in the CPI/r arm. The use of enfuvirtide was allowed if it was pre-declared prior to randomization and could be made available from the start of treatment. The randomization was stratified on both the choice of comparator PI and the use of enfuvirtide.

The use of a single RTV-boosted PI in the comparator arm (e.g., LPV/r) would have simplified the study analyses and allowed for blinding, and BI carefully considered this approach. BI concluded that the limitations of this approach outweighed the benefits. First, the trial would have been very slow to enroll; if there had been just one PI option in the CPI/r arm, patients and investigators might have considered the trial less attractive since that CPI/r option may not have been optimal for their treatment. Second, use of a single RTV-boosted PI in the CPI/r arm would have limited the amount of comparative data in this treatment-experienced population. Third, patients in the comparator arm would not necessarily be taking an "optimized standard of care" regimen, and a large number of comparator arm drop-outs might have resulted that could have invalidated the study efficacy endpoints. Finally, providing the best possible individualized option for each patient who randomized to the comparator arm appeared to be the most ethical approach for such patients since this optimized the opportunity for a treatment response in the CPI/r arm.

4.3.2.2 Open-label study design

BI recognizes the advantages of conducting pivotal registrational trials in a randomized, double-blind study design. However, the open-label design of the two RESIST trials allowed the use of the best possible RTV-boosted PI for patients randomized to the CPI/r arm. Using blinded drug supplies in the study would have required patients to take more capsules and this might have reduced patient adherence in both treatment arms; this would have also required a complex, time-consuming set of blinded drug supply agreements between five different pharmaceutical companies. The open-label nature of the RESIST studies was discussed with the FDA and concurrence was achieved on these important design elements.

To help overcome potential biases in this open-label study design, BI took multiple precautions. First, an objectively defined composite primary endpoint—one log viral load reduction from baseline—was chosen which would be unlikely to be subject to bias. Second, the conservative intent-to-treat, non-completer considered failure approach has been used for

the primary analysis, and multiple sensitivity analyses have been performed[10]. Third, investigators were required to pre-select both the CPI/r and OBR to be used. Finally, BI statistical, data management, and clinical teams were internally blinded to individual patient treatment assignment during the conduct of the study until after database lock. In spite of these precautions, BI was aware that the open-label study design might have a higher rate of discontinuations in the comparator arm since patients were knowingly not receiving TPV/r, a potentially preferred treatment option.

It is important to note that patients in the comparator arm could leave the study after Week 8 if they had confirmed virologic failure in order to receive TPV treatment outside of the RESIST program (in the BI 1182.17 long-term safety follow-up study). To reduce the number of patients who might not strictly adhere to the comparator arm treatments, all RESIST investigators were required to carefully document virologic failure and to provide confirmed comparator PI plasma concentrations prior to patients being able to receive TPV in BI 1182.17. Due to the subjective nature of adverse event reporting, patients leaving the comparator arm of RESIST for safety reasons were not considered for participation in BI 1182.17.

4.3.2.3 Resistance status of study cohort

The RESIST study population was chosen as a representative sample of patients with PI treatment-experience who demonstrated PI resistance.

Prior to patient randomization in the two RESIST studies, the study protocol was amended (Amendment 2) to allow investigators to pre-select a comparator PI that was interpreted as "resistant" on the baseline genotype report.

This important protocol amendment was necessary because initial genotype reports indicated that 57.4-73.8% of patients had resistance to the selected PI, making it impossible to enroll eligible patients and complete the trial within a reasonable time period. Patients with pan-

[10] The results of the sensitivity analyses performed are shown in Section 6.3.3. These analyses demonstrate that the trial design issues did not affect the primary endpoint efficacy analyses.

resistance to available PIs and very limited treatment options would at least have a 50% chance of receiving TPV/r. Additional considerations included the knowledge that the genotype report gives an interpretation of resistance primarily based on unboosted PIs, while RTV-boosted PIs were exclusively used in the comparator PI arm. BI encouraged investigators to review the actual mutations listed on the resistance report (in addition to the interpretation) and to make use of the expert resistance consultant panel[11]. Finally, BI recognized the importance of providing TPV/r to patients in the RESIST studies if they had virologic failure on the CPI/r arm, and this was made available through BI 1182.17, the long term rollover trial.

4.3.2.4 RESIST study amendments and relevant protocol deviations

There were six RESIST protocol amendments by the time of the 24-week interim analysis. These amendments did not fundamentally change the study objectives, nor did their implementation have a clinically relevant impact on patients participating in the study (with the exception of Amendment 2). The primary goals of each amendment are described in the following paragraph.

Amendment 1 was implemented prior to the start of patient treatment to allow the use of tenofovir in Canada, where the drug previously had not been commercially available. As noted above, *Amendment 2* (as discussed above) was implemented prior to the start of patient treatment to allow the entry of patients who had a baseline genotypic interpretation indicating 'resistance' to all of the available PIs[12],[13]. *Amendment 3* was implemented in the first several

[11] The panel had two main objectives; to ensure that the most susceptible CPI on the resistance report was pre-selected by investigators, and to assist investigators in their individual patient drug selections. It was mandatory for investigators to consult the panel if they wished to deviate from the "best choice" on the genotype report provided. Investigators could also seek an optional consult to assist in individual patient drug selection; overall, the resistance expert panel was consulted by investigators in approximately 34% of patient cases.

[12] Amendment #2 was implemented prior to any patient randomizations in response to numerous investigator requests. Without this amendment, many of the patients screened for the studies would not have been eligible and study completion would have been very slow.

[13] Due to Amendment #2, the initially planned non-inferiority comparison of TPV/r and CPI/r in the statistical analysis plan with sequential testing for superiority was deemed inappropriate and demonstration of TPV/r superiority was considered essential to establish the efficacy of TPV/r.

weeks of the study to provide protocol clarifications where the language might have been subject to misinterpretation, and to provide guidelines for the management of vomiting. *Amendment 4* was implemented in the first three months of the study to create a separate pharmacokinetic sub-study of women. *Amendment 5* was implemented in the eighth month of the study to extend the study to 96 weeks from the originally planned 48 weeks. *Amendment 6* was implemented after the data cut-off for the 24-week analysis to correct a DAIDS adverse event severity grading scale that had been erroneously included in the protocol.

The relevant protocol deviations were broadly characterized in the trial protocols and specified in more detail in the trial statistical analysis plans. Final decisions about relevant protocol violations were made independently by the trial teams in the blinded report planning meetings held for each study, and these take place prior to internal unblinding of the data base. It is important to point out that each trial team was permitted to make their own decisions about relevant protocol deviations and reconciliations between the two RESIST study teams was not required. During the review process by the international TPV project team, relevant protocol deviations were re-assessed using the same fundamental criteria as used by each individual trial. As a result, a modified per-protocol set was derived that is slightly smaller than the per-protocol set report analyzed at 24 weeks in the individual RESIST clinical trial reports. This modified per-protocol set reduces the TPV/r group by six patients and the CPI/r group by 14 patients, leaving no substantive impact on the conclusion of superiority for the TPV/r arm.

4.3.2.5 Non-inferiority testing

For the pre-planned analyses at 24 weeks, both RESIST clinical trial protocols had planned to use a test of non-inferiority of TPV/r to CPI/r, followed by a test of superiority of TPV/r to CPI/r if non-inferiority was confirmed. Both tests were to be performed by the calculation of the same 95% confidence interval for the differences in response rates, taking into account the stratified randomization in the two arms of the trials.

The test of non-inferiority was originally included in the protocol statistical analysis plans because the control group was expected to show a response rate comparable to that of the TPV/r arm, at least in a large sub-group of the participating patients who would have viruses sensitive to both TPV and their chosen CPI. However, after Amendment #2 was implemented and it was recognized from the analysis of the composition of the trial population and the response rate of the CPI/r group, it became obvious that the response rate in the CPI/r group was incompatible with a response of a fully active control arm. As a result, BI concluded that a demonstration of non-inferiority was insufficient to demonstrate the antiviral efficacy of TPV/r and that a demonstration of superiority was required.

4.4 ADDITIONAL CLINICAL DATA

In support of the RESIST pivotal program, further extensive clinical data have been generated. These include an initial study of the impact of TPV in very highly treatment experienced patients, too resistant for participation in the RESIST trials (BI 1182.51).

In addition, a large amount of data on the resistance profile of TPV, evaluating the clinical impact of TPV resistance on treatment response and identifying predictors of TPV treatment response, has been generated, providing a resistance profile database superior to that of any currently available ARV.

In parallel, an extensive and highly detailed analysis and characterization of the pharmacokinetic and drug interaction profile of TPV/r has been performed.

At the time of NDA submission, data on 37 pediatric patients with up to four weeks of TPV/r exposure was available. This 48-week, 100-patient pediatric study in HIV-infected children and adolescents between 2 and 18 years of age now has been fully accrued and will be the subject of a future efficacy supplement.

Finally, a Phase III study of TPV/r versus LPV/r in antiretroviral naïve patients has recently completed enrolment.

All studies in the TPV development program have used standard research approaches to design, conduct, and analysis that are consistent with other ARV drug development programs. A listing of all 39 clinical trials conducted in support of TPV may be found in Appendix 2.

5. CLINICAL PHARMACOLOGY

5.1 CLINICAL PHARMACOKINETICS

To achieve effective tipranavir plasma concentrations using a twice-daily (BID) dosing regimen, co-administration of tipranavir with low-dose ritonavir twice-daily is essential. Ritonavir acts by inhibiting hepatic cytochrome P450 3A (CYP 3A), the intestinal P-glycoprotein (Pgp) efflux pump, and possibly intestinal cytochrome P450 3A as well. As demonstrated in a dose-ranging evaluation in 113 HIV-negative healthy male and female volunteers (BI 1182.5), ritonavir increases tipranavir $AUC_{0\text{-}12h}$, C_{max} and C_{min} by decreasing its clearance.

Tipranavir 500 mg, co-administered with low-dose ritonavir 200 mg (TPV/r 500/200 mg), BID for 21 days was associated with a 48-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir as compared with tipranavir 500 mg given BID without ritonavir for 11 days (Figure 5.1: 1).

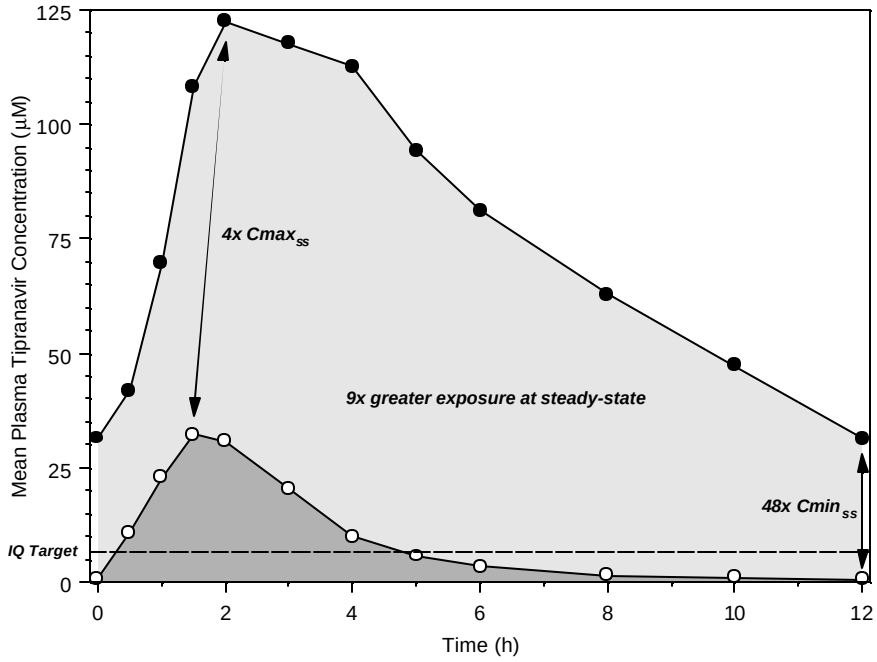

Figure 5.1: 1 Steady state plasma tipranavir concentrations on the 11th-day of 500 mg BID administration without ritonavir (open circles) and following the addition of 200 mg ritonavir BID for 14 days (closed circles)

Given alone, TPV induces hepatic CYP 3A and RTV inhibits CYP 3A. To understand the net effect of coadministration of tipranavir and ritonavir on hepatic CYP 3A, a single 200 mg dose of ritonavir co-administered with 500 mg tipranavir was studied using an erythromycin breath test (ERMBT).

Tipranavir rapidly induced CYP 3A when given alone. When ritonavir was added the expected inhibitory effect on CYP 3A was predominant. This net inhibition of CYP 3A for the TPV/r combination was nearly complete on Study Day 1. Following withdrawal of drug administration, CYP 3A activity returned to baseline levels by Study Day 3, likely due to hepatic enzyme turnover.

These data confirm that tipranavir and ritonavir must be taken together and doses should not be missed. Patients should be cautioned to take their tipranavir and ritonavir together as

prescribed and to not run out of the booster drug, ritonavir. Full hepatic enzyme inhibition is necessary to deliver adequate exposure to tipranavir.

The recommended dose of tipranavir is 500 mg (two 250 mg capsules or 5 mL of oral solution), co-administered with 200 mg ritonavir (low-dose ritonavir), twice daily. Steady state is attained in patients after 7 days of dosing. TPV/r exhibits linear pharmacokinetics at steady state and the half-life is 6.0 hours in HIV-positive patients. Trough concentrations 60-fold above the protein-adjusted IC_{50} for protease inhibitor-resistant HIV-1 clinical isolates (i.e., IQ ≥ 60) are achieved at doses of TPV/r 500/200 mg, and have been associated with a 1 $\log_{10}$ viral load reduction in clinical studies of treatment-experienced patients.

5.1.1 Demographic subpopulations

Demographic subpopulations were also analyzed. For example, evaluation of steady-state plasma trough tipranavir concentrations at 10-14 h after dosing from the RESIST studies demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. The trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

In addition, females generally had higher tipranavir concentrations than males. After 4 weeks of TPV/r 500 mg/200 mg BID, the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males.

Finally, white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races. Table 5.1.1: 1 summarizes pharmacokinetic parameters by gender and HIV status.

Table 5.1.1: 1 Population pharmacokinetic assessment by gender and HIV status

Pharmacokinetic parameter	HIV+ patients		HIV- subjects	
	Females (N = 14)	Males (N = 106)	Females (N = 25)	Males (N = 42)
$Cp_{0h,12h}$ (μM)	30.94	31.63	43.26	32.97
Cmax (μM)	92.33	75.87	114.71	90.08
Tmax (h)	2.9	2.9	3.0	2.9
AUC_{0-12h} (h•μM)	792.8	681.0	1005.3	781.8
CL (L/h)	1.05	1.22	0.83	1.06
V (L)	7.7	10.2	5.3	7.0
$t_{1/2}$ (h)	6.0		4.8	
	5.5	6.0	4.7	4.8
Ka (h^{-1})	0.5142	0.5291	0.4406	0.4780
Ke (h^{-1})	0.1354	0.1200	0.1560	0.1510
free fraction protein binding	0.015% ± 0.006%		0.019% ± 0.076%	

5.1.2 Absorption, distribution, metabolism, elimination (ADME)

5.1.2.1 Absorption

Because tipranavir is a Biopharmaceutics Classification Scheme (BCS) Class II compound, with low solubility and high permeability, absorption of tipranavir in humans is limited, though no quantification of absolute absorption is available.

A self-emulsifying drug delivery system (SEDDS) to create a microemulsion environment in the gastrointestinal tract upon agitation with water is required to get maximum dispersion of tipranavir in the gastrointestinal tract as a solution.

Food

Tipranavir capsules, administered under high fat meal conditions or with a light snack of toast and skim milk, were tested in a multiple dose study. Food enhanced the extent of bioavailability (AUC point estimate 1.31, confidence interval 1.23-1.39), but had minimal effect on peak tipranavir concentrations (C_{max} point estimate 1.16, confidence interval 1.09-1.24). Based on these data, tipranavir may be safely taken with standard or high-fat meals and food appears to improve GI tolerability and aid in the emulsification of the drug.

Antacid

When TRV/r was co-administered with 20 mL of aluminium and magnesium-based liquid antacid, tipranavir $AUC_{0\rightarrow12h}$, C_{max} and C_{12h} were reduced by 25-29%. Consideration should be given to separating TPV/r dosing from antacid administration to prevent reduced absorption of tipranavir.

The effect of a proton pump inhibitor on tipranavir absorption has not been studied in a formal drug interaction trial. However, for the 80 patients on proton pump inhibitors in the RESIST studies, the median trough tipranavir concentration was 41 µM compared to a median 34 µM concentration observed in the group of 570 patients not on proton pump inhibitors.

Formulation Excipients

Despite the significant amounts of the emulsifier Cremophor EL® ingested each day with tipranavir and ritonavir capsules, systemic ricinoleic acid concentrations have not been detected after 6 months of chronic therapy demonstrating that the large molecular weight excipient is not absorbed.

Loperamide

Loperamide is often co-administered with TPV/r to control diarrhea. A pharmacodynamic interaction study in healthy volunteers demonstrated that administration of loperamide 16mg and TPV/r 750 mg/200 mg does not cause any clinically relevant change in the respiratory response to carbon dioxide, a surrogate marker for CNS entry of loperamide and its metabolite.

The pharmacokinetic analysis showed that the AUC and C_{max} of loperamide and its metabolite were reduced by greater than 50%, whereas the AUC and C_{max} for tipranavir remained unchanged and the C_{min} decreased by 26%. Since the primary pharmacologic activity of loperamide is local, lower systemic loperamide concentrations are not of clinical concern. This data does suggest that TPV/r has an inductive effect on efflux transporters *in vivo.*

5.1.2.2 Distribution

Tipranavir is extensively bound to plasma proteins (>99.9%). From clinical samples of healthy volunteers and HIV-1 positive subjects who received tipranavir the mean fraction of tipranavir unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV-positive subjects 0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82 µM. The unbound fraction of tipranavir appeared to be independent of total drug concentration over this concentration range.

Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine in an overdose situation.

5.1.2.3 Metabolism

In vitro

In an *in vitro* drug interaction assessment using tipranavir alone the I/K_i ratios, based on in vivo maximum plasma tipranavir concentrations (bound and free) following ritonavir-boosted tipranavir administration, were greater than 1 (interaction likely) for the inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Follow-up *in vivo* evaluations using probe substrate drugs for these isoforms have not yet been conducted to rule out these potential interactions. During the conduct of the RESIST trials, patients were on co-medications that were substrates for these major human isoforms. A review of the case reports for patients co-prescribed a CYP2C19 substrate carisoprodol (n=5), a CYP1A2 substrate olanzapine (n=6), and a CYP2C9 substrate phenytoin (n=9) failed to show a need for dose adjustment of the substrate drug. For the CYP1A2, CYP2C19, CYP2C9, CYP3A4 substrate warfarin (n=3), frequent INR monitoring due to the ritonavir component of tipranavir therapy is warranted.

In vitro metabolism studies with human liver microsomes indicated that CYP3A is the predominant CYP isoform involved in tipranavir metabolism.

In vivo

Tipranavir is a substrate of intestinal and hepatic CYP3A activity and Pgp, and appears to be

both an inhibitor and an inducer of these metabolic and transport systems, but the clinical significance of these findings is not yet established. Steady state is attained after 7 days of dosing. TPV/r exhibits linear pharmacokinetics at steady state.

As noted above, the ERMBT data confirmed *in vitro* analyses indicating that tipranavir induces the cytochrome P450 CYP3A enzyme system after multiple doses. Hepatic CYP3A activity, as measured by the ERMBT, increased from basal levels following oral administration of 500 mg tipranavir alone for 11 days, thus indicating hepatic CYP3A enzyme auto-induction. With the addition of 200 mg of ritonavir, the percent of erythromycin metabolised per hour dropped to negligible values. This indicates that the net systemic effect of TPV/r is inhibition of the hepatic CYP3A enzyme system.

The oral clearance of tipranavir decreased after the addition of ritonavir which may represent diminished first-pass clearance of the drug at the gastrointestinal tract and the liver. With repeated dosing, tipranavir plasma concentrations are lower than predicted from single dose data, presumably due to efflux transporter induction as the metabolism of tipranavir in the presence of low-dose ritonavir is minimal.

In a ^{14}C-tipranavir human study (BI 1182.24) radio-labelled tipranavir (^{14}C-tipranavir) given with unlabelled RTV 200 mg, unchanged tipranavir was the predominant form detected, accounting for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few TPV metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity).

5.1.2.4 Excretion

Administration of ^{14}C-tipranavir to subjects (n = 8) who received TPV/r 500/200 mg BID dosed to steady-state demonstrated that the majority of radioactivity (median 82.3%) was excreted in feces. Only a median of 4.4% of the radioactive dose administered was recovered in urine.

In addition, 56% was excreted between 24 and 96 hours after dosing. A minor fraction of the dose, attributed to colonic bacteria, was detected as metabolites in the feces; the overwhelming majority of the dose was excreted unchanged.

The effective mean elimination half-life of tipranavir/ritonavir in healthy volunteers (n = 67) and HIV-infected adult patients (n = 120) was 4.8 and 6.0 hours, respectively, at steady state following a dose of TPV/r 500/200 mg BID with a light meal.

5.1.3 Drug interactions

5.1.3.1 Effect on tipranavir

Since tipranavir and ritonavir are both metabolized by CYP3A, studies evaluating the TPV/r co-administration with agents that induce CYP3A (e.g., efavirenz) or inhibit CYP3A (e.g., fluconazole) were performed.

The analyses in Table 5.1.3.1: 1 demonstrate that if ritonavir 200 mg is chronically co-administered with tipranavir, then the CYP3A enzyme induction effect of efavirenz will not decrease the systemic tipranavir or ritonavir exposure. However, both fluconazole and clarithromycin increased the tipranavir concentration even in the presence of 200 mg ritonavir. When only ritonavir 100 mg is co-administered with tipranavir enzyme induction by efavirenz produces significant decreases in tipranavir exposure.

Table 5.1.3.1: 1 Mean Pharmacokinetic Ratios* of Tipranavir in the Presence of Co-administered Drug Based on Historical Tipranavir Data for Normal (HIV-) Volunteers. (No Effect = 1.00)

Regimen	Cmax (µM)	AUC (µM•h)	Cmin (µM)
TPV/r 500/200 mg BID & Clarithromycin 500 mg BID (n=24)	1.40 (1.24 – 1.47)	1.66 (1.43 – 1.73)	2.00 (1.58 – 2.47)
TPV/r 500/200 mg BID & Fluconazole 100 mg QD (n=20)	1.32 (1.18 – 1.47)	1.50 (1.29 – 1.73)	1.69 (1.33 – 2.09)
TPV/r 500/100 mg BID & Efavirenz 600 mg QD (n=24)	0.79 (0.69 – 0.89)	0.69 (0.57 – 0.83)	0.58 (0.36 – 0.86)
TPV/r 750/200 mg BID & Efavirenz 600 mg QD (n=21)	0.97 (0.85 – 1.09)	1.01 (0.85 – 1.18)	0.97 (0.69 – 1.28)

* Mean pharmacokinetic ratios with 90% confidence intervals (5 and 95 percentiles) following 2000 bootstrap samples. Design did not permit a true cross-over comparison.

5.1.3.2 Interactions with reverse transcriptase inhibitors

When administered alone, tipranavir is an inducer of hepatic CYP3A. TPV/r at the recommended dosage, is a net inhibitor of the hepatic CYP3A. TPV/r may therefore increase plasma concentrations of agents that are primarily metabolised by CYP3A similar to other ritonavir-boosted PIs. These increases in plasma concentrations of co-administered agents could increase or prolong their therapeutic effect and adverse effects.

The systemic exposures of stavudine, lamivudine, tenofovir, efavirenz, and nevirapine are not affected by TPV/r (Table 5.1.3.2: 1).

Zidovudine systemic exposure decreases by >40%, with no impact on glucuronidated-ZDV levels. Similarly, TPV/r decreases the extent of abacavir systemic exposure by approximately 40% and co-administration with enteric-coated didanosine is associated with a

10-20% reduction in didanosine levels. Based on the metabolic pathways for NRTIs, an interaction with TPV/r of this magnitude was unexpected and the mechanism(s) is unknown.

It should be noted that the prescribing information for zidovudine states that routine dose adjustment is not warranted for decreases of 25-47% in zidovudine exposure. It is possible that the drug interaction between didanosine and TPV/r was due to food and may be minimized by separating the didanosine administration by at least 2 hours from the dose of TPV/r taken with food. The clinical relevance of the decreases in exposure to ZDV, abacavir, and ddI are not known. No recommendation for dose adjustment of ZDV, abacavir or ddI can be made at this time. No dosage adjustments are necessary when the NNRTIs nevirapine or efavirenz are co-administered with TPV/r at the 500/200 mg dose.

Most NRTIs, without significant changes in plasma concentrations, may be safely co-administered with TPV/r. For ZDV and ABC, the clinical relevance of the reductions in plasma concentrations is not established and further studies are needed. As these drug-drug interaction studies between TPV/r and NRTIs measured only plasma concentrations of the NRTIs, studies to measure intracellular triphosphorylated drug levels of ZDV and abacavir are currently being planned.

Table 5.1.3.2: 1 Comparison of NRTI and NNRTI levels when combined with TPV/r, ritonavir alone, or ritonavir-boosted lopinavir.

Substrate Drug	Ritonavir-boosted tipranavir result	Ritonavir alone result	Ritonavir boosted lopinavir result
Abacavir	↓ 40% AUC ↓ 45% Cmax	NR	NR
Zidovudine	↓ 43% AUC ↓ 56% Cmax	↓ 25% AUC ↓ 27% Cmax	NR
Didanosine	↓ 10% AUC ↓ 20% Cmax	↓ 13% AUC ↓ 16% Cmax	NR
Stavudine	↓ 0-20%	NR	NR
Lamivudine	↓ 5-15%	NR	NR
Tenofovir	no change in AUC, except ↓ 38% Cmax	NR	NR
Efavirenz	↑ 0-12%	NR	↓ 10-15%
Nevirapine	↓ 3-14%	NR	↑ 5-15%

NR = not reported in prescribing information for Norvir® or Kaletra®

5.1.3.3 Interactions with protease inhibitors

Protease inhibitor (PI) levels for dual-boosted protease inhibitor regimens containing TPV/r cannot be predicted without a formal drug interaction study due to the mixed patterns of inhibition and induction of CYP pathways seen with these boosted-drug combinations.

In a clinical study (BI 1182.51) of dual-boosted PI combination therapy in multiple-treatment experienced HIV-positive adults, TPV/r, was combined with ritonavir-boosted lopinavir, saquinavir, or amprenavir. When tipranavir, lopinavir, and ritonavir were co-administered, there was a 55% reduction in lopinavir systemic exposure and a 70% reduction in the C_{min} of lopinavir. When tipranavir, saquinavir, and ritonavir were co-administered, there was a 76% reduction in saquinavir exposure and >80% reduction in the C_{min} of saquinavir. When

tiparanavir, amprenavir, and ritonavir were co-administered, there was a 45% reduction in amprenavir systemic exposure and a 55% reduction in the C_{min} of amprenavir[14].

In the absence of having established appropriate doses for the combination of TPV/r and LPV, SQV, or APV, these combinations are not recommended.

5.1.3.4 Interactions with non-ARV medications

Interactions between TPV/r and medications commonly used by patients with HIV were also performed.

Fluconazole

TPV/r does not substantially affect (≤ 10% decrease) the steady-state pharmacokinetics of fluconazole (Table 5.1.3.4: 1). As previously noted, fluconazole increases the AUC and C_{min} of tipranavir by over 50% when compared to historical data. Fluconazole doses >200 mg/day are not recommended as an initial dose to be combined with TPV/r[15].

Atorvastatin

TPV/r increases the plasma concentrations of atorvastatin (Table 5.1.3.4: 1) by approximately 8-10 fold and reduces the extents of exposures of the hydroxyl-metabolites by >85%. This observed interaction is comparable to the interactions observed with other ritonavir-boosted protease inhibitors. Atorvastatin does not significantly change the AUC, C_{max} or C_{min} of tipranavir. It is recommended to initiate atorvastatin treatment with the lowest possible dose with careful monitoring or, alternatively, to consider the use of other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin or rosuvastatin[16].

Rifabutin

TPV/r increases plasma concentrations of rifabutin (Table 5.1.2.4: 1) by up to 3 fold, and the

[14] The combination of APV and TPV/r was associated with an increased rate of Grade 3 or 4 ALT/AST elevations.

[15] Fluconazole dosage increases to above 200 mg QD should be carefully monitored.

[16] Studies between TPV/r and these alternative lipid-lowering agents have not been conducted, but would not be expected to be substantially increased.

25-O-desacetyl-rifabutin active metabolite by up to 20 fold. Rifabutin increases the C_{min} of tipranavir by 16%. Dosage reductions of rifabutin by at least 75% of the usual 300 mg/day are recommended (i.e., 150 mg three times per week). Further dosage reduction may be necessary for some individuals.

Clarithromycin

TPV/r increases the AUC and C_{min} of clarithromycin by 19% and 68%, respectively, and decreases the extent of exposure of the 18-hydroxy active metabolite by over 95%. These changes are not considered clinically relevant unless treating *Haemophilus influenzae*. As described earlier, clarithromycin 500 mg doubles the C_{min} of tipranavir. This large increase in C_{min} may be clinically relevant. Patients should therefore use the 500 mg BID dose of clarithromycin and should be carefully monitored if higher doses are required. Because the metabolic pathway for clarithromycin elimination has been altered, the renal pathway is expected to predominate. For patients with renal impairment the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 ml/min the dose of clarithromycin should be decreased by 75%. No dosage adjustments for patients with normal renal function are necessary.

Ethinyl Estradiol

TPV/r decreases the AUC and C_{max} of ethinyl estradiol by 50% (Table 5.1.3.4:1), but does not significantly alter the pharmacokinetic behavior of norethindrone. As a result of the reduction in estrogen levels, alternative or additional contraceptive measures should be used when estrogenic-based oral contraceptives are co-administered with TPV/r. Women using ethinyl estradiol co-administered with TPV/r may have an increased rate of nonserious rash.

Table 5.1.3.4: 1 Comparison of non-ARV levels when combined with TPV/r, ritonavir alone, or ritonavir-boosted lopinavir.

Substrate Drug	TPV/r	RTV alone	LPV/r
Clarithromycin	↑ AUC 19%, ↑ Cmin 68%, ↓ metabolite >97%	↑ AUC 77%, ↑ Cmax 31%, ↓ metabolite >99%	NR
Fluconazole	↓ 6-10%	NR	NR
Rifabutin	↑ 3 x, ↑ metabolite 21 x	↑ 4 x, ↑ metabolite 35 x	↑ 3 x, ↑ metabolite 48 x
Atorvastatin	↑ 9.4 x ↓ metabolite >85%	NR	↑ 5.9 x metabolite NR
Ethinyl Estradiol	↓ 45-50%	↓ 40%	↓ 42%

NR = not reported in prescribing information for Norvir® or Kaletra®

5.1.3.5 Potential drug interactions

Theoretical

Based on the drug interaction studies conducted to date and the similarity of the results between ritonavir-boosted tipranavir, ritonavir alone, and other ritonavir-boosted protease inhibitors, the following drugs are contraindicated or not recommended for co-administration with tipranavir (Table 5.1.3.5: 1). These recommendations are based on predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy and specific studies with TPV/r have not been performed.

Table 5.1.3.5: 1 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.
Antihistamines: Astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
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.

Empirical

Based on the drug interaction studies conducted to date and the similarity of the results between ritonavir-boosted tipranavir, ritonavir alone, and other ritonavir-boosted protease inhibitors, the following interactions, which may require dose adjustments or clinical monitoring when TPV/r is co-administered, are summarized in the Table 5.1.3.5: 2. Many of these studies have been performed, but those not performed are indicated in the table.

Table 5.1.3.5: 2 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interactions

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Nucleoside reverse transcriptase inhibitors:		
Abacavir	↓ Abacavir concentrations by approx. 40%	Clinical relevance of reduction in abacavir levels not established. No dose adjustment recommended.
Didanosine (EC)	↓ Didanosine by 10-20%	Clinical relevance of reduction in didanosine levels not established. For optimal absorption, didanosine should be separated from TPV/r dosing by at least 2 hours. No dose adjustment recommended.
Zidovudine	↓ Zidovudine concentrations by approx. 50%. ZDV glucuronide concentrations were unaltered.	Clinical relevance of reduction in zidovudine levels not established. No dose adjustment recommended.
Protease inhibitors (co-administered with low-dose ritonavir): Amprenavir Lopinavir Saquinavir	↓ Amprenavir Cmin by 55%, ↓ Lopinavir Cmin by 70%, ↓ Saquinavir Cmin by >80%,	In the absence of having established appropriate doses for the combination of tipranavir/ritonavir and ritonavir-boosted amprenavir, saquinavir, or lopinavir, these combinations cannot be recommended.
Other Agents for Opportunistic Infections		
Antifungals: Fluconazole Itraconazole Ketoconazole Voriconazole	↑ Tipranavir >50%, ? Fluconazole ↑ Itraconazole (not studied), ↑ Ketoconazole (not studied), ↑ ↓ Voriconazole (not studied)	Fluconazole increases TPV concentrations, but dose adjustments are not needed. Fluconazole doses >200 mg/day are not recommended. Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (200 mg/day) are not recommended.
Antimycobacterials:		
Rifampin	↓ Tipranavir (not studied)	Concomitant use of tipranavir and rifampin is contraindicated. Alternate antimycobacterial agents such as rifabutin should be considered.
Rifabutin	Tipranavir not changed, ↑ Rifabutin 3-fold ↑ Desacetyl-rifabutin 21-fold	Dosage reductions of rifabutin by 75% are recommended (e.g., 150 mg three times a week). Increased monitoring for adverse events in

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
		patients receiving the combination is warranted. Further dosage reduction may be necessary.
Clarithromycin	↑ Tipranavir 2-fold, ↑ Clarithromycin 20-68%, ↓ 18-hydroxy metabolite >97%	No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary. For patients with renal impairment the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%.
	Other Agents Commonly Used	
PDE5 inhibitors: Sildenafil Tadalafil Vardenafil	Combinations with TPV/r not studied. ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil expected	Concomitant use of PDE5 inhibitors with tipranavir and ritonavir should be used with caution and in no case should the starting dose of: • sildenafil exceed 25 mg within 48 hours • tadalafil exceed 10 mg every 72 hours • vardenafil exceed 2.5 mg every 72 hours
HMG-CoA reductase inhibitors: Atorvastatin	Tipranavir unchanged ↑ Atorvastatin 9.4-fold ↓ Hydroxy-metabolites >85%	Start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors.
Narcotic analgesics: Methadone	↓ Methadone by 50%	Dosage of methadone may need to be increased when co-administered with tipranavir and low-dose ritonavir.
Meperidine	Combinations with TPV/r not studied ↓ 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 concentrations	Alternative methods of non-hormonal

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
Ethinyl-estradiol	by 50%	contraception should be used when estrogen based oral contraceptives are co-administered with tipranavir and low-dose ritonavir. Women using estrogens may have an increased risk of non serious rash.
Immunosuppressants: Tacrolimus Sirolimus Cyclosporine	Combination with TPV/r not studied ↑ Tacrolimus ↑ Sirolimus ↑ Cyclosporine	More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilized.
Warfarin	Combination with TPV/r not studied ↑↓ R- and S warfarin metabolized by different isozymes	Frequent INR (international normalized ratio) monitoring upon initiation of tipranavir/ritonavir therapy.
Hypoglycemics: Tolbutamide Glyburide Glipizide Glimepiride Repaglinide Pioglitazone	Combination with TPV/r not studied ↓ Tolbutamide ↓ Glyburide ↓ Glipizide ↓ Glimepiride ↑ Repaglinide ↑ Pioglitazone	Because of the potential for ritonavir CYP3A inhibition or CYP2C9 induction with chronic therapy, careful glucose monitoring is warranted.
SSRIs: fluoxetine paroxetine sertaline	Combination with TPV/r not studied ↑ fluoxetine ↑ paroxetine ↑ sertaline	Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of TPV/r therapy.
Calcium Channel Blockers: verapamil nisoldepine felodipine	Combination with TPV/r not studied ↑ verapamil ↑ nisoldepine ↑ felodipine	Combinations of TPV/r and calcium channel blockers should be avoided because of the CYP3A activity of both agents.
Desipramine	Combination with TPV/r not studied ↑ Desipramine	Dosage reduction and concentration monitoring of desipramine is recommended.
Disulfiram/Metronidazole	Combination with TPV/r not studied	Tipranavir capsules contain alcohol they can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).

5.1.4 Hepatic or renal impairment

The pharmacokinetic profiles of single-dose and steady-state TPV/r 500/200 mg in subjects with mild to moderate hepatic insufficiency were investigated in an open label trial (BI 1182.32). Mildly and moderately hepatically-impaired patients were paired with control patients according to age, weight, and other demographics.

Following 7 days of TPV/r 500/200 mg BID dosing in a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 healthy volunteer controls, the single and multiple dose pharmacokinetic dispositions of tipranavir and ritonavir were found to be increased in patients with hepatic impairment, but still within the range observed in clinical trials. The geometric mean ratios for the population were 1.30 ($AUC_{0\text{-}12h}$), 1.14 (C_{max}) and 1.84 (C_{p12h}). No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) on the pharmacokinetics of either tipranavir or ritonavir has not been evaluated at steady state. Further studies are planned. Because greater than 80% of the doses of both drug entities are excreted in the feces as unchanged drug moieties, close clinical and laboratory monitoring of patients with moderate impaired liver (e.g. Child-Pugh B) function is important.

The use of TPV/r in Child-Pugh C patients is contraindicated, and studies in this population are not planned.

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

5.2 PHARMACOKINETIC CONCLUSIONS

- In treatment-experienced HIV-positive patients, TPV 500 mg must be given simultaneously with ritonavir 200 mg to obtain the desired drug levels with BID dosing.
- Despite TPV being an inducer of CYP3A, when combined with 200 mg of ritonavir TPV/r produces a net hepatic inhibition of CYP3A. The pharmacokinetic drug interactions for most concomitant medications are consistent with other ritonavir-boosted PIs.
- Reductions in zidovudine, abacavir, and didanosine plasma drug levels have been observed with TPV/r, but the clinical relevance of these reductions has not been established. No dose adjustments can be recommended at this time.
- No dosage adjustments of the NNRTIs nevirapine or efavirenz are required when co-administered with TPV/r at the 500/200 mg dose.
- Drug levels for ritonavir-boosted lopinavir, saquinavir, and amprenavir were significantly reduced when combined with TPV/r, therefore these combinations are not recommended. PI levels for novel dual PI regimens containing TPV/r cannot be predicted without formal drug interaction studies possibly due to the mixed patterns of inhibition and induction of CYP pathways seen with these drug combinations.
- Based on the interactions observed with TPV/r, the following additional drug interaction studies are planned: atazanavir, buprenorphine, bupropion, tadalafil, omeprazole, Peg-interferon/ribavirin, carbamazepine, methadone, new investigational antiretrovirals, and a CYP/Pgp-cocktail study.

6. EFFICACY

Since the discovery of tipranavir by Pharmacia and Upjohn (P&U) and its licensing for development by Boehringer Ingelheim (BI) in 2000, 39 tipranavir clinical trials have been conducted. This summary of efficacy presents tipranavir efficacy data from nine clinical trials conducted primarily in treatment-experienced HIV-positive patients.

6.1 EARLY CLINICAL DATA

Early open-label, dose ranging studies (Trials BI 1182.3, 1182.2 and 1182.4, Tables 6.1: 1 and 6.1: 2) showed that TPV reduces viral load in HIV-positive patients with different levels of treatment experience (naïve [BI 1182.3], single- [BI 1182.4] and multiple-PI experienced [BI 1182.2]).

In BI 1182.3, treatment naïve HIV-positive adults were given tipranavir alone or tipranavir with low dose ritonavir for 14 days. These 14 day viral activity data (Table 6.1: 1) clearly demonstrate that the addition of low dose ritonavir is required for an optimal treatment response.

Table 6.1: 1 Median change from baseline in HIV-1 RNA values over 14 days of monotherapy treatment in ARV Treatment Naïve Trial BI 1182.3

	TPV 1200 mg	TPV/r 300 mg/200 mg	TPV/r 1200 mg/200 mg
Baseline VL	4.90	5.20	4.79
Day 14 or 15	-0.77 (10)	-1.43 (7)	-1.64 (10)

In BI 1182.2, multiple PI regimen-experienced patients (NNRTI-naïve) were given two doses of TPV/r with efavirenz. The 48 week treatment response was similar between both dose groups but generally favored the lower dose used (TPV/r 500/100mg) over the high dose (TPV/r 1000/100mg). In BI 1182.4, single PI regimen-experienced patients were given two doses of TPV/r and this was compared against a standard of care regimen containing SQV/RTV 400/400mg. The 48 week treatment response was similar for both of the two TPV/r dose groups but appeared to slightly favour the higher dose (TPV/r 1250/100mg) over the lower dose (TPV/r 500/100mg) (Table 6.1: 2).

Table 6.1: 2 Virologic efficacy data in Trials BI 1182.2 and 1182.4 - FAS **(**LOCF or NCF), using combination therapy

	BI 1182.2 Multiple PI Failure		BI 1182.4 Single PI Failure		
	TPV/r 500 /100mg NRTI and NNRTI	TPV/r 1000 /100mg NRTI and NNRTI	TPV/r 500 /100mg 2 NRTIs	TPV/r 1250 /100mg 2 NRTIs	SQV/r 400 /400mg 2 NRTIs
Median Baseline VL [log_{10} copies/mL]	4.43	4.45	4.44	4.35	4.19
24-week analysis:					
Median VL change from baseline [log_{10} copies/mL]	-2.67	-2.39	-1.41	-1.36	-1.75
Patients < 400 copies/mL [%]	79	50	38	29	24
Patients < 50 copies/mL [%]	58	50	17	21	14
48-week analysis:					
Median VL change from baseline [log_{10} copies/mL]	-2.67	-2.43	-0.50	-0.88	-1.41
Patients < 400 copies/mL [%]	79	50	16	32	17
Patients < 50 copies/mL [%]	68	41	8	27	10

While these trials provided data on the efficacy of TPV/r in patients with variable treatment experience, no definitive dose was established. As a result, BI designed and conducted a dose-finding study (BI 1182.52) using three doses of TPV/r.

6.2 DOSE SELECTION (BI 1182.52)

As noted previously, BI designed and conducted a dose-finding study (BI 1182.52) to determine the optimal dose for use in the Phase III trial program.

Similar to the RESIST study cohort, these patients had two PI-based regimen experience, and baseline viral isolates with at least one primary protease mutation (30N, 46I/L, 48V, 50V, 82A/L/F/T, 84V and 90M), and not more than 2 mutations among 82L/T, 84V or 90M. This was a double-blind study evaluating 3 TPV/r doses: 500/100 mg, 500/200 mg and 750/200 mg, all given BID with a genotypically optimized background regimen (OBR).

The first 2 weeks of the study were a functional monotherapy phase in which patients changed the PI they were taking at study entry to one of three TPV/r doses, but maintained

the same OBR. The antiviral effect from these first 2 weeks was therefore predominantly due to only TPV/r. During this 2-week functional monotherapy phase, the viral load reductions from baseline to Week 2 were: TPV/r 500/100 mg, 0.85 $\log_{10}$ copies/mL; TPV/ r 500/200 mg, 0.93 $\log_{10}$ copies/mL; and TPV/r 750/200 mg, 1.18 $\log_{10}$ copies/mL.

For the full study cohort, there was an inverse relationship between the number of mutations at codons 33, 82, 84, or 90 and viral load reduction at Week 24. Patients with no mutations at these codons demonstrated a -1.51 $\log_{10}$ copies/mL reduction; one mutation, -0.76 $\log_{10}$ copies/mL reduction; two mutations, -0.62 $\log_{10}$ copies/mL reduction; three mutations, -0.13 $\log_{10}$ copies/mL reduction[17].

For patients with virus containing mutations at three of these key positions, the antiviral activity for all three doses was reduced. Across treatment groups, patients with up to two mutations at codons 33, 82, 84, or 90 showed a strong dose-related response at Week 24 in the LOCF analysis (Table 6.2: 1); there was a statistically significant difference between the TPV/r 750/200 and 500/100 doses but not between TPV/r 750/200 and 500/200. This was confirmed when the viral load responses at 24 weeks were stratified by the number of mutations at codons 33, 82, 84 or 90. The 500/100 group showed a significant drop in antiviral activity with 1 mutation while the 500/200 and the 750/200 doses required more mutations before antiviral activity was diminished. Thus, the 500/100 dose underperformed against the drug resistant viruses to be evaluated in the TPV pivotal trial program.

[17] While the entry criteria for BI 1182.52 permitted only two mutations, some patients with three mutations were entered into the study due to mutations at protease codon 33 or at 82 other than L or T.

Table 6.2: 1 Median log_{10} change from baseline in viral load at 2 and 24 Weeks of TPV/r treatment (FAS-LOCF) by number of baseline mutations at codons 33, 82, 84, or 90

Number of Mutations at codons 33, 82, 84, or 90 at Baseline/ Weeks of Treatment	Treatment Group											
	TPV/r 500/100 (n=73)			TPV/r 500/200 (n=72)			TPV/r 750/200 (n=71)			Total (n=216)		
	Log_{10} Change from Baseline in RNA Copies/mL											
	N	Med[a]	IQR	N	Med[a]	IQR	N	Med[a]	IQR	N	Med[a]	IQR
None												
2 weeks	5	-1.32	-1.51, -1.04	1	-0.60	-0.60, -0.60	5	-1.35	-1.35, -1.02	11	-1.32	-1.51, -0.82
24 weeks	5	-1.92	-2.42, -1.51	1	-1.82	-1.82, -1.82	5	-1.16	-1.20, -0.33	11	-1.51	-2.26, -0.97
1												
2 weeks	19	-1.21	-1.48, -0.73	25	-1.15	-1.67, -0.60	31	-1.25	-1.81, -0.58	75	-1.21	-1.61, -0.60
24 weeks	19	-0.29	-1.72, 0.42	25	-1.05	-2.39, -0.14	31	-1.07	-2.17, -0.18	75	-0.76	-2.28, 0.00
2												
2 weeks	36	-0.68	-1.07, -0.18	25	-1.28	-1.84, -0.78	19	-1.24	-1.62, -0.49	80	-0.93	-1.65, -0.26
24 weeks	36	-0.20	-1.68, 0.22	25	-0.59	-2.72, -0.25	19	-1.84	-2.36, -0.42	80	-0.62	-2.28, -0.03
0, 1, or 2												
2 weeks	60	-0.91	-1.41, -0.32	51	-1.16	-1.73, -0.60	55	-1.24	-1.68, -0.58	166	-1.13	-1.61, -0.46
24 weeks	60	-0.44	-1.99, 0.17	51	-1.05	-2.62, -0.24	55	-1.49	-2.26, -0.28	166	-0.87	-2.26, -0.06
3												
2 weeks	13	-0.19	-0.98, 0.20	21	-0.33	-1.10, -0.09	16	-0.54	-1.14, -0.04	50	-0.32	-1.10, 0.12
24 weeks	13	0.23	-1.09, 0.29	21	0.05	-0.63, 0.29	16	-0.25	-0.91, -0.13	50	-0.13	-1.09, 0.27

[a] Median.

Safety analyses of BI 1182.52 demonstrated a dose relationship with higher frequency of severe adverse events, discontinuations due to adverse events and DAIDS Grade 3 or 4 ALT elevations observed with increasing dose. Specifically, 21.2% of patients in the TPV/r 750/200 mg dose group had Grade 3 or 4 ALT elevations over the course of 24 weeks of therapy as compared to 5.5% for the TPV/r 500/100 mg dose group and 11.1% for the TPV/r 500/200 mg dose group. Thus, from the standpoint of optimal safety, PK and efficacy, the TPV/r 500/200 mg dose group was selected for study in Phase III trials, and these data were reviewed with the FDA at the End-of-Phase II meeting in December 2002.

6.3 EFFICACY RESULTS OF PIVOTAL, ACTIVE-CONTROLLED TRIALS (RESIST TRIALS)

6.3.1 Study population

Using a treatment population that was very similar to the cohort studied in BI 1182.52, the RESIST study program studied HIV-positive adults with triple ARV class experience, including at least two PI-based regimens. All patients had to be virologically failing on their current PI-based regimen at the time of study screening in order to get an accurate analysis of PI resistance; no treatment interruptions prior to study entry were allowed.

A total of 3309 patients were screened for participation in the two RESIST studies, and 1816/3309 (54.9%) of these patients failed screening. Of the 1816 patients who failed screening, the most common reasons for screening failure were: failure to meet baseline resistance criteria (66.4%), failure to meet baseline safety lab criteria (26.7%), unacceptable medical history (15.3%), and failure to have a viral load of at least 1000 copies/mL (12.9%).

A total of 1483 patients were randomized and treated in the combined RESIST trials (Table 6.3.1: 1). By 12 March 2004, 1159 patients had reached the 24-week visit date and data for these patients are included in full analysis set (FAS) analyses. Within the FAS, a subgroup of patients (n=731) without any protocol deviations formed the per-protocol set (PPS) population used in sensitivity analyses.

Table 6.3.1: 1 Summary of population sets for the RESIST trials

	RESIST-1 BI 1182.12		RESIST-2 BI 1182.48		Combined RESIST Trials	
	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)
All treated patients; achieve 16 weeks of efficacy by interim cut-off	311 (100.0)	309 (100.0)	435 (100.0)	428 (100.0)	746 (100.0)	737 (100.0)
Full analysis set (FAS); achieve 24 weeks of efficacy by interim cut-off	311 (100.0)	309 (100.0)	271 (62.3)	268 (62.6)	582 (78.0)	577 (78.3)
Per protocol set (PPS); subset of FAS without any protocol deviations	191 (61.4)	193 (62.5)	180 (41.4)	167 (39.0)	371 (49.7)	360 (48.8)

The integrated RESIST trial population included in the interim 24-week efficacy analyses consisted of 1159 patients, 582 randomized to TPV/r and 577 to CPI/r. Demographic characteristics were comparable between the two treatment groups (Table 6.3.1: 2).

Patients in the RESIST-1 trial had a lower CD4+ cell count (median 123 cells/mm^3 in both treatment groups) than the RESIST-2 trial (median 175 cells/mm^3 for TPV/r and 200 cells/mm^3 for CPI/r), potentially reflective of geographic differences in the treatment strategies of investigators.

Table 6.3.1: 2 Baseline demographic data, HIV-1 RNA values, and CD4+ cell counts – RESIST trials (FAS [a])

	RESIST-1 BI 1182.12		RESIST-2 BI 1182.48		Combined RESIST Trials	
	TPV/r	CPI/r	TPV/r	CPI/r	TPV/r	CPI/r
Total treated	311	309	271	268	582	577
Age [years]						
N	311	309	271	268	582	577
Median	45.0	43.0	42.0	42.0	43.0	43.0
Range	24-80	28-70	17-76	21-72	17-80	21-72
Subgroups [N (%)]						
<18	0	0	1 (0.4)	0	1 (0.2)	0
18 – 40	86 (27.7)	94 (30.4)	115 (42.4)	118 (44.0)	201 (34.5)	212 (36.7)
41 – 55	191 (61.4)	190 (61.5)	128 (47.2)	122 (45.5)	319 (54.8)	312 (54.1)
56 – 64	29 (9.3)	23 (7.4)	25 (9.2)	21 (7.8)	54 (9.3)	44 (7.6)
≥ 65	5 (1.6)	2 (0.6)	2 (0.7)	7 (2.6)	7 (1.2)	9 (1.6)
Gender [N (%)]						
Male	278 (89.4)	287 (92.9)	225 (83.0)	229 (85.4)	503 (86.4)	516 (89.4)
Female	33 (10.6)	22 (7.1)	46 (17.0)	39 (14.6)	79 (13.6)	61 (10.6)
Race [N (%)]						
White	241 (77.5)	235 (76.1)	189 (69.7)	179 (66.8)	430 (73.9)	414 (71.8)
Black	68 (21.9)	69 (22.3)	15 (5.5)	11 (4.1)	83 (14.3)	80 (13.9)
Asian	2 (0.6)	5 (1.6)	2 (0.7)	3 (1.1)	4 (0.7)	8 (1.4)
Not Collected[b]	0	0	65 (24.0)	75 (28.0)	65 (11.2)	75 (13.0)
Median baseline HIV-1 RNA [$\log_{10}$ copies/mL]	4.81	4.84	4.84	4.81	4.83	4.82
Median baseline CD4+ cell count [cells/mm^3]	123	123	175	200	155	158

a FAS, full analysis set of patients in 24-week efficacy analyses. The reader is cautioned against making comparison to the Summary of Clinical Safety Module 2.7.4 since the FAS used here includes patients who could have achieved 24 weeks of treatment whereas the Summary of Clinical Safety uses the all treated population.

b In France, race data collection not allowed.

Patients enrolled in the RESIST trials were highly treatment experienced, with a history of using a median of 12 ARVs before entry into the trial (Table 6.3.1: 3). More than 70% of patients had used four or more PIs, although PI use was slightly lower in RESIST-2. The median number of NRTIs that had been used was 6 (range 2-8) and the median number of NNRTIs was 1 (range 0-3), thus representing a population of patients with extensive ARV treatment experience and few ARV options with which to construct a viable regimen. Enfuvirtide had been previously used by 12% of patients. There were no differences between treatment groups in past ARV use within the combined study population.

Table 6.3.1: 3 Number of antiretroviral agents used prior to study randomization, by class – RESIST trials (FAS [a])

	RESIST-1 BI 1182.12		RESIST-2 BI 1182.48		Combined RESIST Trials	
	TPV/r	CPI/r	TPV/r	CPI/r	TPV/r	CPI/r
Total treated	311	309	271	268	582	577
Total of all ARVs						
Median	12	12	12	12	12	12
Range	3-19	4-20	4-18	3-18	3-19	3-20
ENF						
N (%)	39 (12.5)	37 (12.0)	30 (11.1)	31 (11.6)	69 (11.9)	68 (11.8)
PIs [b]						
Median	4	4	4	4	4	4
Range	1-7	1-7	1-7	1-7	1-7	1-7
Subgroups [N (%)]						
1	2 (0.6)	6 (1.9)	3 (1.1)	4 (1.5)	5 (0.9)	10 (1.7)
2	25 (8.0)	18 (5.8)	26 (9.6)	34 (12.7)	51 (8.8)	52 (9.0)
3	50 (16.1)	54 (17.5)	54 (19.9)	52 (19.4)	104 (17.9)	106 (18.4)
4	87 (28.0)	77 (24.9)	76 (28.0)	66 (24.6)	163 (28.0)	143 (24.8)
$\geq$ 5	147 (47.3)	154 (49.8)	112 (41.3)	112 (41.8)	259 (44.5)	266 (46.1)
NRTIs						
Median	6	6	6	6	6	6
Range	2-8	2-8	2-8	2-8	2-8	2-8
NNRTIs						
Median	2	1	1	1	1	1
Range	0-3	0-3	0-3	0-3	0-3	0-3

[a] FAS, full analysis set of patients in 24-week efficacy analyses

[b] RTV was only counted if given at a therapeutic dose.

6.3.1.1 Baseline genotypic resistance

The combined RESIST population was well balanced between treatment groups for the frequencies of protease gene mutations, per-protocol primary protease mutations, and number of mutations at codons 33, 82, 84, or 90 (Table 6.3.1: 4). The median number of protease gene mutations, defined as any change deviation from the Los Alamos database consensus sequence for HIV-1 subtype B, was 16 for the combined population. Patients in both treatment groups in both trials had a median of three per-protocol protease gene mutations (defined as mutations at codons 30, 33, 46, 48, 50, 82, 84, or 90). The majority of patients (~65%) entering the trial had mutations at two of the key protease mutations 33, 82, 84, or

90. Patients with three or more mutations at these key positions could enter the companion BI 1182.51 although a small number were enrolled in the RESIST trials and were categorized as protocol deviations and not major violations. Overall, the mutation patterns seen in the RESIST population describe a PI-experienced population, and one in which there was broad resistance to the commercially available agents including available PIs.

Table 6.3.1: 4 Distribution of baseline protease gene mutations – RESIST trials (FAS [a])

	RESIST-1 BI 1182.12		RESIST-2 BI 1182.48		Combined RESIST Trials	
	TPV/r	CPI/r	TPV/r	CPI/r	TPV/r	CPI/r
Total treated	311 (100.0)	309 (100.0)	271 (100.0)	268 (100.0)	582 (100.0)	577 (100.0)
No. of protease gene mutations [b]						
Median	15	15	16	16	16	16
Subgroups [N (%)]						
≤ 12	70 (22.5)	79 (25.6)	47 (17.3)	42 (15.7)	117 (20.1)	121 (21.0)
13 – 15	90 (28.9)	86 (27.8)	70 (25.8)	74 (27.6)	160 (27.5)	160 (27.7)
16 – 18	93 (29.9)	78 (25.2)	88 (32.5)	76 (28.4)	181 (31.1)	154 (26.7)
≥ 19	57 (18.3)	66 (21.4)	66 (24.4)	76 (28.4)	123 (21.1)	142 (24.6)
Missing	1 (0.3)	0	0	0	1 (0.2)	0
No. of protease mutations at 33, 82, 84, 90 [N (%)]						
0	11 (3.5)	13 (4.2)	12 (4.4)	7 (2.6)	23 (4.0)	20 (3.5)
1	91 (29.3)	77 (24.9)	74 (27.3)	83 (31.0)	165 (28.4)	160 (27.7)
2	192 (61.7)	204 (66.0)	182 (67.2)	174 (64.9)	374 (64.3)	378 (65.5)
Subtotal ≤ 2	294 (94.5)	294 (95.1)	268 (98.9)	264 (98.5)	562 (96.6)	558 (96.7)
3	16 (5.1)	15 (4.9)	2 (0.7)	4 (1.5)	18 (3.1)	19 (3.3)
4	0	0	1 (0.4)	0	1 (0.2)	0
Missing	1 (0.3)	0	0	0	1 (0.2)	0

[a] FAS, full analysis set of patients in 24-week efficacy analyses

[b] Protease gene mutations include any deviation from Los Alamos database consensus sequence for subtype B

6.3.1.2 Baseline phenotypic resistance

Although baseline phenotypic testing was not performed in real time and results were therefore not available to investigators to determine patient eligibility or to make baseline drug choices, these data were later obtained on a randomly selected sub-set of the patients participating in the RESIST studies. These data showed high level phenotypic resistance of

the baseline HIV-1 isolates against each of the currently marketed PIs with the majority of isolates remaining sensitive to TPV.

The median IC_{50} fold-change for each PI tested was:

- ✓ Tipranavir (n=454) 1.7
- ✓ Lopinavir (n=452) 87.4
- ✓ Indinavir (n=423) 41.0
- ✓ Saquinavir (n=450) 20.1
- ✓ Amprenavir (n=445) 12.2
- ✓ Nelfinavir (n=452) 40.7
- ✓ Ritonavir (n=449) 194.7
- ✓ Atazanavir (n=456) 55.3.

6.3.2 Pre-selection of comparator PI and enfuvirtide

6.3.2.1 Stratification by pre-selected PI and enfuvirtide use

In the RESIST studies, investigators had the option to pre-select a comparator PI that was either new or ongoing. A new PI was one that was not in use at the time of randomization, but could have been recycled from a previous regimen. Investigators also had the option to pre-select a genotypically available or a genotypically resistant PI. Where possible, investigators pre-selected a genotypically available PI for use in the CPI/r arms, but when the baseline genotype report provided an interpretation that there was no PI that was genotypically available, investigators could pre-select a PI that was considered genotypically resistant.

The resistance expert consultant panel was made available to assist investigators in interpreting the actual mutation pattern provided on the genotype report and to select an optimal PI for use in the CPI/r arm in context with the patient's treatment history.

The comparator PIs pre-selected by investigators and the use of a "new" CPI/r is provided in Table 6.3.2.1: 1. LPV/r was the most common comparator PI pre-selected (50.3%), followed

by APV/r (25.8%), SQV/r (20.5%), and IDV/r (3.5%). Nearly two thirds of patients had a "new" CPI/r pre-selected, indicating that it was not the PI that the patient had been taking at the time of randomization. Of those who actually received treatment in the CPI/r arms, the PI used was "new" for 122/290 (42.1%) of those receiving LPV/r, 17/20 (85.0%) of those receiving IDV/r, 97/118 (82.2%) of those receiving SQV/r, and 127/149 (85.2) of those receiving APV/r.

Table 6.3.2.1: 1 Summary of patient treatment with respect to PI strata and use of a new PI – RESIST trials (FAS)

	Total	
	TPV/r	CPI/r
	N (%)	N (%)
Total	582 (100.0)	577 (100.0)
PI strata		
LPV	293 (50.3)	290 (50.3)
IDV	21 (3.6)	20 (3.5)
SQV	117 (20.1)	118 (20.5)
APV	151 (25.9)	149 (25.8)
New pre-selected PI	375 (64.4)	363 (62.9)
New pre-selected PI by strata		
LPV	128 (22.0)	122 (21.1)
IDV	20 (3.4)	17 (2.9)
SQV	96 (16.5)	97 (16.8)
APV	131 (22.5)	127 (22.0)

The pre-selected use of enfuvirtide by investigators is provided in Table 6.3.2.1: 2. Overall, 158/582 (27.1%) of patients receiving TPV/r also used enfuvirtide and 128/577 (22.2%) of patients receiving CPI/r also used enfuvirtide.

Table 6.3.2.1: 2 Summary of patient treatment with respect to enfuvirtide use by PI strata – RESIST trials (FAS)

	Total	
	TPV/r	CPI/r
	N (%)	N (%)
Total	582 (100.0)	577 (100.0)
Total ENF use	158 (27.1)	128 (22.2)
ENF use by strata		
LPV	85 (14.6)	71 (12.3)
IDV	8 (1.4)	3 (0.5)
SQV	37 (6.4)	32 (5.5)
APV	28 (4.8)	22 (3.8)

It is important to note that patients who pre-selected enfuvirtide had different baseline characteristics than those patients who did not. Table 6.3.2.1: 3 provides the baseline data of those patients who pre-selected enfuvirtide and those who did not. In general, patients pre-selected enfuvirtide had higher baseline viral load, lower CD4 count, more prior ARV drug use, and more baseline drug resistance than patients who did not pre-select enfuvirtide.

Table 6.3.2.1: 3 Baseline demographic data and HIV characteristics of patients receiving or not receiving enfuvirtide – RESIST trials (FAS)

	Receiving ENF		Not Receiving ENF	
	TPV/r	CPI/r	TPV/r	CPI/r
Total treated	158	128	424	449
Median baseline HIV-1 RNA [$\log_{10}$ copies/mL]	5.07	5.10	4.74	4.75
Median baseline CD4+ cell count [cells/mm^3]	72	77	177	182
Median ARV use (range)	13 (8-19)	14 (4-20)	11 (3-18)	11 (3-19)
Median prior PI use (range)	5 (2-7)	5 (1-7)	4 (1-7)	4 (1-7)
Median NRTI use (range)	6 (3-8)	6 (2-8)	6 (2-8)	6 (2-8)
Median NNRTI use (range)	2 (0-3)	2 (0-3)	1 (0-3)	1 (0-3)
Median number of protease gene mutations [a]	17	17	15	15
Mutations at 33, 82, 84, 90 [N, (%)]				
0	4 (2.5)	1 (0.8)	19 (4.5)	19 (4.2)
1	31 (19.6)	25 (19.5)	134 (31.6)	135 (30.1)
2	114 (72.2)	95 (74.2)	260 (61.3)	283 (63.0)
3	9 (5.7)	7 (5.5)	9 (2.1)	12 (2.7)
4	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

[a] Protease gene mutations include any deviation from Los Alamos database consensus sequence for subtype B

6.3.2.2 Use of new vs. ongoing or susceptible vs. resistant comparator PIs

Overall, most patients who randomized to the CPI/r arms (62.9%) of the RESIST studies used a new PI, one that was not being used at the time of randomization. These data are shown in table 6.3.2.2: 1. In contrast, most patients who randomized to the CPI/r arms (66.7%) of the RESIST studies used a PI that was considered "resistant" in the interpretation of the baseline genotype report. These data are also shown in Table 6.3.2.2: 1.

Table 6.3.2.2: 1 Choice of pre-selected PI as new or ongoing and resistance interpretation from the genotype report – RESIST trials (FAS)

	TPV/r		CPI/r	
	N	(%)	N	(%)
Total treated	582	(100.0)	577	(100.0)
New or ongoing pre-selected PI				
New PI	375	(64.4)	363	(62.9)
Ongoing PI	207	(35.6)	214	(37.1)
Resistance to pre-selected PI				
Susceptible [a]	76	(13.1)	80	(13.9)
Possibly Resistant [b]	135	(23.2)	112	(19.4)
Resistant [c]	369	(63.4)	385	(66.7)
Missing	2	(0.3)	0	
Genotypically available and new pre-selected PI	152	(26.1)	140	(24.3)

[a] TruGene®: No evidence of resistance. Virtual Phenotype™: within normal susceptibility range or resistance unlikely; for IDV $\leq$ 3.0, for SQV $\leq$ 2.5, for APV $\leq$ 2.0, and for LPV <10.

[b] TruGene®: Possible resistance. Virtual Phenotype™: for LPV only 10 to <40.

[c] TruGene®: Resistance. Virtual Phenotype™: resistance or resistance likely as defined by being above normal susceptibility range; for IDV >3.0, for SQV >2.5, for APV >2.0, and for LPV $\geq$ 40.

6.3.3 Differences between RESIST studies

There were several noteworthy differences between the RESIST trials. One difference was a higher frequency of new pre-selected PIs in the RESIST-2 study (70.3% for both treatment groups combined) than in the RESIST-1 study (57.9% for both treatment groups combined). The difference might have been a result of more patients in the RESIST-2 trial not having exhausted all of their PI options; whereas more patients in the RESIST-1 trial had used five or more PIs before screening. Another difference between the trials concerned the genotypic

resistance interpretation, with more patients in the RESIST-2 trial (73.8%) than patients in the RESIST-1 trial (57.4%) testing resistant to the pre-selected PI. This difference may be attributed to geographic differences in treatment strategies or due to the different algorithms used by the resistance testing laboratories, TruGene® (exclusively used in RESIST-1) and Virtual Phenotype™ (primarily used in RESIST-2). In addition, the VIRCO Virtual Phenotype™ interpretation used only one cut-off for all PIs except LPV.

Enfuvirtide was used more frequently in the RESIST-1 trial (38.3% of the TPV/r group and 34.0% of the CPI/r group) than in the RESIST-2 trial (only 14.4% in the TPV/r group and 8.6% in the CPI/r group). In the integrated analyses, 27.1% of TPV/r patients and 22.2% of CPI/r patients received E concomitantly with study medication. Enfuvirtide was most frequently co-administrated with LPV in the comparator arm. The lower use of enfuvirtide in the RESIST-2 trial was due to the limited access to the drug in Europe and Latin America at the time the trial was recruiting patients. Patients taking enfuvirtide differed from patients not taking enfuvirtide for median VL (higher), median CD4+ cell count (lower), prior ARV medication use (more), and median number of protease gene mutations (more). The differences between enfuvirtide and non-enfuvirtide users were similar for TPV/r and CPI/r patients for all of these characteristics

6.3.4 Patient disposition

Of the 1,159 randomized patients, 475 (81.6%) in the TPV/r group and 247 (42.8%) in the CPI/r group completed Week 24 (Table 6.3.4: 1). This difference between treatment groups was driven by early trial discontinuation because of lack of virologic response in the CPI/r group.[18]

A higher level of patients in the CPI/r arms had missing or incomplete data at Week 24 than in the TPV/r arms. This higher number of patients with missing or incomplete data appears to reflect the fact that more patients in the CPI/r discontinued than patients in the TPV/r arms.

[18] Patients in the CPI/r arms of the RESIST studies were permitted to discontinue and receive TPV/r in BI 1182.17 only if objectively confirmed virologic failure occurred. Since AEs may be considered 'subjective,' RESIST CPI/r patients could not rollover in BI 1182.17 if discontinuation was exclusively due to AEs.

Table 6.3.4: 1 Patient disposition – RESIST trials (FAS)

	RESIST-1 Trial BI 1182.12		RESIST-2 Trial BI 1182.48		Combined RESIST Trials	
	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)
Total treated	311 (100.0)	309 (100.0)	271 (100.0)	268 (100.0)	582 (100.0)	577 (100.0)
Completing to Week 24	263 (84.6)	151 (48.9)	212 (78.2)	96 (35.8)	475 (81.6)	247 (42.8)
Missing or incomplete data at Week 24 a	0 (0.0)	19 (6.1)	9 (3.3)	48 (17.9)	9 (1.5)	67 (11.6)
Study drug discontinued prematurely	48 (15.4)	139 (45.0)	50 (18.5)	124 (46.3)	98 (16.8)	263 (45.6)

a Missing or incomplete at Week 24 consists of two subgroups of patients. The first subgroup had a premature discontinuation of the study based on the end of treatment case report form page filled out with a date up to Day 196, but no date or reason for the stop of study medications was indicated on the protease inhibitor case report form page. The second subgroup did neither have a documentation of a premature discontinuation nor did it have documentation of continued use of the study medication on the protease inhibitor case report form page because this page was not received by BI for the Week 24 visit.

6.3.5 Analysis of treatment response: primary and secondary endpoints

6.3.5.1 Treatment response

The primary endpoint for accelerated approval is treatment response through Week 24. Treatment response is a composite primary endpoint of the proportion of patients with two consecutive VL measurements >1 $\log_{10}$ below baseline after 24 weeks of treatment without prior (1) evidence of a confirmed virological failure, (2) introduction of a new ARV to the regimen for reasons other than toxicity or intolerance to a background drug, (3) permanent discontinuation of the study drug, (4) death, or (5) loss to follow-up.

The primary endpoint treatment response is shown below in Table 6.3.5.1: 1. At 24 weeks, 41.2% of TPV/r patients achieved this confirmed treatment response as compared with 18.9% of CPI/r patients ($p < 0.0001$). This difference, adjusted for the stratification by PI strata and enfuvirtide strata was 21.3%, with a lower limit of the two-sided 95% CI of 16.3% superiority (Table and Figure 6.3.2.1: 1).

The proportion of treatment responders in the TPV/r group was similar across both the RESIST-1 and RESIST-2 studies, though a lower proportion of CPI/r patients in RESIST-2

(14.9%) achieved a treatment response at Week 24 than CPI/r patients in RESIST-1 (22.3%), which resulted in a larger weighted treatment difference favoring TPV/r in RESIST-2 (Table 6.3.5.1: 1).

Table 6.3.5.1: 1 Primary endpoint treatment response (2 consecutive VL measurements >1 $\log_{10}$ below baseline) at Week 24 – RESIST trials (FAS)

		Treatment Response [a] by Treatment Group						Treatment Difference [b]		
		TPV/r			CPI/r			Weighted	95% CI	
Trial	Analysis	n	(%)	N	n	(%)	N	Diff. (%)	LL (%)	UL (%)
1182.12	FAS (NCF)	129	(41.5)	311	69	(22.3)	309	(18.4)	(11.4)	(25.3)
1182.48	FASS24 (NCF)	111	(41.0)	271	40	(14.9)	268	(25.0)	(17.8)	(32.2)
Total	FAS (NCF)	240	(41.2)	582	109	(18.9)	577	(21.3)	(16.3)	(26.4)

a Treatment response is the composite endpoint of the proportion of patients with two consecutive VL measurements >1 $\log_{10}$ below baseline after 24 weeks without prior (1) evidence of a confirmed virological failure, (2) introduction of a new ARV to the regimen for reasons other than toxicity or intolerance to a background drug, (3) permanent discontinuation of the study drug, (4) death, or (5) loss to follow-up

b Treatment difference and confidence interval weighted for the sizes of ENF strata and PI strata.

n = number of responders, N = number of evaluable patients.

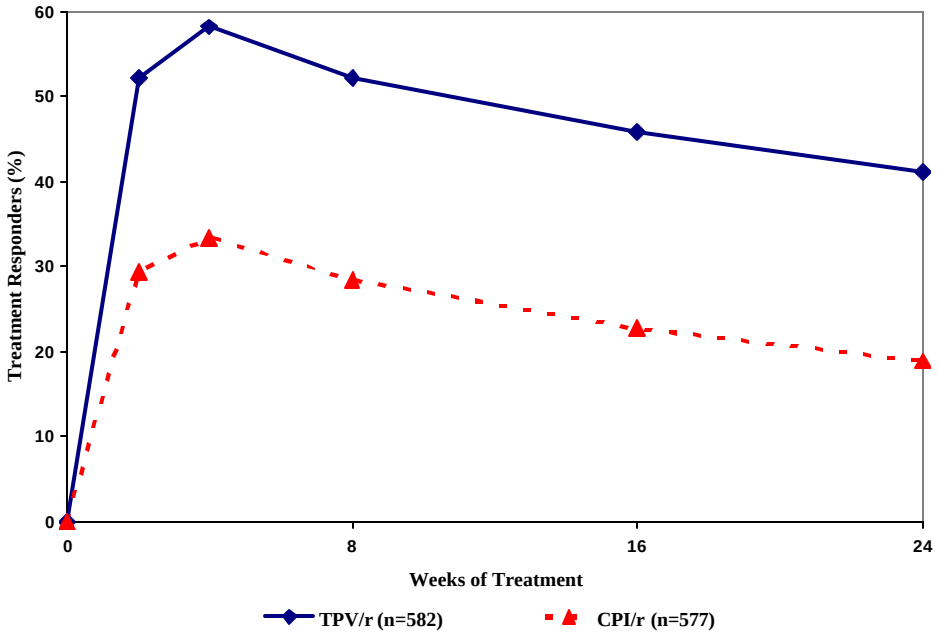

Figure 6.3.5.1: 1 Treatment response over time through 24 weeks – Combined RESIST trials, (FAS [NCF])

24-week difference: p <0.0001

For patients in the TPV/r treatment arms, the proportion of treatment responders reached a peak at Week 4. At each time point the proportion of treatment responders was larger among TPV/r patients than CPI/r patients ($p < 0.0001$). At Week 24 the proportion of treatment responders in the TPV/r group was larger than the peak proportion of responders in the CPI/r group during the 24 weeks.

The primary reason for a lack of treatment response was lack of a confirmed 1 $\log_{10}$ reduction below baseline, which occurred in 45.9% of TPV/r patients and 71.4% of CPI/r patients (Table 6.3.5.1: 2). Specific reasons that led to failure were (1) a 1 $\log_{10}$ drop from baseline without confirmation; (2) viral load never being suppressed ;(3) rebound; and (4) a drug change or discontinuation due to virologic failure. The two treatment groups differed especially for drug change or discontinuation due to virologic failure, which occurred in 37.3% of CPI/r patients and 6.4% of TPV/r patients and for viral rebound, which occurred in 15.3% of TPV/r patients and 10.9% of CPI/r patients.

The higher rate of rebound in the TPV/r group is likely due to the fact that there were more virologic responders in the TPV/r group and only responders can show rebound.

Discontinuations of study medication due to AEs were more frequent in the TPV/r group (8.1%) than CPI/r group (3.8%). The RESIST study design may have contributed to this imbalance, as patients in the CPI/r arms could leave the study to receive TPV/r in BI 1182.17 for virologic failure, but not due to AEs. The rate of discontinuation for reasons other than AEs (e.g., consent withdrawn, lost to follow-up) were comparable between the two treatment groups, with 5.0% in the CPI/r group and 3.8% in the TPV/r group.

Table 6.3.5.1: 2 Treatment outcomes at Week 24 – RESIST trials (FAS [NCF])

	RESIST-1 BI 1182.12		RESIST-2 BI 1182.48		Combined RESIST Trials	
	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)
Total treated	311 (100.0)	309 (100.0)	271 (100.0)	268 (100.0)	582 (100.0)	577 (100.0)
Primary endpoint treatment response at Week 24	129 (41.5)	69 (22.3)	111 (41.0)	40 (14.9)	240 (41.2)	109 (18.9)
No confirmed 1 $\log_{10}$ drop from baseline	140 (45.0)	209 (67.6)	127 (46.9)	203 (75.7)	267 (45.9)	412 (71.4)
1 $\log_{10}$ drop from baseline without confirmation	31 (10.0)	16 (5.2)	19 (7.0)	16 (6.0)	50 (8.6)	32 (5.5)
Rebound [a]	51 (16.4)	39 (12.6)	38 (14.0)	24 (9.0)	89 (15.3)	63 (10.9)
Never suppressed through Week 24	45 (14.5)	45 (14.6)	46 (17.0)	57 (21.3)	91 (15.6)	102 (17.7)
Drug change or discontinuation due to virologic failure [b]	13 (4.2)	109 (35.3)	24 (8.9)	106 (39.6)	37 (6.4)	215 (37.3)
Death [c]	5 (1.6)	3 (1.0)	1 (0.4)	2 (0.7)	6 (1.0)	5 (0.9)
Study drug discontinuation due to adverse events [d]	25 (8.0)	9 (2.9)	22 (8.1)	13 (4.9)	47 (8.1)	22 (3.8)
Study drug discontinuation due to other reasons	12 (3.9)	19 (6.1)	10 (3.7)	10 (3.7)	22 (3.8)	29 (5.0)
Consent withdrawn	3 (1.0)	3 (1.0)	3 (1.1)	2 (0.7)	6 (1.0)	5 (0.9)
Loss to follow-up	4 (1.3)	4 (1.3)	0	0	4 (0.7)	4 (0.7)
Non-adherence	3 (1.0)	9 (2.9)	1 (0.4)	0	4 (0.7)	9 (1.6)
Pregnancy	1 (0.3)	0	1 (0.4)	0	2 (0.3)	0
Protocol violation	1 (0.3)	1 (0.3)	2 (0.7)	0	3 (0.5)	1 (0.2)
Other	0	2 (0.6)	3 (1.1)	8 (3.0)	3 (0.5)	10 (1.7)

[a] Confirmed loss of virologic response or loss of virologic response and missing confirmatory visit.

[b] Includes premature discontinuation of the study PI due to virologic failure and the addition of a drug to the background regimen (if not introduced to replace a background drug discontinued due to AEs attributable to the discontinued background drug).

[c] Death as primary reason for treatment failure.

[d] The reader is cautioned against making comparison to the Summary of Clinical Safety Module 2.7.4 since the count used here is discontinuation as reason for virologic failure and is based on the FAS population whereas the Summary of Clinical Safety counts all treated patients.

6.3.5.2 Response by pre-selected PI strata

Data from each of the two RESIST trials were combined to analyze treatment response within each pre-selected PI stratum.

To evaluate the impact of the extensive treatment experience of patients in the RESIST trials, analyses were conducted according to choice of the pre-selected PI: whether the pre-selected PI was new to the study regimen constructed at randomization (new PI), whether the virus was susceptible to the PI or the PI was genotypically available based on genotypic report interpretation of susceptible or possibly resistant, or whether the PI was both new to the study regimen and virus was susceptible or PI was genotypically available.

The TPV/r group had significantly greater treatment responses than LPV/r, SQV/r, or APV/r groups and these data are provided in Table 6.3.5.2: 1. The IDV stratum had too few patients to make a valid definitive comparison.

Table 6.3.5.2: 1 Treatment response at Week 24 by PI strata - RESIST trials (FAS)

		Treatment Group						Treatment Difference [a]		
		TPV/r			CPI/r			Weighted	95% CI	
PI Strata	Analysis	n	(%)	N	n	(%)	N	Diff. (%)	LL (%)	UL (%)
LPV	FAS (NCF)	116	(39.6)	293	62	(21.4)	290	(17.7)	(10.5)	(25.0)
IDV	FAS (NCF)	10	(47.6)	21	1	(5.0)	20	[b]	[b]	[b]
SQV	FAS (NCF)	51	(43.6)	117	18	(15.3)	118	(27.4)	(16.5)	(38.3)
APV	FAS (NCF)	63	(41.7)	151	28	(18.8)	149	(22.0)	(12.1)	(31.9)

n = Number of responders; N = Number of evaluable patients

[a] Treatment difference and confidence interval weighted for the size of ENF strata and PI strata.

[b] Weighted difference and confidence interval not presented for the IDV stratum due to small sample size.

It is important for the reviewer to interpret these data cautiously. While the treatment response for patients receiving TPV/r was superior to the treatment response of those receiving LPV/r, SQV/r, or APV/r, the comparator PI being used was not always "new" and was not always considered "genotypically available" on the baseline resistance report. In the LPV/r stratum, for example, if the LPV/r was "new" the treatment response was 45.3% in the TPV/r arm and 36.1% in the CPI/r arm (p=NS). Alternatively, in the LPV/r stratum, if the LPV/r was "ongoing" the treatment response was 35.2% in the TPV/r arm and 10.7% in the CPI/r arm, a statistically significant result.

The response by status of pre-selected PI (new or ongoing) and whether or not it was genotypically available[19] *for the aggregate CPI/r population* was examined and these data are provided in Table 6.3.5.2: 2. These data demonstrate that patients who pre-selected a "new" PI had a superior treatment response if they received TPV/r than if they received CPI/r. In addition, the data show that those patients who pre-selected a "genotypically available" PI had a superior treatment response if they received TPV/r than if they received CPI/r.

Table 6.3.5.2: 2 Treatment responses at Week 24 by choice of and resistance to pre-selected PIs *for the aggregate CPI/r population* – RESIST trials (FAS)

	Treatment Group						Treatment Difference [a]		
	TPV/r			CPI/r			Weighted	95% CI	
	n	(%)	N	n	(%)	N	Diff. (%)	LL (%)	UL (%)
Pre-selected PI									
New PI	165	(44.0)	375	88	(24.2)	363	(18.4)	(11.9)	(24.9)
Ongoing PI	75	(36.2)	207	21	(9.8)	214	(25.1)	(17.6)	(32.7)
Resistance to pre-selected PI									
Genotypically available [a]	92	(43.6)	211	55	(28.6)	192	(14.2)	(5.0)	(23.3)
Genotypically resistant	147	(39.8)	369	54	(14.0)	385	(24.3)	(18.4)	(30.2)
Missing	1	(50.0)	2	0		0			
Genotypically available and new pre-selected CPI/r	70	(46.1)	152	46	(32.9)	140	(11.7)	(1.1)	(22.4)

n = number of responders, N = number of evaluable patients

[a] Treatment difference and confidence interval weighted for the size of PI strata

Pre-specified secondary efficacy endpoints included viral load change from baseline, proportion of patients with undetectable viral load (BLQ 400 copies/mL, BLQ 50 copies/mL, CD4 count change, and AIDS progression events). These data are described in the following sections.

6.3.5.3 Viral load change from baseline at 24 weeks (FAS population)

Viral load reduction from baseline was rapid and substantial in the TPV/r group

[19] From the TruGene report, viral isolates were "genotypically available" if they were listed as "no evidence of resistance," or "possible resistance." From the Virtual Phenotype report, viral isolates were "genotypically available" if they were listed as "within normal susceptible range or resistance unlikely."

(Figure 6.3.5.3: 1). For the TPV/r group, the peak median change from baseline (LOCF) was -1.53 $\log_{10}$ copies/mL at Week 4. After 24 weeks of treatment, the median change in VL from baseline in the combined RESIST trials was -0.80 $\log_{10}$ copies/mL for the TPV/r group compared to -0.25 for the CPI/r group ($p < 0.0001$).

Table 6.3.5.3: 1 VL change from baseline at Week 24 – RESIST trials (FAS)

	RESIST-1 BI 1182.12				RESIST-2 BI 1182.48				Combined RESIST Trials			
	TPV/r		CPI/r		TPV/r		CPI/r		TPV/r		CPI/r	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Baseline VL [$\log_{10}$ copies/mL]	311	4.81	309	4.84	271	4.84	268	4.81	582	4.83	577	4.82
VL change (LOCF)	311	-0.88	309	-0.28	271	-0.72	268	-0.22	582	-0.80	577	-0.25

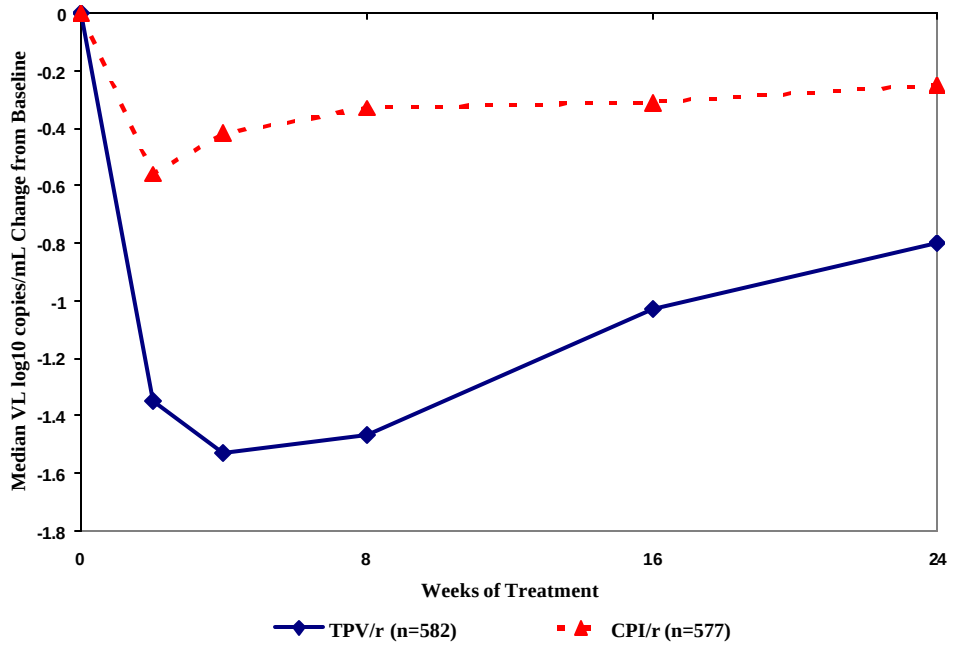

Figure 6.3.5.3: 1 Median log10 copies/mL change from baseline in viral load through Week 24 in combined RESIST trials – (FAS [LOCF])

24-week difference: $p < 0.0001$

6.3.5.4 Virologic response (< 400 and < 50 copies/mL) and immunologic response at 24 weeks (FAS population)

At Week 24, the proportion of patients who achieved a VL < 400 copies/mL was greater among TPV/r patients (34.2%) than CPI/r patients (14.9%), and the proportion of patients who achieved a VL < 50 copies/mL was also greater among TPV/r patients (23.9%) than CPI/r patients (9.4%) (p <0.0001) (Table 6.3.5.4: 1; Figures 6.3.5.4: 1, 6.3.5.4: 2). Slightly larger proportions of CPI/r patients in RESIST-1 achieved responses of < 400 copies/mL and < 50 copies/mL compared with CPI/r patients in RESIST-2.

Table 6.3.5.4: 1 Summary of Week 24 virologic response (< 400 and < 50 HIV RNA copies/mL) and immunologic response – RESIST trials (FAS)

	RESIST-1 BI 1182.12				RESIST-2 BI 1182.48				Combined RESIST Trials			
	TPV/r		CPI/r		TPV/r		CPI/r		TPV/r		CPI/r	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	311	(100.0)	309	(100.0)	271	(100.0)	268	(100.0)	582	(100.0)	577	(100.0)
VL < 400 copies/mL (NCF)	108	(34.7)	51	(16.5)	91	(33.6)	35	(13.1)	199	(34.2)	86	(14.9)
VL < 50 copies/mL (NCF)	78	(25.1)	31	(10.0)	61	(22.5)	23	(8.6)	139	(23.9)	54	(9.4)
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Baseline CD4+ cell count [cells/mm^3]	310	123	309	123	269	175	265	200	579	155	574	158
Absolute change CD4+ cell count [cells/mm^3] (LOCF)	310	36	309	6	269	31	265	1	579	34	574	4

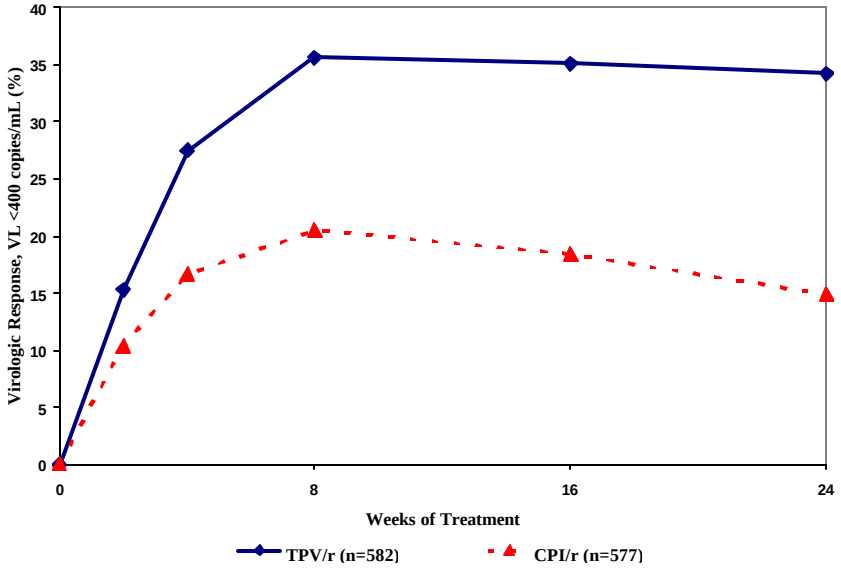

Figure 6.3.5.4: 1 Virologic response (VL < 400 copies/mL) over time through 24 weeks in combined RESIST trials – (FAS [NCF])

24-week difference: p <0.0001

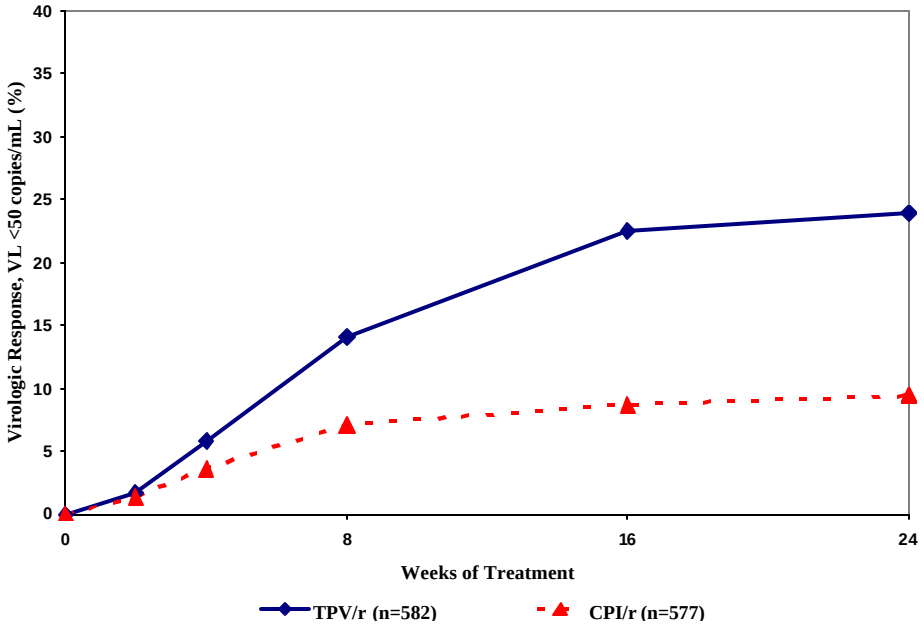

Figure 6.3.5.4: 2 Virologic response (VL < 50 copies/mL) over time through 24 weeks in combined RESIST trials – (FAS [NCF])

24-week difference: p <0.0001

In the combined RESIST trials, TPV/r patients achieved a larger median increase in CD4+ cell count (34 cells/mm^3) than CPI/r patients (4 cells/mm^3) at Week 24 ($p < 0.0001$) (Figure 6.3.5.4: 3). The mean increase in the patients receiving TPV/r was 52 cells/mm^3.

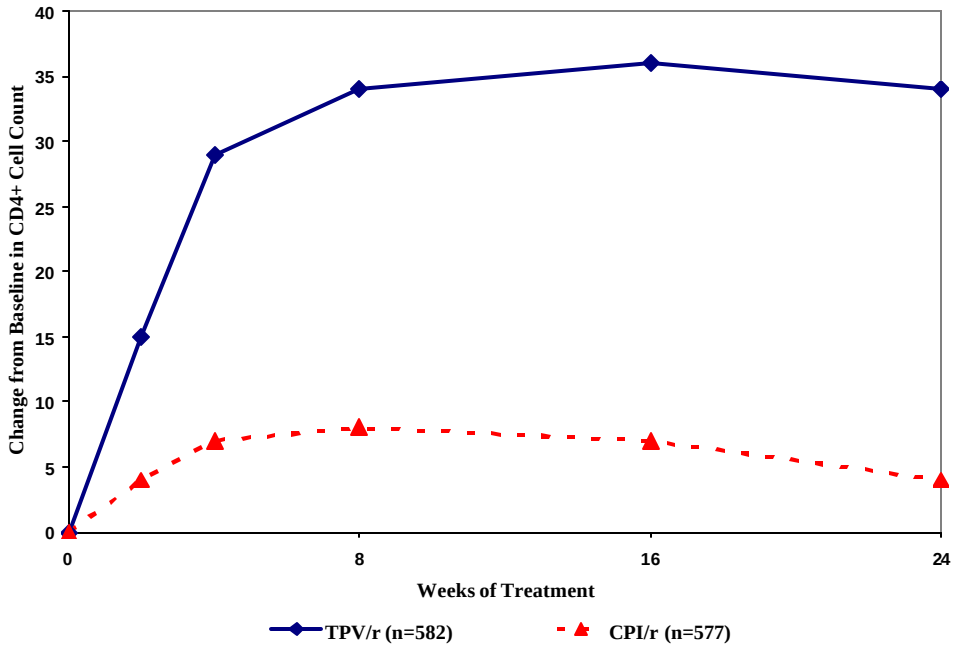

Figure 6.3.5.4: 3 Median change from baseline in CD4+ cell count (cells/mm^3) in combined RESIST trials – (FAS [LOCF])

24-week difference: $p < 0.0001$

6.3.5.5 New onset of AIDS events

In the combined RESIST study population, the proportion of patients who developed a new AIDS event was a secondary efficacy endpoint. The frequency of AIDS events was 3.4% for patients in the TPV/r arms and 4.6% for patients in the CPI/r arms, despite a greater duration of exposure in the TPV/r group. This difference did not achieve statistical significance, an anticipated result as the study was not powered to discriminate between treatment arms for this outcome.

6.3.6 Impact of active background antiretroviral drugs

The OBR of patients in the RESIST trials consisted predominantly of two NRTIs, although some patients received up to 5 NRTIs. Overall, 52-57% of the patients in the RESIST trials

had 2 or more genotypically available background ARVs to support the RTV-boosted protease (tipranavir or comparator) in the regimen.

The genotypic sensitivity score (GSS) was the total number of drugs in the OBR to which a patient's viral isolate showed genotypic sensitivity according to the algorithmic interpretations of the TruGene® or *Virtual Phenotype*™. By pre-established definition, enfuvirtide was always considered genotypically available, even if enfuvirtide had been previously administered, and it therefore counts in the calculation of GSS for those patients who chose to use it as part of their ARV regimen.

Table 6.3.6: 1 Genotypic sensitivity score of the background regimen in patients treated – RESIST trials (FAS)

	Total	
	TPV/r	CPI/r
Total treated	582	577
Genotypic sensitivity score for OBR	N (%)	N (%)
0	61 (10.5)	77 (13.3)
1	190 (32.6)	186 (32.2)
2	236 (40.5)	206 (35.7)
≥ 3	95 (16.3)	108 (18.7)

As noted previously, enfuvirtide use was declared by investigators prior to randomization and it could not be added after study treatment had already been initiated. A total of 286 patients in the RESIST studies used enfuvirtide in their treatment regimen; 27.1% in the TPV/r group (158 of 582) and 22.2% in the CPI/r group (128 of 577).

For patients who used enfuvirtide, there was a higher treatment response than for those who did not use it. The treatment response increased to 58.2% for those on TPV/r who used enfuvirtide and to 25.8% for those on CPI/r who used the drug. For those not taking enfuvirtide, the proportion of treatment responders was also twice as high in the TPV/r group (34.9%) than in the CPI/r group (16.9%).

Even in the absence of enfuvirtide, a treatment response was achieved with TPV/r in more than 40% of patients when used with 2 or more background ARV drugs that were considered genotypically available at baseline to the patient. A comparable response in patients treated with CPI/r was achieved when the CPI/r drug was used with at least three other genotypically available ARVs (GSS $\geq$ 3).

Table 6.3.6: 2 Treatment responses at Week 24 according to enfuvirtide use and number of sensitive background ARVs - RESIST trials (FAS [NCF])

	ENF strata											
	With ENF						Without ENF					
	TPV/r			CPI/r			TPV/r			CPI/r		
	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N
Total	92	(58.2)	158	33	(25.8)	128	148	(34.9)	424	76	(16.9)	449
Genotypic sensitivity score for OBR [a]												
0	34	(57.6)	59	6	(13.6)	44	8	(13.1)	61	7	(9.1)	77
1	37	(55.2)	67	10	(23.8)	42	37	(28.2)	131	18	(12.7)	142
2	17	(68.0)	25	12	(38.7)	31	72	(42.6)	169	31	(18.9)	164
$\geq$ 3	4	(57.1)	7	5	(45.5)	11	31	(49.2)	63	20	(30.3)	66

n = number of responders, N = number of evaluable patients.

[a] ENF not counted; always considered susceptible.

Co-administration of enfuvirtide influenced other categories of virologic response. Within both treatment groups, patients taking enfuvirtide had higher proportions of responders achieving a reduction in VL $\geq$ 1 $\log_{10}$, a VL of < 400 copies/mL, or a VL < 50 copies/mL than patients not taking enfuvirtide.

Changes in VL and CD4+ cell count from baseline to Week 24 were also influenced by enfuvirtide use even though these patients had a higher baseline VL and lower CD4+ cell count. For patients taking enfuvirtide, the median reduction in VL at Week 24 was -2.06 $\log_{10}$ copies/mL in the TPV/r group and -0.40 $\log_{10}$ copies/mL in the CPI/r group; and for patients not taking enfuvirtide the median reduction in VL at Week 24 was -0.57 $\log_{10}$ copies/mL in the TPV/r group and -0.20 $\log_{10}$ copies/mL in the CPI/r group. TPV/r patients taking enfuvirtide had a median increase of 55 cells/mm^3, while TPV/r patients not taking enfuvirtide had a median increase of 27 cells/mm^3; and CPI/r patients taking enfuvirtide had

a median increase of 6 cells/mm^3, while CPI/r patients not taking enfuvirtide had a median increase of 3 cells/mm^3.

Table 6.3.6: 3 Summary of secondary efficacy endpoints at Week 24 according to enfuvirtide use - RESIST trials (FAS)

Endpoint / Genotypic sensitivity score [a]	ENF Strata: With ENF				Without ENF			
	TPV/r		CPI/r		TPV/r		CPI/r	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
VL ≥ 1 $\log_{10}$ reduction (NCF)	93/158	(58.9)	35/128	(27.3)	161/424	(38.0)	83/449	(18.5)
0	0		0		9/61	(14.8)	7/77	(9.1)
1	34/59	(57.6)	6/44	(13.6)	41/131	(31.3)	19/142	(13.4)
2	38/67	(56.7)	10/42	(23.8)	79/169	(46.7)	35/164	(21.3)
≥ 3	21/32	(65.6)	19/42	(45.2)	32/63	(50.8)	22/66	(33.3)
VL < 400 copies/mL (NCF)	71/158	(44.9)	26/128	(20.3)	128/424	(30.2)	60/449	(13.4)
0	0		0		7/61	(11.5)	4/77	(5.2)
1	24/59	(40.7)	5/44	(11.4)	31/131	(23.7)	13/142	(9.2)
2	28/67	(41.8)	9/42	(21.4)	66/169	(39.1)	24/164	(14.6)
≥ 3	19/32	(59.4)	12/42	(28.6)	24/63	(38.1)	19/66	(28.8)
VL < 50 copies/mL (NCF)	48/158	(30.4)	16/128	(12.5)	91/424	(21.5)	38/449	(8.5)
0	0		0		3/61	(4.9)	2/77	(2.6)
1	18/59	(30.5)	4/44	(9.1)	21/131	(16.0)	9/142	(6.3)
2	16/67	(23.9)	3/42	(7.1)	48/169	(28.4)	16/164	(9.8)
≥ 3	14/32	(43.8)	9/42	(21.4)	19/63	(30.2)	11/66	(16.7)
	N	Median	N	Median	N	Median	N	Median
Baseline VL [$\log_{10}$ copies/mL]	158	5.07	128	5.10	424	4.74	449	4.75
VL change [$\log_{10}$ copies/mL] (LOCF)	158	-2.06	128	-0.40	424	-0.57	449	-0.20
Baseline CD4+ cell count [cells/mm^3]	158	72	127	77	421	177	447	182
Absolute change in CD4+ cell count [cells/mm^3] (LOCF)	158	55	127	6	421	27	447	3

a ENF not counted; always considered susceptible.

The number of patients with prior enfuvirtide treatment experience was 69/582 (11.9%) in the TPV/r arms and 68/577 (11.8%) in the CPI/r arms. A greater percentage of those patients without prior enfuvirtide experience achieved a treatment response.

The greatest response was seen in patients who were enfuvirtide naïve and received the combination of TPV/r and enfuvirtide where nearly 70% achieved a treatment response.

Table 6.3.6: 4 Treatment response by prior enfuvirtide use

	TPV/r			CPI/r		
ENF Use	N	%	N	N	%	N
ENF Naive	80	69.6%	115	27	28.7%	94
ENF	12	27.9%	43	6	17.6%	34
No ENF Use						
ENF Naive	146	36.7%	398	73	17.6%	415
ENF	2	7.7%	26	3	8.8%	34

For most participants in the RESIST trials enfuvirtide was a drug from a new class of antiretroviral agents. To characterize the relative contribution of the different components of the regimen started after randomization into RESIST, an ANOVA analysis of the Week 24 viral load change considering treatment group, preselected PI, enfuvirtide use, and genotypic susceptibility to background drugs (other than enfuvirtide) was performed. This analysis confirmed the superiority of TPV/r compared to CPI/r after adjustment for the other factors. The Week 24 viral load reduction attributable to TPV/r over and above the Week 24 viral load reduction attributable to CPI/r was 0.64 $\log_{10}$ copies/mL. Similarly, after controlling for other factors including treatment group, the magnitude of Week 24 viral load reduction attributable to a new class of drug (enfuvirtide) was of approximately the same order of magnitude as that for TPV/r, i.e., 0.67 $\log_{10}$ copies/mL.

6.3.7 Impact of baseline viral load and CD4+ count

In the TPV/r group, the proportion with a treatment response increased from 34.9% in patients with high baseline VL (>100,000-1,000,000 copies/mL) to 56.3% in patients with low baseline VL (1,000-10,000 copies/mL). In the CPI/r group, the proportion of patients with a treatment response was 13.7% and 31.5% in patients with high and low baseline viral loads respectively. In the TPV/r group, the proportion of patients with a treatment response increased from 26.3% for patients in the < 50 cells/mm^3 baseline CD4+ group to 46.0% for

patients in the >350 cells/mm^3 group. In the CPI/r group, the response rate increased from 9.5% for patients in the < 50 cells/mm^3 baseline CD4+ group to 21.2% for patients in the >350 cells/ mm^3 group.

6.3.8 Sensitivity analyses

Multiple sensitivity analyses were conducted to evaluate the potential for bias. One sensitivity analysis explored the influence of protocol violations on the Week 24 treatment responses (PPS [NCF]). In this analysis, only patients who did not have protocol violations or relevant protocol deviations[20] (PPS) were considered in the assessment of Week 24 treatment responses. Consistent with the primary analysis, this analysis showed that a larger proportion of TPV/r patients (44.7%) achieved a treatment response than did CPI/r patients (22.5%). The weighted difference in the proportion of treatment responders was 21.3% and the lower bound of the 95% CI was 14.7% superiority, which again indicated a large treatment effect.

Table 6.3.8: 1 Sensitivity analyses of treatment response at Week 24 – RESIST trials (FAS and PPS[21])

		Treatment Group						Treatment Difference		
			TPV/r			CPI/r		Weighted	95% CI	
Trial	Analysis	n	(%)	N	n	(%)	N	Diff. (%)	LL (%)	UL (%)
1182.12	FAS (NCC)	129	(42.3)	305	69	(23.7)	291	(17.7)	(10.5)	(24.8)
	FAS TPV/r (NCF) CPI/r (NCC)	129	(41.5)	311	69	(23.7)	291	(17.0)	(9.9)	(24.1)
	PPS24 (NCF)	86	(45.0)	191	50	(25.9)	193	(18.5)	(9.3)	(27.6)
1182.48	FASS24, (NCC)	111	(42.4)	262	40	(15.3)	261	(26.1)	(18.7)	(33.4)
	FAS TPV/r (NCF) CPI/r (NCC)	111	(41.0)	271	40	(15.3)	261	(24.6)	(17.4)	(31.9)
	PPSS24 (NCF)	80	(44.4)	180	31	(18.6)	167	(24.6)	(15.4)	(33.8)
Total	FAS (NCC)	240	(42.3)	567	109	(19.7)	552	(21.4)	(16.3)	(26.6)

[20] Relevant protocol deviations were determined by the individual trial teams prior to the unblinding of data and were those that may have potentially affected the primary or secondary endpoint results.
[21] FAS is the 'full analysis set' for all patients who were randomized and received at least one dose of treatment. PPS is the 'per-protocol set' where patients with relevant protocol deviations have been omitted.

		Treatment Group						Treatment Difference		
			TPV/r			CPI/r		Weighted	95% CI	
Trial	Analysis	n	(%)	N	n	(%)	N	Diff. (%)	LL (%)	UL (%)
	FAS TPV/r (NCF) CPI/r (NCC)	240	(41.2)	582	109	(19.7)	552	(20.4)	(15.3)	(25.5)
	PPS (NCF)	166	(44.7)	371	81	(22.5)	360	(21.3)	(14.7)	(27.8)

6.4 EFFICACY RESULTS IN SPECIAL POPULATIONS

Within the TPV/r clinical development program, the highly treatment experienced adult patients in BI 1182.51, who by design harbored more resistant virus (more than 2 mutations at codons 33, 82, 84, or 90), represent an important treatment population. Efficacy results for this trial are summarized here. Direct comparison to the RESIST trials cannot be made, however, due to the fact that different primary endpoints were used. BI 1182.51 was primarily a PK and safety trial with 2- and 4-week efficacy results. Patients in BI 1182.51 were allowed to have background medication adjustments at 4 weeks (after completing the PK portion of the trial), thus interpretation of 24-week efficacy results is limited.

Patients who screened for either of the two RESIST studies but were not able to enrol because they had more than 2 key mutations at codons 33, 82, 84, or 90 in the protease gene were offered TPV/r in a study evaluating the safety and pharmacokinetics of TPV/r of dual boosted PI regimens. Of those who failed screening for the RESIST studies, 315 patients were randomized into BI 1182.51 and received at least one dose of study medication.

At baseline, all patients received an individually selected OBR and were randomized to receive either TPV/r (n = 67) or LPV/r (n = 83), SQV/r (n = 82), or APV/r (n = 83). Fourteen percent of patients pre-selected enfuvirtide as part of the background regimen.

After 2 weeks using one of the four single RTV-boosted regimens, TPV/r was added to patients in the LPV/r, SQV/r, and APV/r treatment arms; patients in the TPV/r control arm either maintained their same drug regimen or had a second PI added to their treatment regimen although the primary trial objective was to evaluate the safety and pharmacokinetics

of dual boosted PI regimens the first 4 weeks of the trial allow for comparison of intrinsic activity of the individual PIs.

Patients in BI 1182.51 tended to have a lower baseline CD4+ count (median 138 compared with 155 cells/mm^3 in the TPV/r group of the combined RESIST trials), a higher baseline viral load (4.97 compared with 4.83 log_{10} copies/mL in the TPV/r group of the combined RESIST trials), and had been exposed to more antiretroviral agents (13 compared with 12 in the TPV/r group of the combined RESIST trials).

During the first 2 weeks of therapy in which patients received a single boosted PI, the median viral load reduction among patients randomized to TPV/r was 1.06 log_{10} copies/mL, while it was below 0.4 log_{10} copies/mL in the 3 other arms (Table 6.4.1: 1 and Figure 6.4.1: 1).

Table 6.4.1: 1 Median Baseline VL [log_{10} copies/mL] change in BI 1182.51 - FAS (LOCF/NCF)

Week	TPV/r [a] N = 67	LPV/r [b] N = 83	SQV/r [b] N = 82	APV/r [b] N = 83
Baseline VL	4.78	4.97	5.02	4.99
2	-1.06	-0.38	-0.19	-0.15
4 [c]	-1.27	-1.19	-0.96	-1.12
8	-0.76	-0.63	-0.54	-0.69
24	-0.28	-0.43	-0.24	-0.47

a Enrollment into the TPV/r arm was halted when the trial monitoring team found that >25% of patients on the TPV/r arm had at Week 4 VL reduction below 0.5 log_{10}. Since the sample size for the primary PK objective was 60, enrollment into the TPV/r arm was stopped.
b TPV/r added after 2 weeks.
c Patients were allowed to switch both background ARVs and PIs after Week 4.

At Week 2, TPV/r was added to the individual PIs and, the virologic response at Week 4 was similar for each of the four treatment arms to that seen for TPV alone during the first 2 weeks of the study. After Week 4, the virologic response began to decay across all treatment arms and after 8 weeks of therapy, there was no significant difference in virologic response across all four treatment arms. Viral load responses diminish after 4 weeks due to a combination of impaired TPV activity and limited active background drugs available to support the TPV/r resulting in the development of viruses resistant to TPV. (Figure 6.4.1: 1).

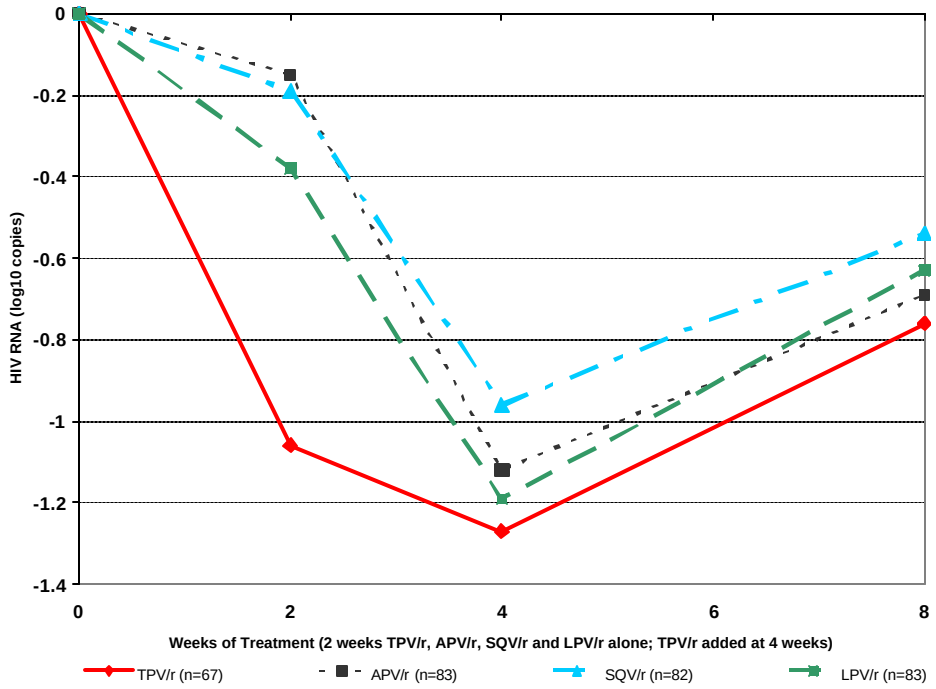

Figure 6.4.1: 1 Reduction in HIV-1 viral load from baseline in each of the four treatment arms in BI 1182.51 during the single boosted and dual boosted PI treatment phases (Weeks 0-8)

6.5 EFFICACY CONCLUSIONS

- TPV/r has proved to be a potent PI in patients who have been previously exposed to 2 or more PI-containing antiretroviral regimens.
- In multiple PI-experienced patients, TPV/r was virologically and immunologically superior to CPI/r across multiple efficacy analyses confirmed by sensitivity analyses of the overall results and for individual randomized CPI comparisons.
- For patients with PI-resistant virus, superior efficacy was demonstrated for TPV/r compared to the best available alternate ritonavir-boosted PI.
- The superior virological and immunological responses seen with TPV/r at 24 weeks were associated with a nonsignificant decrease in AIDS progression events in patients with PI-resistant HIV-1.
- The antiviral effect seen with regimens containing TPV/r is greater in regimens with additional active ARVs (e.g. other genotypically available background drugs, for example enfuvirtide). TPV/r had potent early antiviral responses despite high-level protease inhibitor resistance, but to obtain a durable response with TPV/r additional active background drugs are needed.
- Consistent with established NIH and IAS guidelines for the use of ARV drugs in treatment-experienced patients, knowledge of baseline resistance can be used to choose the optimal background regimen to combine with TPV/r to obtain a durable antiviral response.

7. RESISTANCE

7.1 DEVELOPMENT OF TIPRANAVIR RESISTANCE *IN VITRO*

The development of resistance to tipranavir *in vitro* is slow and complex. In one *in vitro* resistance experiment starting with wild type HIV-1, an HIV-1 isolate that was 87-fold resistant to tipranavir was selected after 9 months and contained 10 mutations in the protease: L10F, I13V, V32I, L33F, M36I, K45I, I54V/T, A71V, V82L, I84V as well as a mutation in the gag polyprotein CA/P2 cleavage site. Reverse genetic experiments showed that the presence of 6 mutations in the protease (I13V, V32I, L33F, K45I, V82L, I84V) was required to confer >10-fold resistance to tipranavir while the full 10-mutation genotype conferred 69-fold resistance to tipranavir.

In vitro, there is an inverse correlation between the degree of resistance to tipranavir and the capacity of viruses to replicate. Recombinant viruses showing $\geq$ 3-fold resistance to tipranavir grow at less than 1% of the rate detected for wild type HIV-1 in the same conditions. Tipranavir-resistant viruses which emerged *in vitro* from wild-type HIV-1 showed decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remained sensitive to saquinavir.

7.2 CLINICAL RESISTANCE (*IN VIVO)*

Current treatment of HIV-1 infection involves the concomitant administration of at least three ARV medications among the classes of non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), PIs, and to a lesser extent HIV entry inhibitors. There are currently eight PIs approved for the treatment of HIV infection. Varying degrees of cross resistance among the PIs approved for HIV therapy have been observed and have resulted in limited options for patients with PI-resistant virus. There is clearly a need for novel PIs with activity against PI-resistant HIV-1 and distinct patterns of PI cross resistance. Tipranavir (TPV) demonstrates unique resistance characteristics that offer potential therapeutic advantages to PI-experienced patients. In a study of 105 highly

PI-resistant viruses at VIRCO, Larder, et. al. showed that 90% remained sensitive to TPV (< 4-fold WT) while only 2% showed high level resistance (> 10-fold WT).[22]

Experiments by Larder, et al also demonstrated that clinical HIV-1 strains resistant to TPV had a high frequency of mutations V82T and I84V. Specifically, two clusters of mutation patterns were identified: V82T with I84V and I84V with L90M (both with numerous secondary mutations). In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with TPV/r treatment are L33F/I/V, V82T/L and I84V. Combination of all three of these mutations is usually required for reduced TPV susceptibility. Mutations at position 82 occur via two pathways: one from pre-existing mutation 82A selecting to 82T, the other from V82-wild type selecting to 82L.

These *in vitro* observations led BI to emphasize analyses of patient responses according to the presence of multiples of mutations at four protease codons: 33, 82, 84, and 90 which were associated with decreased viral load responses to TPV/r in Phase II studies and broad, high level resistance to other available PIs in *in vitro* studies. At various times, these positions have been called "key TPV-associated mutations", "universal protease-associated mutations" (UPAMs), or "protease resistance-associated mutations" (PRAMs). This section will provide a comprehensive review of resistance data obtained from all TPV clinical trials, including evaluation of effect of the genotype on susceptibility phenotype and genotype or phenotype on antiviral responses.

7.3 GENOTYPIC SCORES

HIV drug susceptibility genotyping and phenotyping are the two methods currently in use to determine whether an HIV-1 isolate has decreased susceptibility to ARV agents. With either of these methods, physicians can construct regimens for treatment-experienced patients that provide enhanced antiviral response compared with regimens designed using treatment history alone.

[22] Larder BA, Hertogs K, Bloor S, Eyne C van den, DeCian W, Yenyun W, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS (Phila) 2000;14(13):1943-48.

In the context of the RESIST trials, genotypic resistance testing was performed at screening for all patients. Phenotyping was conducted in a subset of 500 randomly selected baseline plasma samples (400 for patients randomized to TPV/r and 100 for patients randomized to CPI/r). A total of 454 paired genotypic and phenotypic results of screening samples were available for analyses of the relationship between protease mutations and phenotype (phenotyping was unsuccessful for 46 samples). To broaden the range of TPV susceptibilities evaluated, 356 samples from patients in the Phase II program (Trials BI 1182.52 and 1182.51) were added to some analyses. Virologic responses of patients on the 500/200 mg dose of TPV/r in Phase II trials were also included in some response analyses.

To examine the relationship between protease mutations detected by genotypic resistance testing and TPV phenotypic susceptibility results, several patterns of protease inhibitor resistance mutations were investigated:

- *Key protease mutations*: *protease codons* 33, 82, 84, 90
- *TPV score mutations: protease codons* 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V
- *FDA protease mutations: protease codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88, 90*

7.3.1 Key protease mutations (HIV protease codons 33, 82, 84 and 90)

The relationship between the presence of key mutations (mutations at HIV-1 protease codons 33, 82, 84, and 90) and associated change in phenotypic susceptibility to available protease inhibitors was evaluated using the clinical samples from the TPV development program (Table 7.3.1: 1). HIV-1 isolates with one key mutation showed resistance to lopinavir, indinavir, nelfinavir, ritonavir and atazanavir, and decreased susceptibility to saquinavir and amprenavir while TPV had a median susceptibility of 1.1-fold WT. HIV-1 isolates with 2 key mutations demonstrated high level resistance to all currently available PIs but remained susceptible to TPV with a median susceptibility of 1.7-fold WT. Tipranavir susceptibility was

decreased (≥ 3-fold WT) for HIV-1 with protease enzymes containing 3 key mutations and high level resistance (≥ 10-fold WT) usually requires 4 key mutations to be present.

Table 7.3.1: 1 Comparative phenotype of all protease inhibitors tested in Phase II and III TPV trials according to number of key protease mutations

		Protease inhibitor median IC_{50} fold WT							
Number of key mutations 33, 82, 84, 90	N	TPV	LPV	IDV	SQV	APV	NFV	RTV	TAZ
0	82	0.7	1.0	1.1	0.9	0.6	2.3	1.1	1.8
1	232	1.1	49.7	12.2	4.4	4.6	32.4	43.9	13.4
2	371	1.7	90.6	43.5	33.2	15.1	41.8	199.1	76.6
3	112	3.4	102.8	53.9	42.2	30.9	43.1	361.0	102.9
4	13	12.0	100.1	36.7	46.2	32.3	41.7	361.0	95.8

7.3.2 Tipranavir score

Through a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies, mutations at 16 protease codons have been associated with reduced tipranavir susceptibility and/or reduced 2 or 24-week viral load responses: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. As shown in Figure 7.3.2: 1, a number of TPV score mutations have not been previously associated with resistance to other PIs – at codons 13, 35, 43, 58, 69, 74, and 83. Similarly, many IAS-USA mutations are not associated with resistance to TPV – at codons 24, 30, 32, 48, 50, 53, 88, and 90. This may explain the low level of cross resistance between TPV and other currently available protease inhibitors.

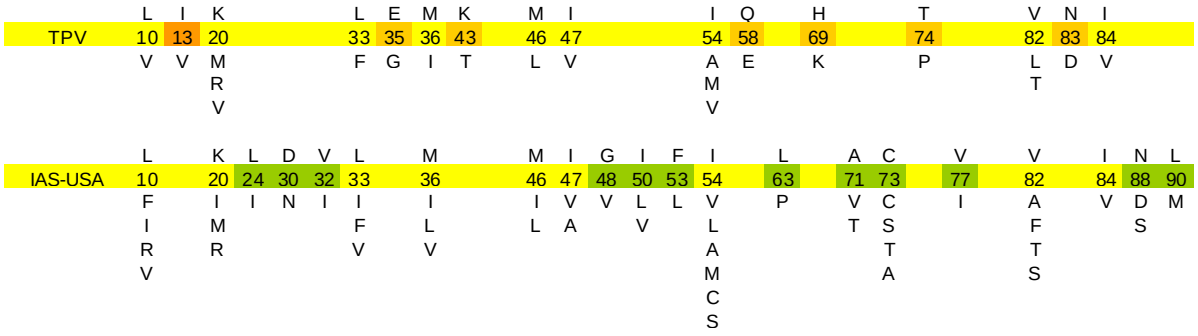

Figure 7.3.2: 1 Comparison of TPV Score Mutations with IAS-USA Mutations for Currently Available Protease Inhibitors

The accumulation of greater than 4 protease mutations among the 16 TPV-associated codons is required to predict decreased phenotypic TPV susceptibility ($\geq$ 3-fold WT) and decreased antiviral responses to TPV. High level resistance to TPV ($\geq$ 10 fold WT) usually requires > 7 TPV-associated mutations. The mutation L90M does not appear to be related to decreased TPV susceptibility or decreased antiviral responses to TPV. V82A, the most common mutation at codon 82 selected by currently available PIs, also does not appear related to TPV susceptibility. L90M when combined with mutations at codons 82 or 84 may be a marker for viruses with multiple associated protease resistance mutations.

7.3.3 FDA protease gene mutations

The FDA protease mutation score was determined by counting any alteration at codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88, 90 in HIV-1 protease as defined by the FDA.

7.4 RELATIONSHIP OF GENOTYPE TO PHENOTYPE

During the course of the Tipranavir Phase II/III clinical development program genotypic resistance testing was performed at screening in all participants. The data presented in this section concern the results of paired genotypic and phenotypic resistance screening sample results for 810 participants. To examine the relationship between protease mutations detected by genotypic resistance testing and TPV phenotypic susceptibility results, the three categories of mutations were used (Table 7.4: 1).

Table 7.4: 1 Median IC_{50} fold change from wild type for TPV by number of mutations in the protease gene among participants in Phase II and III TPV trials

Number of mutations	N	Median TPV Fold Change (IQR)
FDA Protease gene mutations[1]		
0 - 1	75	0.9 (0.5, 1.1)
2 - 3	179	1.0 (0.6, 1.9)
4 - 5	417	1.8 (0.9, 3.7)
6+	139	2.6 (1.0, 6.0)
Key protease mutations[2]		
0	82	0.7 (0.4, 1.0)
1	232	1.1 (0.7, 2.1)
2	371	1.7 (0.9, 3.7)
3	112	3.4 (1.9, 8.4)
4	13	12.0 (2.5, 16.6)
TPV score mutations[3]		
0	80	0.7 (0.4, 1.0)
1	105	0.9 (0.6, 1.4)
2	118	1.1 (0.6, 1.9)
3	159	1.4 (0.7, 2.6)
4	153	2.0 (1.0, 4.1)
5	114	3.1 (1.7, 7.0)
6	49	3.3 (1.6, 8.7)
7	25	3.9 (2.7, 12.5)
8	6	14.7 (4.9, 19.8)
9	1	52.5 (52.5, 52.5)

1 FDA protease mutation: 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88, 90
2 Key protease mutations: 33, 82, 84, and 90.
3 TPV score mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V.

In general, as the number of mutations in the protease gene increased, TPV susceptibility progressively decreased.

In summary, among the 810 screening isolates with paired genotype and phenotype resistance testing from participants in the TPV Phase II and III programs, an increased number of FDA protease mutations were associated with decreased TPV phenotypic susceptibility but despite the presence of a large number of these mutations in the protease gene, the change in TPV phenotypic susceptibility was modest. Counting TPV score mutations or key protease mutations appeared the best predictors of changes in TPV phenotypic susceptibility.

Table 7.4: 2 Relationship of different protease gene scores to TPV susceptibility

Fold-change at baseline in tipranavir IC_{50}	FDA Mutation Score	Key Mutation Score (33, 82, 84, 90)	Tipranavir Score
0 to < 3	1 to 6+	0 to 2	0 to 4
3 to <10	N.A.	3	5 to 7
$\geq$ 10	N.A	4	8+

7.5 IMPACT OF GENOTYPE ON VIROLOGIC RESPONSE

The relationship between screening genotype and VL response was examined for 810 participants on the 500/200 mg dose of TPV/r in the TPV clinical development program with data available at baseline. Virologic responses were evaluated at 2 weeks (for TPV/r antiviral activity) and 24 weeks (for the durability of TPV/r-containing regimens). A problem complicating these analyses is that patients with viruses with higher levels of TPV resistance had very limited options for active background drugs. Thus, lower GSS scores were correlated with higher TPV scores.

Three mutation scores (i.e., FDA protease mutations, TPV score mutations, and key protease mutations) are presented in this section. All response analyses were ITT using all patients with complete data available for the analysis.

Table 7.5: 1 Change in viral load at Weeks 2 and 24 according to baseline genotypic mutations among participants in all Phase II and III trials using the TPV/r 500/200 mg dose

Mutation Category and Count	TPV/r Change in Viral Load from Baseline					
	Week 2 (OT)			Week 24 (LOCF [d])		
	N	Median	(IQR)	N	Median	(IQR)
FDA Protease [a]						
0 - 1	31	-1.09	(-0.58, -1.61)	24	-0.64	(-0.12, -2.34)
2 - 3	162	-1.40	(-0.83, -1.76)	132	-1.65	(-0.47, -2.65)
4 - 5	466	-1.36	(-0.66, -1.86)	397	-0.63	(-0.11, -2.29)
6 +	147	-1.37	(-0.43, -1.85)	135	-0.48	(-0.05, -2.28)
Key protease[b]						
≤ 1	255	-1.35	(-0.77, -1.86)	205	-1.27	(-0.24, -2.62)
2	473	-1.39	(-0.67, -1.83)	402	-0.78	(-0.14, -2.42)
3	68	-1.25	(-0.26, -1.68)	71	-0.24	(0.13 -1.87)
4	10	-1.08	(-0.33, -1.54)	10	-0.33	(-0.14, -0.66)
TPV score [c]						
≤ 1	135	-1.25	(-0.91, -1.78)	114	-2.10	(-0.82, -2.77)
2	112	-1.38	(-0.87, -1.83)	91	-1.30	(-0.31, -2.54)
3	177	-1.36	(-0.72, -1.83)	151	-0.64	(-0.16, -2.29)
4	190	-1.42	(-0.64, -1.87)	156	-0.60	(-0.11, -2.39)
5	112	-1.38	(-0.37, -1.89)	104	-0.30	(0.13 -1.54)
6	56	-1.35	(-0.23, -1.81)	50	-0.51	(-0.05, -1.44)
7	20	-1.06	(-0.18, -1.79)	18	-0.49	(0, -2.84)
8	4	-0.33	(0.11, -0.83)	4	-0.08	(0.01, -0.18)

[a] FDA protease mutations: 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88, 90

[b] Key mutations: 33, 82, 84, and 90.

[c] TPV score mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V.

[d] LOCF: last observation carried forward.

For all three analyses TPV/r-containing regimens showed a median 1.1 to 1.4 $\log_{10}$ copies/mL response except for mutation score cells with very few patients at 2 weeks (Table 7.5: 1). The clearest relationship with reduced HIV RNA responses at 24 weeks was seen with increasing scores with either the key mutations or the TPV score. None-the-less, >25% of patients had a durable 1 log or greater response to TPV-containing regimens, even with 3

key mutations or a TPV score of 7. These results are confirmed in the RESIST trials for viral endpoints of < 400 copies/ml or < 50 copies/ml in Table 7.5: 2 below.

Table 7.5: 2 Summary of TPV/r 24-week virologic response according to baseline genotypic categories in Combined RESIST Trials

Mutation Category and Count	% < 400 Copies (NCF) n/N[a] (%)	% < 50 Copies (NCF) n/N[a] (%)	% 1 $\log_{10}$ Drop from Baseline (NCF) n/N[a] (%)	% 0.5 $\log_{10}$ Drop from Baseline (OT) n/N[a] (%)
Key (33, 82, 84, 90)				
≤ 1	74 / 188 (39.4)	50 / 188 (26.6)	87 / 188 (46.3)	97 / 144 (67.4)
2	121 / 374 (32.4)	86 / 374 (23.0)	161 / 374 (43.0)	192 / 324 (59.3)
3	4 / 18 (22.2)	3 / 18 (16.7)	6 / 18 (33.3)	5 / 15 (33.3)
4	0 / 1 (0.0)	0 / 1 (0.0)	0 / 1 (0.0)	
TPV score[b]				
≤ 1	59 / 104 (56.7)	45 / 104 (43.3)	70 / 104 (67.3)	75 / 89 (84.3)
2	29 / 80 (36.3)	25 / 80 (31.3)	34 / 80 (42.5)	42 / 62 (67.7)
3	38 / 127 (29.9)	26 / 127 (20.5)	48 / 127 (37.8)	56 / 10 (54.4)
4	44 / 139 (31.7)	22 / 139 (15.8)	58 / 139 (41.7)	68 / 123 (55.3)
5	17 / 83 (20.5)	13 / 83 (15.7)	24 / 83 (28.9)	30 / 67 (44.8)
6	7 / 36 (19.4)	4 / 36 (11.1)	13 / 36 (36.1)	16 / 29 (55.2)
7	5 / 12 (41.7)	4 / 12 (33.3)	7 / 12 (58.3)	7 / 10 (70.0)

[a] N = number within the specified genotypic category; n = number (out of N) of patients who achieved the respective virologic response.

[b] TPV score mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V.

7.6 IMPACT OF PHENOTYPE ON VIROLOGIC RESPONSE

For the RESIST trials, the relationship between the change in TPV phenotypic susceptibility at baseline and Week 2 and Week 24 virologic responses was analyzed.

Analyses of treatment response at 24 weeks and viral load responses at 2 and 24 weeks show apparent TPV breakpoints at 3-fold and 10-fold wild type with the clearest dose response relationship in patients who did not receive enfuvirtide (Tables 7.6: 1 and 7.6: 2). In all susceptibility strata, addition of enfuvirtide improved the virologic response seen with TPV/r, especially in the patients with high level TPV resistance.

Table 7.6: 1 Treatment Response [a] at Week 24 for TPV/r by Baseline Tipranavir Susceptibility, Stratified by Enfuvirtide Use, in Combined RESIST Trials

Enfuvirtide Use	Fold-change at baseline in TPV IC_{50}	TPV/r treatment response
No	0 to < 3	75/193 (38.9%)
	3 to < 10	10/53 (18.9%)
	$\geq$ 10	0/12 (00.0%)
Yes	0 to < 3	45/61 (73.8%)
	3 to < 10	12/32 (37.5%)
	$\geq$ 10	5/10 (50.0%)

[a] Treatment response is the composite endpoint of the proportion of patients with two consecutive VL measurements >1 $\log_{10}$ below baseline after 24 weeks without prior (1) evidence of a confirmed virological failure, (2) introduction of a new ARV to the regimen for reasons other than toxicity or intolerance to a background drug, (3) permanent discontinuation of the study drug, (4) death, or (5) loss to follow-up.

Table 7.6: 2 HIV Viral Load Response at Weeks 2 and 24 for TPV/r by Baseline Tipranavir Susceptibility, Stratified by Enfuvirtide Use, in Combined RESIST trials

	TPV/r Change in Viral Load from Baseline					
	2 weeks (OT)			24 weeks (LOCF)		
Fold-change at baseline in tipranavir IC_{50}	N	Median	(IQR)	N	Median	(IQR)
No Enfuvirtide Use						
1 to < 3	176	-1.39	(-0.81, -1.87)	193	-0.66	(-0.16, -2.24)
3 to < 10	50	-0.67	(-0.21, -1.61)	53	-0.32	(+0.03, -0.64)
$\geq$ 10	11	-0.52	(+0.21, -1.03)	12	-0.15	(+0.10, -0.72)
Enfuvirtide included in regimen						
1 to < 3	59	-1.72	(-1.27, -2.22)	61	-2.57	(-1.21, -3.16)
3 to < 10	30	-1.85	(-0.15, -2.38)	32	-0.85	(+0.02, -2.78)
$\geq$ 10	10	-1.70	(-1.07, -2.12)	10	-0.94	(-0.27, -2.77)

7.7 PREDICTORS OF VIRAL LOAD RESPONSE AT 24 WEEKS

A multivariate analysis was conducted of factors that were associated with the viral load responses seen at 24 weeks on TPV/r-containing regimens. Factors associated with an increased viral load reduction were TPV/r, addition of Enfuvirtide, and each additional active NRTI/NNRTI in the regimen. Increasing TPV mutation scores were associated with decreased antiviral responses with each mutation reducing the 24 week viral load response by 0.2 log (Table 7.7: 1).

Table 7.7: 1 Predictors of viral load responses at 24 weeks to TPV/r-containing regimens

	24 weeks	
Parameter	Estimate	P-value
Tipranavir/r	-1.25	<0.01
Enfuvirtide use	-0.91	<0.01
Per available NRTI/NNRTI in background	-0.24	<0.01
Per TPV score mutation	0.17	<0.01

7.8 RESISTANCE CONCLUSIONS

- TPV/r is virologically active against the majority of HIV-1 with broad PI resistance.
- There is a high genetic barrier to resistance with TPV. It takes 3 key protease gene mutations or > 4 TPV-associated mutations to produce decreased susceptibility ($\geq$ 3-fold WT) *in vitro* or reduced antiviral responses in the clinic. High level TPV resistance ($\geq$ 10-fold WT) was seen when all 4 key mutations or > 7 TPV-associated mutations were present.
- Key mutations at PI codons 33, 82, 84, 90 can produce high level resistance to currently available PIs. Viruses with 3 or more key mutations showed $\geq$ 3-fold resistance to TPV/r.
- In viruses from PI-experienced patients, many of the mutations which produce resistance to TPV are different than the mutations that produce drug resistance to currently available PIs. This may explain the diminished cross resistance seen between TPV and other currently available protease inhibitors.
- The predominant emerging mutations with virologic failure in PI-experienced patients receiving TPV/r are 33F/I/V, 82T/L, and 84V.
- The drug resistance pattern which will result from treatment of drug naïve patients is still being evaluated.
- The TPV score, enfuvirtide use, and available NRTI/NNRTI in background are all strong predictors of sustained 24 week virologic response. The associated contribution to VL response was:
  - Tipranavir/r: 1.25 $\log_{10}$ copies/mL increase
  - Enfuvirtide: 0.9 $\log_{10}$ copies/mL increase
  - Per active NRTI/NNRTI in OBR increase: 0.2 $\log_{10}$ copies/mL
  - Per TPV score mutation: 0.2 $\log_{10}$ copies/mL decrease

8. SAFETY

Safety data from the Safety Update utilizing a 30 September 2004 cut-off date are summarized in this section.

8.1 EXPOSURE

Overall, a total of 3,367 HIV-positive patients and 769 HIV-negative subjects have been exposed to TPV/r in clinical trials. Adult HIV-positive patients have been treated with TPV/r in Phase II dose-finding trials (n=579), in a Phase IIb PK/Safety Trial BI 1182.51 (n=315), Phase III RESIST trials (n=748), the rollover Trial BI 1182.17 (n=772) and the Emergency Use/Expanded Access Program (n=879). Seventy-four pediatric HIV-positive patients from Trial BI 1182.14 have also been treated with TPV/r. A total of 1,411 patients have been treated with the TPV/r 500/200 mg dose, and of these 1,206 patients have been exposed for at least 24 weeks.

In the subsequent sections, safety observations from early Phase I and II trials will be summarized, followed by comprehensive comparative analyses of adverse events, serious adverse events, and laboratory abnormalities for the Phase III RESIST trials.

8.2 SAFETY DATA FROM EARLY CLINICAL TRIALS

In Phase I drug interaction studies HIV-negative subjects who were exposed to TPV/r for between 1 to 32 days, 88.3% reported any adverse event, 0.3% (2 subjects) reported any serious adverse event, and 11.1% discontinued due to adverse events. The most common adverse events reported in Phase I and II trial participants were diarrhea, nausea, vomiting, abdominal pain, flatulence, headache, and fatigue. This was found to be consistent with Phase II and III trials, although the frequency of some adverse events was higher in the Phase II trials. The slightly higher frequency of adverse events reported in Phase I and II trials are likely related to lower tolerability thresholds and non-induced hepatic 3A enzyme systems in HIV-negative subjects and the use of an hard filled capsule formulation and higher doses of TPV/r (up to TPV/r 1250/100 mg) in early trials of HIV-positive patients.

Five TPV Phase I studies were conducted prior to full development of QTc regulatory guidance documents. The ECG data collected in these trials were analyzed to understand the potential for ECG abnormalities. No evidence of QTc prolongation was observed in nearly 200 subjects administered TPV/r for up to 32 days.

In a drug interaction study of TPV/r co-administered with ethinyl estradiol and norethindrone, female healthy volunteers experienced rash and arthralgias that resolved upon discontinuation of these medications. This observation of non-serious rash occurring in women receiving ethinyl estradiol with TPV/r was confirmed in Phase III trials of HIV-positive women. Women using estrogens may have an increased risk of non-serious rash.

In Phase II trials in HIV-positive patients who received at least one dose of TPV/r, 85.1% reported any adverse event, 10.8% reported any serious adverse event, and 7.8% discontinued treatment due to adverse events.

The most common laboratory abnormalities noted in Phase I and II trials were elevations in serum transaminases and plasma lipids. An analysis of these trials combining TPV/r doses into groups of TPV/r <500/200 mg, 500/200 mg, and >500/200 mg revealed a dose-related increase in Grade 3 and 4 abnormalities for ALT: 0.8%, 5.7% and 11.8% respectively. Values for AST showed a similar dose dependent pattern (0.8%, 3.3%, 4.9%, respectively). The dose-finding Trial BI 1182.52 showed KM estimated probabilities of Grade 3 or 4 ALT and/or AST abnormalities through 24 weeks of TPV/r treatment for 7.5% of patients treated with TPV/r 500/100 mg, for 11.3% of patients treated with TPV/r 500/200 mg, and for 24.5% of patients treated with TPV/r 750/200 mg. At a constant dose of TPV (500 mg bid), a dose-related risk of Grade 3 or 4 ALT and/or AST abnormalities is apparent with 7.5% of patients treated with RTV 100 mg bid developing Grade 3 or 4 ALT and/or AST abnormalities as compared to 11.3% of patients treated with RTV 200 mg bid for at least 24 weeks. At a constant dose of RTV (200 mg bid), a dose-related risk of Grade 3 or 4 ALT and/or AST abnormalities is apparent with 11.3% of patients treated with TPV 500 mg bid developing Grade 3 or 4 ALT and/or AST abnormalities as compared to 24.5% of patients treated with

TPV 750 mg bid for at least 24 weeks. Most of the hepatic transaminase and plasma lipid elevations were mild and not associated with clinical symptoms, and resolved spontaneously or with treatment discontinuation. No TPV dose relationship with elevated plasma lipid levels was observed in these trials.

The safety signals identified in the Phase I and II TPV/r studies were gastrointestinal adverse events including nausea, vomiting and diarrhea, skin rash, and abnormalities of hepatic transaminases and elevated plasma lipids. The findings also were observed in the Phase III trials.

8.3 CLINICAL SAFETY DATA OF PIVOTAL, ACTIVE-CONTROLLED TRIALS (RESIST-1 AND RESIST-2)

While efficacy analyses focused on RESIST trial patients who reached the Week 24 timepoint cut-off for NDA submission for accelerated approval, safety analyses include all treated patients. For efficacy, 582 patients in the TPV/r group and 577 patients in the CPI/r group were included. Overall however, a total 748 patients received TPV/r 500/200 mg and 737 received CPI/r in the RESIST trials (mainly due to RESIST-2 patients who had reached 16 weeks for European analyses but not 24 weeks for the FDA analyses). For the CPI/r group, doses were as follows: LPV/r 400/100 mg (n=358), IDV/r 800/100 mg (n=23), SQV/r 1000/100 mg or 800/200 mg (n=162), and APV/r 600/100 mg (n=194). All doses were administered twice daily.

A number of factors in the design of the RESIST trials complicate analyses of safety including: the open-label design, the selection of comparator PI based on ARV medication history in addition to resistance data, and the differential dropout from the study arms. The design of the RESIST trials, which allowed patients with documented virological failure – but not adverse events - to leave the CPI/r arm of the study after 8 weeks, confounds comparison of safety between the treatment arms. For the NDA submission analyses at Week 24, 85.7% (639 of 746) patients remained in the TPV/r arm as compared to 48.4% (357 of 737) in the CPI/r arm. This difference continues to increase and at the cut-off for the

Safety Update, 70.1% (524 of 748) patients in the TPV/r group as compared to 31.3% (231 of 737) patients in the CPI/r group remained in the study (Table 8.3: 1).

Table 8.3: 1 Disposition of RESIST trial patients

	NDA Submission		Safety Update	
Disposition:	TPV/r	CPI/r[a]	TPV/r	CPI/r[a]
Total Treated	746 (100.0)	737 (100.0)	748 (100.0)	737 (100.0)
Currently Continuing in Trials	639 (85.7)	357 (48.4)	524 (70.1)	231 (31.3)
Prematurely Discontinued	107 (14.3)	380 (51.6)	224 (29.9)	506 (68.7)
Adverse Event	56 (7.5)	27 (3.7)	78 (10.4)	35 (4.7)
Non-compliant with Protocol	8 (1.1)	15 (2.0)	16 (2.1)	22 (3.0)
Lost to Follow-up	5 (0.7)	4 (0.5)	5 (0.7)	5 (0.7)
Consent Withdrawn	6 (0.8)	5 (0.7)	8 (1.1)	6 (0.8)
Lack of Efficacy	22 (2.9)	248 (33.6)	68 (9.1)	316 (42.9)
Other	7 (0.9)	18 (2.4)	15 (2.0)	29 (3.9)
Missing	3 (0.4)	63 (8.5)	34 (4.5)	93 (12.6)

a CPI/r = LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, and APV/r 600/100; all doses in mg.

Of the 43% (316 of 737) of patients who left the comparator arm of the RESIST trials, 298 (94%) rolled over into Trial BI 1182.17 and received TPV/r. Patients leaving the CPI/r arm of the trial due to virological failure had lower median CD4+ counts (117 cells/mm^3) and higher viral loads (4.8 $\log_{10}$ copies/mL) compared to patients remaining in the trial on CPI/r (median CD4+ count of 238 cells/mm^3; viral load 3.7 $\log_{10}$ copies/mL). Thus, patients remaining in the comparator arm of the study were more immune competent, on average, than patients originally randomized into the RESIST trials, or patients remaining on TPV/r. As a result, comparisons of TPV/r and CPI/r safety data beyond the first 8 weeks of treatment should be interpreted cautiously.

The number of patients stopping trial participation due to an adverse event was twice as frequent in the TPV/r group (10.4%) as in the CPI/r group (4.7%). However, these data may have been influenced by entry criteria that allowed patients with virological failure, but not adverse events leading to CPI/r discontinuation, to rollover to Trial BI 1182.17.

8.3.1 Exposure and disposition

In the Safety Update, exposure for the TPV/r group represents 615.0 person exposure years (PEY) while exposure for the CPI/r group represents 405.7 PEY, an exposure difference of 50%. The large difference exposure after 8 weeks between the TPV/r and CPI/r treatment groups occurred largely from patients who virologically failed the CPI/r regimen and exited the trial to receive TPV/r in the open label rollover Trial BI 1182.17 (Table 8.3: 1 and Figure 8.3.1: 1). Nearly 50% of TPV/r patients have been treated for at least 48 weeks, although not all patients have had the opportunity to achieve the 48 week milestone by the Safety Update cut-off (Table 8.3.1: 1).

Table 8.3.1: 1 Treatment exposure to trial medication in the RESIST trials at time of NDA submission and in Safety Update

	NDA Submission		Safety Update	
Duration:	TPV/r	CPI/r[a]	TPV/r	CPI/r[a]
Total treated [N (%)]	746 (100.0)	737 (100.0)	748 (100.0)	737 (100.0)
≥ 8 weeks	713 (95.6)	703 (95.4)	715 (95.6)	703 (95.4)
≥ 16 weeks	665 (89.1)	526 (71.4)	683 (91.3)	536 (72.7)
≥ 24 weeks	385 (51.6)	245 (33.2)	645 (86.2)	395 (53.6)
≥ 32 weeks	--	--	576 (77.0)	285 (38.7)
≥ 48 weeks	--	--	354 (47.3)	135 (18.3)
Median [days]	168.0	124.0	330.0	172.0
Range [days]	1 - 274	1 – 313	1 - 523	1 - 511
Total person exposure years[b]	300.3	264.6	615.0	405.7

a CPI/r = LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, and APV/r 600/100; all doses in mg.
b Definition of total person exposure years [PEY]: (sum of total duration across all patients)/365.25.

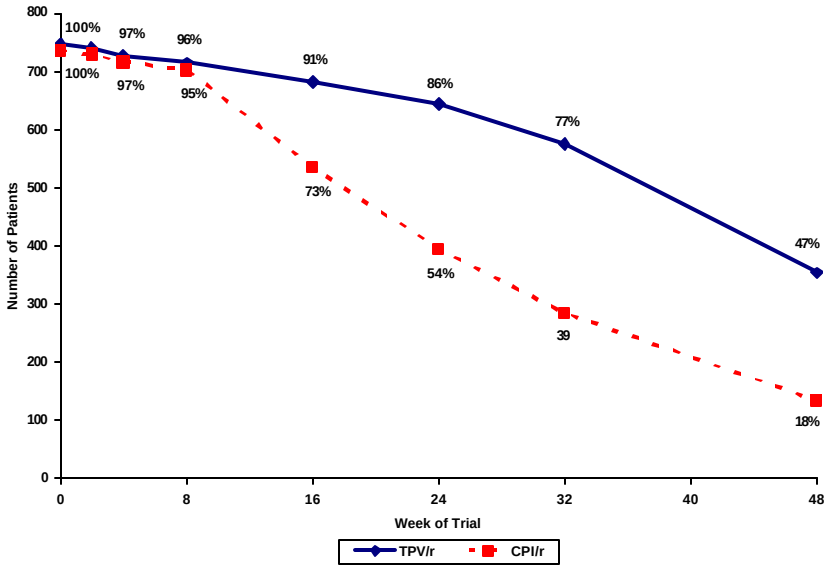

Figure 8.3.1: 1 Patients remaining in the RESIST trials by treatment group up to 48 weeks

8.3.2 Adverse Events in RESIST trials

In the following sections, comparative frequencies of the most commonly reported adverse events as reported in the Safety Update for TPV/r and CPI/r patients in the RESIST trials are displayed. The order of presentation is: (1) adverse events of any severity considered related to study treatment, (2) serious adverse events, and (3) adverse events leading to study drug discontinuation.

Adverse events of any severity in RESIST trials

According to BI standards, intensity of adverse events was collected using a mild, moderate, severe scale. Investigators were provided the DAIDS grading scale and graded adverse events as follows: mild = DAIDS Grade 1, moderate = Grade 2, severe = Grade 3 or 4.

The TPV/r group had a higher overall percentage of patients reporting study drug-related adverse events of any severity: 41.7% compared with 27.8% in the CPI/r group. In general, for study drug-related adverse events, no major differences were observed between the 2 treatment groups. The only adverse events with >2% differences between TPV/r and CPI/r were diarrhea, nausea, and headache.

Table 8.3.2: 1 Study drug-related adverse events occurring in 1% or more of RESIST trial patients in either treatment group in the Safety Update

SOC / Preferred Term	Unadjusted Rate		Crude adjusted rate per 100 PEY	
	TPV/r [a]	CPI/r [a]	TPV/r	CPI/r
Total Treated or Total Exposure	748 (100.0)	737 (100.0)	615 PEY	405.7 PEY
Total with Any AE	**361 (48.3)**	**220 (29.9)**	**361 (58.7)**	**220 (54.2)**
Gastrointestinal Disorders	**233 (31.1)**	**161 (21.8)**	**233 (37.9)**	**161 (39.7)**
Diarrhea	109 (14.6)	84 (11.4)	109 (17.7)	84 (20.7)
Nausea	93 (12.4)	62 (8.4)	93 (15.1)	62 (15.3)
Vomiting	32 (4.3)	23 (3.1)	32 (5.2)	23 (5.7)
Abdominal Pain	19 (2.5)	20 (2.7)	19 (3.1)	20 (4.9)
Flatulence	23 (3.1)	15 (2.0)	23 (3.7)	15 (3.7)
Abdominal Distension	20 (2.7)	13 (1.8)	20 (3.3)	13 (3.2)
Abdominal Pain Upper	8 (1.1)	8 (1.1)	8 (1.3)	8 (2.0)
Loose Stools	12 (1.6)	9 (1.2)	12 (2.0)	9 (2.2)
Dyspepsia	8 (1.1)	6 (0.8)	8 (1.3)	6 (1.5)
Nervous System Disorders	**53 (7.1)**	**39 (5.3)**	**53 (8.6)**	**39 (9.6)**
Headache	28 (3.7)	9 (1.2)	28 (4.6)	9 (2.2)
Dizziness	11 (1.5)	7 (0.9)	11 (1.8)	7 (1.7)
General Disorders	**49 (6.6)**	**32 (4.3)**	**49 (8.0)**	**32 (7.9)**
Fatigue	34 (4.5)	19 (2.6)	34 (5.5)	19 (4.7)
Metabolism and Nutrition	**61 (8.2)**	**30 (4.1)**	**61 (9.9)**	**30 (7.4)**
Anorexia	8 (1.1)	7 (0.9)	8 (1.3)	7 (1.7)
Hypertriglyceridemia	24 (3.2)	6 (0.8)	24 (3.9)	6 (1.5)
Hyperlipidemia	17 (2.3)	4 (0.5)	17 (2.8)	4 (1.0)
Skin	**46 (6.1)**	**27 (3.7)**	**46 (7.5)**	**27 (6.7)**
Rash	13 (1.7)	7 (0.9)	13 (2.1)	7 (1.7)
Pruritus	11 (1.5)	3 (0.4)	11 (1.8)	3 (0.7)
Investigations	**48 (6.4)**	**10 (1.4)**	**48 (7.8)**	**10 (2.5)**
ALT increased	17 (2.3)	1 (0.1)	17 (2.8)	1 (0.2)
AST increased	12 (1.6)	1 (0.1)	12 (2.0)	1 (1.2)
GGT increased	13 (1.7)	1 (0.1)	13 (2.1)	1 (0.2)
Triglycerides increased	9 (1.2)	4 (0.5)	9 (1.5)	4 (1.0)

a BID Doses: TPV/r 500/200; CPI/r: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or 800/200, APV/r 600/100.

The frequency of adverse events for each of the individual protease inhibitors in the CPI/r group was examined and the highest percentage of patients with study drug-related adverse

events was 34.6% in the SQV/r group compared with 25.3% in the APV/r group and 25.1% in the LPV/r groups. There were only 23 patients in the IDV/r group, thus no comparisons for this group were made. The SQV/r group had the highest percentage of patients with study drug-related gastrointestinal adverse events: 26.5% compared with 19.1% and 19.0% in the APV/r and LPV/r groups, respectively. In addition, the SQV/r group had the highest percentage of patients with study drug-related nervous system disorder adverse events: 7.4% compared with 6.2% and 3.6% in the APV/r and LPV/r groups, respectively. The APV/r group had the highest percentage of patients (4.6%) with study drug-related skin and subcutaneous disorder adverse events (1.1% in the LPV/r group and 2.5% in the SQV/r group).

Diarrhea was self-limiting, manageable, and similar across both treatment arms in the RESIST studies. Frequencies of patients with diarrhea were higher in the Phase II trials likely due to the higher doses of TPV used in early Phase II trials.

Although individual variability in the type and frequency of adverse events was observed in evaluation of adverse events by age, gender, race and geographic location, clinically, no unusual adverse event patterns or other safety concerns were identified in the RESIST trials that would suggest that TPV/r should be restricted or have the dose adjusted based on these factors.

Severe adverse events in RESIST trials

Severe adverse events (DAIDS Grade 3 to 4) were reported in 16.1% of the 1483 patients; the most frequently reported severe adverse event was diarrhea (TPV/r, 1.3%; CPI/r, 1.8%).

8.3.3 Serious adverse events

SAEs in the RESIST trials

In the Safety Update of RESIST trials, 18.9% of patients in the TPV/r arm as compared to 14.7% of patients in the CPI/r arm experienced SAEs, regardless of causality. The most frequently observed SAEs were in the infections and infestations system organ class (SOC). Most events were associated with advanced HIV disease and were comparable between the

two treatment groups. Many of the excess SAEs seen with TPV/r are no longer present after exposure adjustment. The SAEs which remain more prevalent with TPV/r are in the general disorders, metabolism and investigations SOC (Table 8.3.3: 1).

Table 8.3.3: 1 Any Serious Adverse Events occurring in 0.5% or more of RESIST trial patients in the Safety Update

	Unadjusted Rate		Crude adjusted rate per 100 PEY	
SOC / Preferred Term	TPV/r[a]	CPI/r[a]	TPV/r	CPI/r
Total Treated or Total Exposure	748 (100.0)	737 (100.0)	615 PY	405.7 PY
Total with Any SAE	**141 (18.9)**	**108 (14.7)**	**141 (22.9)**	**108 (26.6)**
Infections and Infestations	**53 (7.1)**	**49 (6.6)**	**53 (8.6)**	**49 (12.1)**
Pneumonia	10 (1.3)	5 (0.7)	10 (1.6)	5 (1.2)
Gastroenteritis	4 (0.5)	1 (0.1)	4 (0.7)	1 (0.2)
CMV Chorioretinitis	4 (0.5)	2 (0.3)	4 (0.7)	2 (0.5)
Esophageal Candidiasis	4 (0.5)	5 (0.7)	4 (0.7)	5 (1.2)
PCP Pneumonia	4 (0.5)	3 (0.4)	4 (0.7)	3 (0.7)
PML	1 (0.1)	4 (0.5)	1 (0.2)	4 (1.0)
General Disorders	**30 (4.0)**	**18 (2.4)**	**30 (4.9)**	**18 (4.4)**
Pyrexia	17 (2.3)	11 (1.5)	17 (2.8)	11 (2.7)
Rigors	4 (0.5)	0 (0.0)	4 (0.7)	0 (0.0)
Gastrointestinal Disorders	**27 (3.6)**	**18 (2.4)**	**27 (4.4)**	**18 (4.4)**
Diarrhea	9 (1.2)	5 (0.7)	9 (1.5)	5 (1.2)
Pancreatitis	4 (0.5)	0 (0.0)	4 (0.7)	0 (0.0)
Abdominal Pain	4 (0.5)	1 (0.1)	4 (0.7)	1 (0.2)
Vomiting	4 (0.5)	3 (0.4)	4 (0.7)	3 (0.7)
Metabolism and Nutrition	**14 (1.9)**	**7 (0.9)**	**14 (2.3)**	**7 (1.7)**
Dehydration	8 (1.1)	3 (0.4)	8 (1.3)	3 (0.7)
Respiratory Disorders	**14 (1.9)**	**10 (1.4)**	**14 (2.3)**	**10 (2.5)**
Dyspnea	3 (0.4)	4 (0.5)	3 (0.5)	4 (1.0)
Nervous System Disorders	**13 (1.7)**	**14 (1.9)**	**13 (2.1)**	**14 (3.5)**
Headache	5 (0.7)	2 (0.3)	5 (0.8)	2 (0.5)
Investigations	**11 (1.5)**	**5 (0.7)**	**11 (1.8)**	**5 (1.2)**
ALT Increased	5 (0.7)	0 (0.0)	5 (0.8)	0 (0.0)
Renal and Urinary Disorders	**11 (1.5)**	**5 (0.7)**	**11 (1.8)**	**5 (1.2)**
Renal Failure Acute	5 (0.7)	2 (0.3)	5 (0.8)	2 (0.5)
Psychiatric Disorders	**4 (0.5)**	**8 (1.1)**	**4 (0.7)**	**8 (2.0)**
Depression	1 (0.1)	5 (0.7)	1 (0.2)	5 (1.2)
Blood and Lymphatic System	**8 (1.1)**	**10 (1.4)**	**8 (1.3)**	**10 (2.5)**
Anemia	4 (0.5)	7 (0.9)	4 (0.7)	7 (1.7)

a BID Doses: TPV/r 500/200; CPI/r: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or 800/200, APV/r 600/100.

Based on the data in the comparative RESIST trials, there are no indications that TPV/r therapy contributes to more SAEs or has a unique safety profile compared with other ritonavir-boosted PIs.

8.3.4 Adverse events leading to discontinuation of treatment

In the RESIST trials, 12.3% of patients in the TPV/r group and 4.9% of patients in the CPI/r group experienced adverse events which led to study drug discontinuation (Table 8.3.4: 1).

The SOC with the highest percentage of patients with adverse events leading to discontinuation of study medication was the gastrointestinal disorders SOC (4.5% TPV/r and 3.0% CPI/r).

The percentages of patients with adverse events leading to discontinuation of study medication were consistently higher in the TPV/r group. While numbers were small, it should be noted that the TPV/r group had many more patients discontinuing with events in the SOC of investigations (TPV/r 2.7%, CPI/r 0.1%), and this difference between treatment groups remained with crude adjustment for exposure. The investigations SOC includes laboratory test abnormality events which are discussed in detail in the laboratory data section.

The most frequently reported adverse events leading to discontinuation of study medication in the RESIST trials consisted of the following: nausea (1.7% TPV/r, 1.1% CPI/r), diarrhea (1.7% TPV/r, 1.1% CPI/r), vomiting (1.1% in both TPV/r and CPI/r groups), and increased ALT (0.9% TPV/r, 0.0% CPI/r). All other adverse events leading to discontinuation of study medication occurred in ≤0.5% of all patients (≤ 4 patients).

Table 8.3.4: 1 Adverse events leading to discontinuation of study medication in 3 or more RESIST trial patients in the Safety Update

	Unadjusted rate		Crude adjusted rate per 100 PEY	
	TPV/r[a]	CPI/r[a]	TPV/r	CPI/r
Total Treated or Total Exposure	748 (100.0)	737 (100.0)	615 PY	405.7 PY
Total with Any AE Leading to Discontinuation	**92 (12.3)**	**47 (6.4)**	**92 (15.0)**	**47 (11.6)**
Gastrointestinal Disorders	**34 (4.5)**	**22 (3.0)**	**34 (5.5)**	**22 (5.4)**
Nausea	13 (1.7)	8 (1.1)	13 (2.1)	8 (2.0)
Vomiting	8 (1.1)	8 (1.1)	8 (1.3)	8 (2.0)
Diarrhea	13 (1.7)	8 (1.1)	13 (2.1)	8 (2.0)
Abdominal Pain	2 (0.3)	4 (0.5)	2 (0.3)	4 (1.0)
Investigations	**20 (2.7)**	**1 (0.1)**	**20 (3.3)**	**1 (0.2)**
ALT Increased	7 (0.9)	0 (0.0)	7 (1.1)	0 (0.0)
AST Increased	3 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)
GGT Increased	4 (0.5)	0 (0.0)	4 (0.7)	0 (0.0)
Hepatic Enzyme Increased	3 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)
Triglycerides Increased	3 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)
General Disorders	**15 (2.0)**	**7 (0.9)**	**15 (2.4)**	**7 (1.7)**
Fatigue	4 (0.5)	1 (0.1)	4 (0.7)	1 (0.2)
Pyrexia	4 (0.5)	3 (0.4)	4 (0.7)	3 (0.7)
Metabolism and Nutrition	**11 (1.5)**	**6 (0.8)**	**11 (1.8)**	**6 (1.5)**
Anorexia	4 (0.5)	1 (0.1)	4 (0.7)	1 (0.2)
Hepatobiliary Disorders	**9 (1.2)**	**1 (0.1)**	**9 (1.5)**	**1 (0.2)**
Cytolytic Hepatitis	2 (0.3)[b]	0 (0.0)	2 (0.3)	0 (0.0)
Skin Disorders	**7 (0.9)**	**5 (0.7)**	**7 (1.1)**	**5 (1.2)**
Rash	4 (0.5)	1 (0.1)	4 (0.7)	1 (0.2)

a BID Doses: TPV/r 500/200; CPI/r: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or 800/200, APV/r 600/100.

The rate of discontinuation from the trial is slightly higher in the TPV/r group than the CPI/r group, but this rate is offset by the high rate of discontinuations due to virologic failure in the CPI/r group, leaving a disproportionately higher number of patients on TPV/r treatment in the RESIST trials.

There were no new or unexpected events identified that lead to discontinuation of study medication in the RESIST trials; data are consistent to early Phase II findings.

8.3.5 Exploratory analyses of medically selected terms

An exploratory analysis of adverse events was conducted to evaluate PI-specific class effects (e.g., fat redistribution), events warranting evaluation because of preclinical or early clinical

experience with TPV/r (e.g., hepatitis, bleeding, rash), or identified as issues of concern for the development of any drug product or effects of concern for the development of any drug product (e.g., QTc prolongation). For this analysis, a broad range of preferred terms were included to comprise each medically selected term (MST); the MST name is a descriptor of the preferred terms and only one of the collection of preferred terms, thus the MST name is used with quotes (" ") around the term.

Figure 8.3.5: 1 summarizes the relative risk of individual Medically Selected Terms observed with TPV/r as compared to CPI/r in the NDA Summary of Clinical Safety (SCS) and in the Safety Update. In the Safety Update population there was no overall increased risk for TPV/r compared to the CPI/r of "hyperglycemia," "ischemic heart disease," "pancreatitis", "rash", "renal failure" and "QTc prolongation" events. The relative risk (RR) of these MSTs ranged from 0.44 to 1.00, however, these measures were moderately precise.

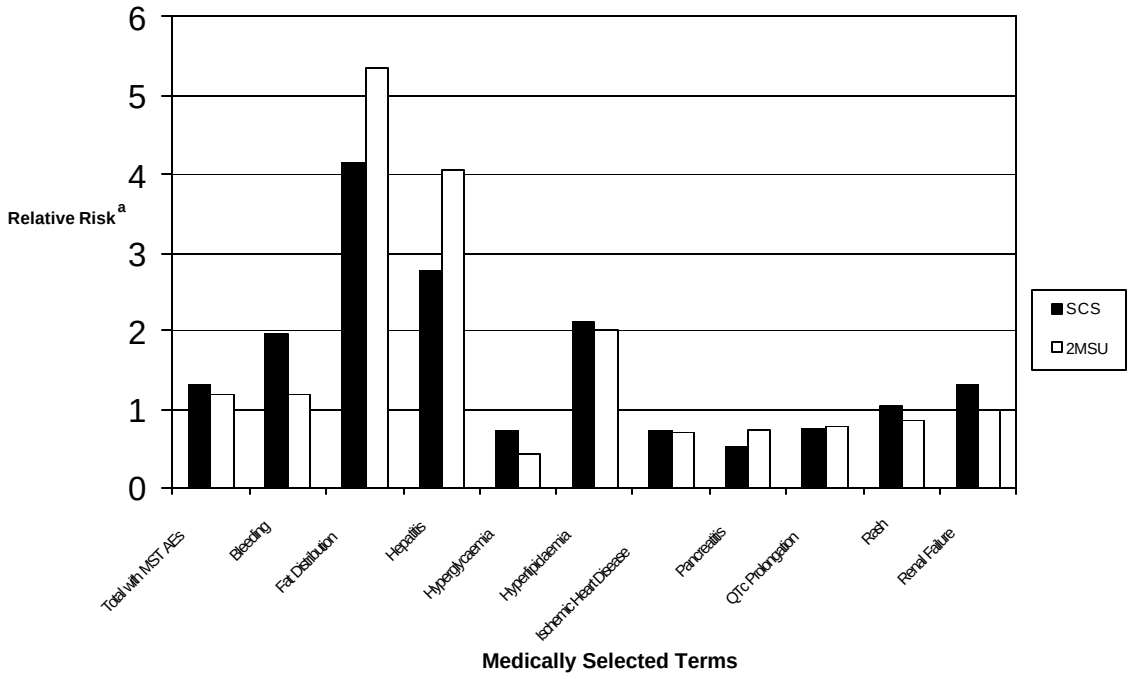

Figure 8.3.5: 1 Relative risk of medically selected term adverse events between treatment groups in RESIST trials: Comparison of NDA Summary of Clinical Safety and Safety Update populations

a Relative risk = TPV/r to CPI/r.

The overall relative risk of "bleeding" events decreased from 1.98 (95% CI = 1.03, 3.80) in the Summary of Clinical Safety population to 1.19 (95% CI = 0.67, 2.12) in the Safety Update population. There appears to be no consistent pattern of "bleeding" events. There are no notable differences between treatment groups in Grade 3 or 4 laboratory parameters for decreased hemoglobin, decreased platelets, or prolonged PT (see laboratory section). Overall, there seems to be normalization of the relative risk of bleeding between the TPV/r and CPI/r arm with the Safety Update.

The RESIST trials evaluated a highly PI-experienced patient population, with many patients entering the trials with significant lipodystrophy. In the Safety Update, TPV/r patients continue to have a greater risk of "fat redistribution" than CPI/r patients. The ultimate impact of TPV/r on "fat redistribution" will need to be assessed with longer term data from the

RESIST trials and a metabolic substudy including DEXA exams in Trial BI 1182.33 of treatment naïve HIV-positive patients.

Elevated liver enzymes (ALT/AST) and clinical "hepatitis" were more common in patients receiving TPV/r than patients receiving CPI/r. This will be described in the laboratory section below.

"Hyperlipidemia" was more common in TPV/r patients than CPI/r patients. These lipid elevations were not associated with increased rates of "pancreatitis" or "ischemic heart disease". Given the short duration of follow-up, it is not possible to draw definitive conclusions regarding risk of potential long term sequelae of elevated plasma lipids, e.g. ischemic heart disease. Long term follow-up data will be needed to adequately assess this potential risk.

Treatment with TPV/r does not appear to increase the risk of "rash" compared to other ritonavir-boosted PIs. However, based on the signal from the Phase I drug interaction study of oral contraceptive use in women and analyses conducted on the Phase III RESIST data, patients with lower CD4+ counts and women using estrogens appear to be at greater risk of developing non-serious rashes.

8.4 LABORATORY EVALUATIONS OF PIVOTAL, ACTIVE-CONTROLLED TRIALS (RESIST-1 AND RESIST-2)

An evaluation of DAIDS Grade 3 and 4 laboratory abnormalities, including assessments of risk factors and patterns of elevations, is presented in this section.

8.4.1 Overview of DAIDS Grade 3 and 4 Laboratory Abnormalities in the Safety Update

For the hematology parameters, with the exception of Grade 3 or 4 decreased WBC in 4.9% of TPV/r patients and 5.5% of CPI/r patients, few patients had hematology abnormalities (Table 8.4.1: 1). For most chemistry analytes, Grade 3 or 4 abnormalities were relatively few and similar between treatment groups, with the exception of ALT, AST, total cholesterol and triglycerides.

Table 8.4.1: 1 DAIDS Grade 3 or 4 laboratory abnormalities in the RESIST trials, reported in the Safety Update

	TPV/r N=733			CPI/r N=737		
Laboratory Test	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Hematology						
Haemoglobin	2 (0.3)	1 (0.1)	3 (0.4)	2 (0.3)	0 (0.0)	2 (0.3)
WBC Count (decrease)	34 (4.6)	2 (0.3)	36 (4.9)	32 (4.4)	8 (1.1)	40 (5.5)
Platelets	5 (0.7)	3 (0.4)	8 (1.1)	6 (0.8)	1 (0.1)	7 (1.0)
Prothrombin Time	6 (0.8)	2 (0.3)	8 (1.1)	6 (0.8)	2 (0.3)	8 (1.1)
Chemistry						
ALT	38 (5.2)	28 (3.8)	66 (9.0)	12 (1.7)	4 (0.6)	16 (2.2)
AST	34 (4.6)	10 (1.4)	44 (6.0)	11 (1.5)	3 (0.4)	14 (1.9)
ALT and/or AST	44 (6.0)	28 (3.8)	72 (9.8)	17 (2.3)	5 (0.7)	22 (3.0)
Bilirubin, Total	3 (0.4)	2 (0.3)	5 (0.7)	3 (0.4)	1 (0.1)	4 (0.6)
Alkaline phosphatase	3 (0.4)	0 (0.0)	3 (0.4)	1 (0.1)	1 (0.1)	2 (0.3)
Amylase	40 (5.5)	2 (0.3)	42 (5.7)	45 (6.2)	5 (0.7)	50 (6.9)
Lipase	17 (2.3)	2 (0.3)	19 (2.6)	15 (2.1)	3 (0.4)	18 (2.5)
Total Cholesterol	22 (3.0)	7 (1.0)	29 (4.0)	2 (0.3)	1 (0.1)	3 (0.4)
Triglycerides	117 (16.0)	53 (7.2)	170 (23.2)	59 (8.1)	30 (4.1)	89 (12.2)
Glucose (increase)	11 (1.5)	2 (0.3)	13 (1.8)	7 (1.0)	1 (0.1)	8 (1.1)
Glucose (decrease)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.4)
Creatinine	2 (0.3)	0 (0.0)	2 (0.3)	1 (0.1)	0 (0.0)	1 (0.1)

a Total number of patients with Grade 3 or 4 elevations as worst intensity during 24 weeks. For inclusion in this analysis both a baseline and at least one on-treatment lab value had to be present.

b Grade (DAIDS or BI) and lab value units: ALT or AST Grade 3 = >5.0 - 10.0 x ULN or 201 – 400 U/L; Grade 4 = >10.0 x ULN or >400 U/L; Total bilirubin Grade 3 = >2.5 – 5.0 x ULN or >3.0 – 6.0 mg/dl; Grade 4 = >5.0 x ULN or >6.0 mg/dl; Total cholesterol Grade 3 = 400 – 500 mg/dl; Grade 4 - >500 mg/dl; Fasting triglycerides Grade 3 = 751-1200 mg/dl; Grade 4 = >1200 mg/dl.

8.4.2 Hepatic transaminase elevations in the Safety Update

8.4.2.1 Evaluation of ALT and/or AST abnormalities

In the Safety Update, Grade 3 or 4 ALT and/or AST combined (ALT/AST) abnormalities were found in 72 (9.8%) of 733 patients in the TPV/r group compared to 26 (3.6%) of 727 patients in the CPI/r group. Two additional patients in the TPV/r group were found to have Grade 3 total bilirubin. Grade 4 ALT/AST abnormalities were found in 28 (3.8%) of 733 patients in the TPV/r group compared to 5 (0.7%) of 727 patients in the CPI/r group.

The relative risk of Grade 3 or 4 ALT/AST abnormalities (Table 8.4.2.1: 1), adjusted for patient exposure years to study medication, was higher in the TPV/r group compared to CPI/r group (RR=2.41, 95% CI 1.49, 3.88).

The Kaplan-Meier (K-M) estimates of the time to first Grade 3 or 4 ALT/AST laboratory abnormalities up to 48 weeks are shown in Figure 8.4.2.1: 1. The K-M cumulative probability for Grade 3 or 4 ALT/AST in the TPV/r group was 10.3% at 48 weeks; while the cumulative probability for Grade 3 or 4 ALT/AST in the CPI/r group was 3.9% at 48 weeks ($p = 0.0002$, log rank test).

The K-M cumulative probability of developing Grade 4 ALT/AST abnormalities at 48 weeks was 4.2% in the TPV/r group compared to 0.9% in the CPI/r group ($p = 0.0014$, log rank test).

Table 8.4.2.1: 1 Number and cumulative probability of DAIDS Grade 3 or 4 ALT or AST abnormalities in RESIST trials

Weeks in Trial	TPV/r		CPI/r	
	No. (%) Patients with Grade 3 or 4	No. Patients Entering Interval	No. (%) Patients with Grade 3 or 4	No. Patients Entering Interval
< 0 - 2	7 (0.9)	748	0 (0.0)	737
> 2 - 4	9 (2.2)	733	6 (0.8)	729
> 4 - 8	6 (3.0)	714	4 (1.4)	711
> 8 - 16	7 (4.0)	696	5 (2.1)	693
> 16 - 24	13 (5.9)	659	2 (2.6)	524
> 24 - 32	11 (7.7)	613	3 (3.4)	384
> 32 - 40	9 (9.4)	539	0 (3.4)	276
> 40 - 48	4 (10.3)	445	1 (3.9)	201

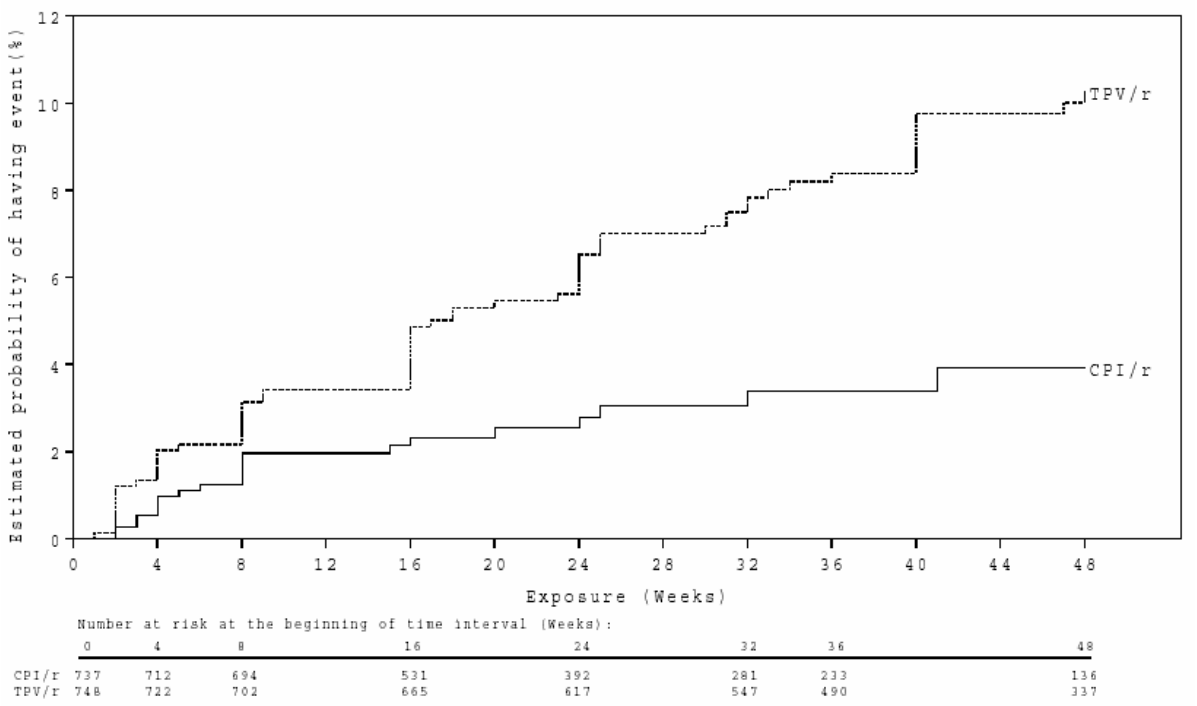

Figure 8.4.2.1: 1 Kaplan-Meier estimates for time to onset of DAIDS Grade 3 or 4 ALT or AST abnormalities up to 48 weeks in RESIST trials

8.4.2.2 Multivariable analysis for risk of LFT elevations

A Cox regression multivariable analysis was performed to identify factors predicting the risk of liver laboratory test abnormality for TPV/r and CPI/r patients (Table 8.4.2.2: 1). Liver laboratory test abnormalities were defined as any Grade 3 or 4 ALT, AST, or total bilirubin elevation during treatment as these three parameters are deemed to be reflective of potential liver injury.

The analysis considered treatment group, age, gender, race, CD4+ cell count at baseline, HIV RNA count at baseline, Center for Disease Control (CDC) HIV infection classification category, time since first diagnosis of HIV infection, use of NRTIs with the potential for hepatotoxicity (ddI, d4T, or ddC), HBV or HCV co-infection, number of prior ARV medications, NNRTI usage, the maximum baseline Grade for ALT, AST and total bilirubin, and elevated baseline triglycerides.

The model identified TPV/r treatment as a significant risk factor associated with the development of liver test abnormalities (RR=2.4, 95% CI =1.5-3.8). Other risk factors were elevated baseline liver tests, co-infection with HBV and/or HCV, and CD4+ cell count >200 cell/mm^3. The risk posed by TPV/r treatment is similar to that of elevated baseline liver function tests.

Table 8.4.2.2: 1 Cox regression assessing risk [a] for Grade 3 or 4 ALT, AST or total bilirubin abnormalities

Factor/Comparison	Risk Ratio	95% CI
Baseline ALT, AST total bilirubin: Grade 2 or 3 vs Grade 0 to 1:	2.5	1.3-4.8
Treatment Group: TPV/r vs CPI/r	2.4	1.5-3.8
CD4+ Cell Count at Baseline (cells/mm^3): =200 vs <200	2.0	1.3-2.5
HBV or HCV Co-infection: Co-infected vs not co-infected	2.3	1.4-3.7

[a] Risk factors for Grade 3-4 ALT/AST are similar in TPV/r and CPI/r

8.4.2.3 Actions taken with LFT abnormalities

Following the onset of Grade 3 or 4 ALT, AST or total bilirubin liver test abnormalities, investigators in the RESIST trials had protocol management guidelines, but were able to continue, interrupt or discontinue a patient's study medication. Most patients who developed Grade 3 or 4 liver test abnormalities remained on treatment or temporarily interrupted treatment without permanent discontinuation as detailed below:

Among patients treated with TPV/r, 74 who had Grade 3/4 liver test abnormalities:

- 57 (77.0%) of the 74 TPV/r patients with Grade 3 or 4 liver test abnormalities continued TPV/r treatment:
    - 46 (62.2%) patients continued treatment without interruption:
        - 7 (9.5%) patients had Grade 3 or 4 liver test abnormalities at their last observed visit and were not discontinued;
        - 30 (40.5%) patients continued study treatment, and the liver test abnormalities returned to values of Grade 2 or less;
        - 8 (10.8%) patients continued study treatment, and the liver test abnormalities remained stable (Grade 3 or higher);
        - 1 (1.4%) patient continued study treatment, and a Grade 3 elevated ALT/AST/bilirubin level increased to Grade 4.
    - 11 (14.8%) of the 74 TPV/r patients had a treatment interruption associated with Grade 3 or 4 liver test abnormalities that subsequently returned to Grade 2 or less
- 17 (23.0%) of the 74 TPV/r patients had study medication discontinued due to a liver test abnormalities. The reason for discontinuation was directly related to transaminase elevation and/or a liver-related AE preferred term.

Among patients treated with CPI/r, 26 who had Grade 3/4 liver test abnormalities:

- 26 (100.0%) of the 26 CPI/r patients with Grade 3 or 4 liver test abnormalities continued CPI/r treatment without permanent discontinuation.
    - 23 (88.5%) of the 26 CPI/r patients with Grade 3 or 4 liver test abnormalities continued treatment without interruption:
        - 5 (19.2%) patients had Grade 3 or 4 liver test abnormalities at their last observed visit and were not discontinued;
        - 18 (69.2%) patients continued study treatment, and the Grade 3 or 4 liver test abnormalities returned to values of Grade 2 or less;
    - 3 (11.5%) of the 26 CPI/r patients had a treatment interruption associated with a Grade 3 or 4 liver test abnormalities that subsequently returned to Grade 2 or less;
- There were no patients in the CPI/r group who had study medication discontinued due to a Grade 3 or 4 liver test abnormalities.

8.4.2.4 Clinical hepatic adverse events

In an evaluation of clinical hepatic adverse events associated with Grade 3 or 4 LFT abnormalities (ALT, AST, or total bilirubin), each of the 74 patients treated with TPV/r and 26 patients treated with CPI/r were reviewed and categorized as having (1) adverse events potentially related to liver injury, i.e., hepatobiliary disorders, investigations indicative of an elevation in a liver test reported as an adverse event, or infection associated with HBV or HCV; or (2) other adverse events not attributable to liver injury (Table 8.4.2.4: 1).

Of the 74 TPV/r patients with Grade 3 or 4 LFT elevations, 39 (52.7%) patients had liver-related adverse events compared with 5 (19.2%) of the 26 patients in the CPI/r group. Serious adverse events in any SOC were reported in 22 (29.7%) of the 74 TPV/r patients with Grade 3 or 4 liver test elevations as compared with 5 (19.2%) of the 26 patients in the CPI/r group. There were 8 (10.8%) liver-related SAEs in the TPV/r group and no liver-related SAEs in the CPI/r group.

Thirty (40.5%) of 74 TPV/r patients and 18 (69.2%) of 26 CPI/r patients discontinued treatment for any reason. Of all patients with Grade 3 or 4 test abnormalities who discontinued study drug, 17 (23.0%) of the 30 patients in the TPV/r group and none of the 18 patients in the CPI/r group were discontinued due to a liver-related adverse event.

Three TPV/r treated patients in the RESIST trials who died had a hepatic event reported as part of the clinical course prior to their death. These patients are discussed in the context of mortality observed in the entire TPV development program in Section 8.5.

Table 8.4.2.4: 1 Potential liver-related clinical events associated with Grade 3 or 4 liver test abnormalities in the RESIST trials

	TPV/r	CPI/r
Total Treated	748 (100.0)	737 (100.0)
Total with Laboratory Information[a]	735 (98.3)	728 (98.8)
Total with Grade 3 or 4 ALT, AST, or Total Bilirubin Event	74 (10.1)	26 (3.6)
Total with Any SAE	22 (29.7)	5 (19.2)
Total with Liver-related SAE	8 (10.8)	0
Total Discontinued for Any Reason	30 (40.5)	18 (69.2)
Total Discontinued for Liver-related Event	17 (23.0)	0
Clinical Events	72 (97.39)	23 (88.5)
Hepatobiliary Disorders[b]	17 (23.0)	0
Investigations[c]	26 (35.1)	5 (19.2)
Infections and Infestations[d]	1 (1.4)	1 (3.8)
Other System Organ Classes	66 (89.2)	23 (88.5)
Total of Hepatobiliary, Investigations, and Infections and Infestations	39 (52.7)	5 (19.2)

a All on-treatment laboratory test values used, regardless of whether baseline value was available.
b Preferred terms: cholestasis, cytolytic hepatitis, hepatitis toxic, hyperbilirubinemia, jaundice, and liver disorder.
c Preferred terms: alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased.
d Preferred terms: Hepatitis B and Hepatitis C.

8.4.2.5 Summary of Hepatic Findings

During the Phase I and II trials, a dose related increase in Grade 3/4 elevations in ALT or AST was observed. Most of the hepatic transaminase elevations were mild; not associated with clinical symptoms; and resolved spontaneously or with treatment discontinuation. These findings were confirmed in the Phase III RESIST trials. The majority of TPV/r patients with Grade 3/4 elevated ALT or AST continued TPV/r treatment without permanent discontinuation.

A Cox regression model identified treatment with TPV/r, elevated baseline LFTs (Grade 2/3), CD4+ cell count $\geq$ 200 and co-infection with Hepatitis B or C as risk factors for developing Grade 3/4 elevations in hepatic transaminases.

An exploratory analysis of medically selected hepatic terms from the RESIST trials, laboratory and clinical outcomes, suggested that TPV/r treated patients were at greater risk of developing laboratory or clinical hepatic events compared to CPI/r.

8.4.3 Fasting lipid elevations

8.4.3.1 Triglyceride elevations

Grade 3 or Grade 4 triglyceride elevations occurred in 23.2% patients in the TPV/r group and 12.2% patients in the CPI/r group. These abnormalities continued to develop in both treatment groups through 48 weeks. The Kaplan-Meier estimates of time to first Grade 3 or 4 triglyceride abnormality are shown in Figure 8.4.3.1:1. The estimated probability of a Grade 3 or 4 triglyceride elevation was higher in the TPV/r group (7.7%) than in the CPI/r group (5.4%) at 4 weeks and increased with time ($p < 0.0001$, log rank test). At 48 weeks the probability was 25.2% in the TPV/r group compared with 15.6% in the CPI/r group.

Patients have had longer median duration of exposure to TPV/r than with CPI/r study medication (330.0 days and 172.0 days, respectively). Adjusting for patient exposure, the relative risk of Grade 3 or 4 triglyceride elevations with TPV/r is higher than with CPI/r (RR=1.53, 95% CI 1.19, 1.97).

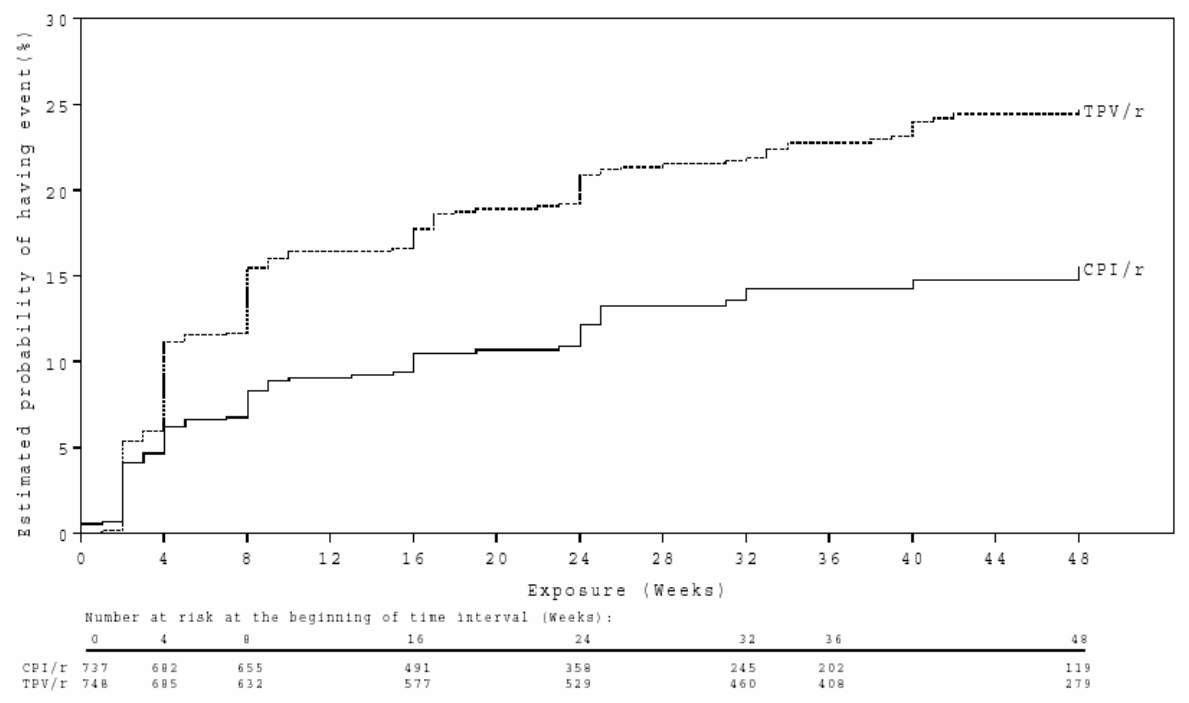

Figure 8.4.3.1: 1 Kaplan-Meier estimates for time to onset of Grade 3 or 4 triglyceride abnormalities in RESIST trial patients

Adverse events related to ischemic heart disease (IHD) were reported in 38 (5.1%) of 748 patients treated with TPV/r and 35 (4.7%) of 737 patients treated with CPI/r. Eight (21.1%) of the 38 TPV/r patients, and 8 (22.9%) of the 35 CPI/r patients with IHD adverse events, had Grade 3 or 4 triglyceride abnormalities.

In the TPV/r group, 27.3% of patients with Grade 3 or 4 triglycerides abnormalities had study medication discontinued, compared to 49.5% patients in the CPI/r group. Discontinuation of study medication due to IHD adverse events was observed in 3 (7.9%) of the 38 TPV/r group patients and 0 (0.0%) of the 35 CPI/r group patients.

The most clinically relevant potential risk factors for the occurrence of Grade 3 or 4 triglyceride abnormalities are elevated triglyceride levels at baseline, male gender, and age.

8.4.3.2 Cholesterol elevations

Grade 3 or Grade 4 total cholesterol elevations occurred in 4.0% patients in the TPV/r group and 0.4% patients in the CPI/r group.

In the TPV/r group, the risk of Grade 3 or 4 total cholesterol elevations continued through 48 weeks, while it remained flat in the CPI/r group. The Kaplan-Meier estimates of time to first Grade 3 or 4 total cholesterol elevation are shown in Figure 8.4.3.2: 1. The estimated probability of a Grade 3 or 4 total cholesterol elevation was higher in the TPV/r group (1.5%) than in the CPI/r group (0.0%) at 8 weeks and increased with time ($p < 0.0001$, log rank test). At 48 weeks the probability was 4.4% in the TPV/r group compared with 0.5% in the CPI/r group.

Patients have had longer median duration of exposure to TPV/r than with CPI/r study medication (330.0 days and 172.0 days, respectively). Adjusting for patient exposure, the relative risk of Grade 3 or 4 total cholesterol elevations with TPV/r is significantly higher than with CPI/r (RR=7.07, 95% CI 2.15, 23.2), although associated with a low frequency.

Adverse events related to ischemic heart disease (IHD) were reported in 38 (5.1%) of 748 patients treated with TPV/r and 35 (4.7%) of 737 patients treated with CPI/r. Four (10.5%) of the 38 TPV/r patients, and 0 (0.0%) of the 35 CPI/r patients with IHD adverse events, had Grade 3 or 4 total cholesterol abnormalities.

In the TPV/r group, 44.8% of patients with Grade 3 or 4 total cholesterol abnormalities had study medication discontinued, compared to none of the patients in the CPI/r group. Discontinuation of study medication due to IHD adverse events was observed in 3 (7.9%) of

the 38 TPV/r group patients and 0 (0.0%) of the 35 CPI/r group patients.

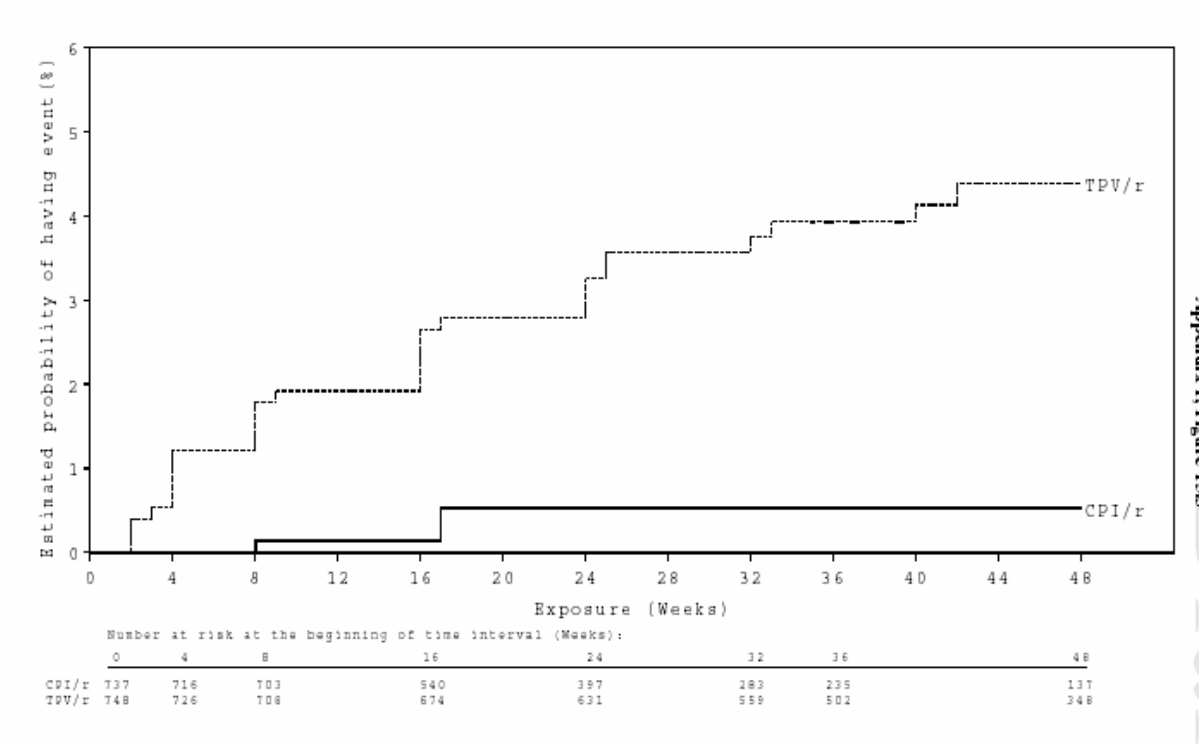

Figure 8.4.3.2: 1 Kaplan-Meier estimates for time to onset of Grade 3 or 4 total cholesterol abnormalities in RESIST trials

8.5 MORTALITY AND AIDS PROGRESSION

8.5.1 Deaths in all TPV trials

From the beginning of the TPV program through 30 September 2004, 131 patients died in clinical trials of HIV-positive patients. There have been 13 deaths that occurred in the screening period, prior to beginning trial medication. This underlines the advanced disease status of the patients studied. There have been a total of 104 deaths across all trials among 3,367 HIV-positive patients treated with TPV/r, for an overall incidence of 3.1%. With the exception of the two RESIST trials, one Phase II Trial BI 1182.4, and the naïve Trial BI 1182.33, the TPV development program has been non-comparative. There have been 14 deaths among patients randomized to a comparator PI. The comparative incidence of CPI/r deaths is described in the context of the RESIST trials in detail in the following sections.

There have been no deaths as of September 30th in HIV-negative subjects, the pediatric Trial BI 1182.14 or the naïve Trial BI 1182.33.

Each fatal case in the TPV program was reviewed by BI Medical Officers and classified if it was associated with an AIDS-defining opportunistic illness (OI) as defined by the Center for Disease Control, an AIDS-related illness (an illness clearly attributable to immunosuppression or that is known to occur in excess among HIV-positive patients) or both as the cause of death or contributing to the death (Table 8.5.2: 1). For all fatal cases, the overwhelming majority (81.7%) were attributable to HIV disease: 38.2% AIDS-defining OI, 26.7% AIDS related illness and 16.8% both.

Table 8.5.2: 1 Classification of fatal cases as attributable to Opportunistic Infections, an AIDS-related illness, or both in all HIV-positive patients

Trial Number	Pre-exposure	Post-exposure TPV/r	Post-exposure CPI/r	Total (%)
Patient deaths	13	104	14	131 (100.0)
AIDS-defining OI	3	40	7	50 (38.2)
AIDS-related illness	5	29	1	35 (26.7)
Both	0	19	3	22 (16.8)
Neither	5	16	3	24 (18.3)

8.5.2 AIDS progression events in RESIST Trials

Using the methodology established to classify fatal outcomes, BI Medical Officers retrospectively reviewed treatment emergent outcomes in both treatment arms in order to assess AIDS progression events occurring in the RESIST trials. Outcomes were classified as treatment emergent AIDS progression events if they met the following criteria: AIDS-defining opportunistic illness (OI) as defined by the Center for Disease Control, or an AIDS-related illness (an illness clearly attributable to immunosuppression or that is known to occur in excess among HIV-positive patients). In the RESIST trials, the proportion of patients who developed a new AIDS-progression event was less in the TPV/r group (3.4%) than in the CPI/r group (4.6%). This finding did not reach statistical significance; the RESIST trials were not powered to detect differences in AIDS progression events.

8.5.3 Deaths in RESIST trials

As of 30 September 2004, there were 39 deaths in the RESIST trials: 25 (3.3%) in patients receiving TPV/r, and 14 (1.9%) in patients receiving CPI/r. Table 8.5.3: 1 summarizes the duration of therapy in days that patients received study medication prior to their death in the RESIST trials. Fifty percent (50.0%) of CPI/r deaths occurred within 90 days of randomization compared with 38.0% of TPV/r patient deaths. In addition, 48.0% of TPV/r deaths occurred in patients exposed to TPV/r for >180 days compared with 14.3% of the CPI/r patient deaths.

Table 8.5.3: 1 Summary of duration of therapy in days for patients that died in RESIST trials

Treatment	Median (days)	0-30 days	31-90 days	91-180 days	>180 days
Patient deaths	134.5	4	10	12	13
CPI/r (n=14)	95.0	1 (7.1%)	6 (42.9%)	5 (35.7%)	2 (14.3%)
TPV/r (n=25)	156.0	3 (12.0%)	4 (16.0%)	6 (24.0%)	12 (48.0%)

Table 8.5.3: 2 summarizes the number of days after study medication was discontinued until the patient died. The majority of deaths (87.2%, 34 of 39 deaths) occurred within 30 days of stopping study medication. However, in all presentations of fatalities, the deaths occurring >30 days beyond stopping study therapy have been included. Greater than 50% of TPV/r patients and >70% of CPI/r patients died within 7 days after stopping their study medication.

Table 8.5.3: 2 Summary of days off of study medication until death in RESIST Trials

Treatment	0-7 days	8-30 days	>30 days	Total
Patient deaths	24	10	5	39
CPI/r	10 (71.4%)	2 (14.3%)	2 (14.3%)	14
TPV/r	14 (56.0%)	8 (32.0%)	3 (12.0%)	25

8.5.4 Adjustment for exposure in RESIST trials

As of September 30, 2004, the mortality rates in the RESIST trials were 4.1 deaths per 100 years exposure for patients receiving TPV/r and 3.5 deaths per 100 years exposure for

patients receiving a CPI/r. A Kaplan-Meier curve of mortality in the RESIST trials reveals no significant difference (log rank p = 0.64) between the two treatment arms (Figure 8.5.4: 1). This finding is not unanticipated given the fact that the RESIST trials were not powered to detect differences in mortality between the two treatment groups.

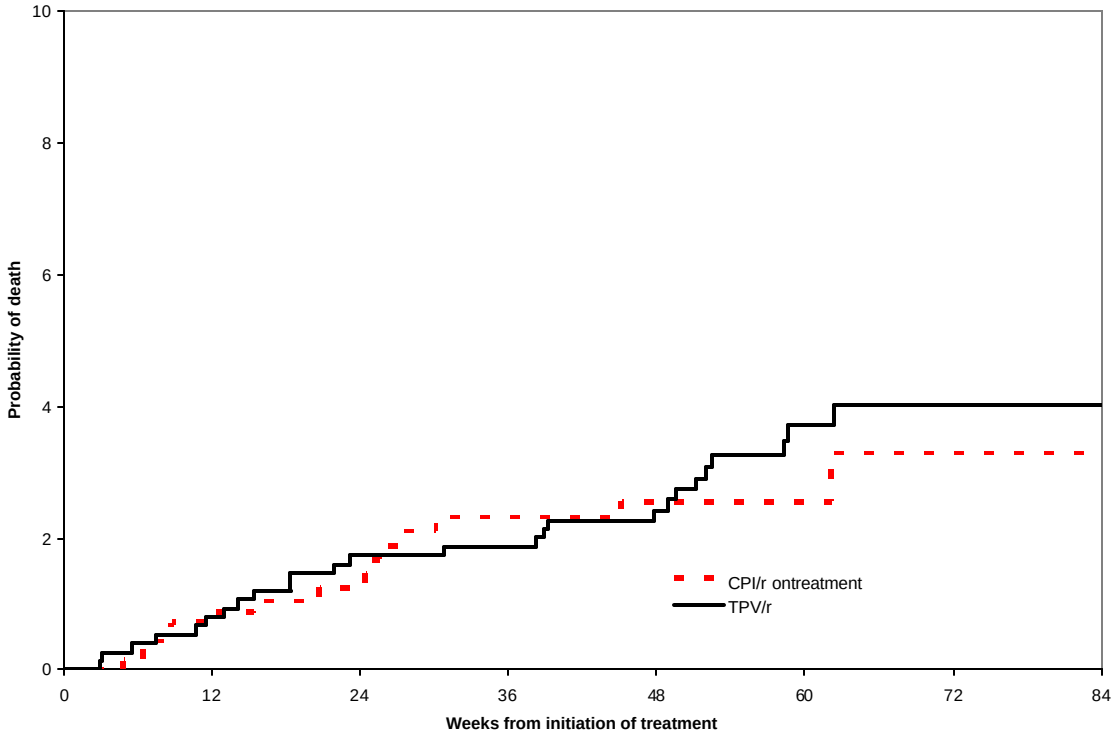

Figure 8.5.4: 1 Mortality in RESIST trials

A comparison of the causes of death, as identified by investigators, for patients in the RESIST trials revealed the majority, in either treatment arm, were attributable to progression of underlying HIV disease or HIV related opportunistic complications (Table 8.5.4: 1).

Table 8.5.4: 1 Comparison of mortality in the RESIST clinical program

TPV/r (n=25)	CPI/r (n=14)
AIDS / Infections (9)	AIDS / Infections (4)
Lymphoma (4)	Lymphoma (4)
Neoplasm (2)	Neoplasm (2)
General medical:	General medical:
Respiratory (4)	
Cardiac (1)	Cardiac (2)
Hepatorenal (1)	Multi-organ failure (1)
Sepsis (2)	
Unknown (2)	Unknown (1)

This finding is consistent with the fact that the median CD4+ cell count of the patients who died in the RESIST trials was 17 cells/mm3 for TPV/r patients and 53 cells/mm3 for CPI/r patients.

8.5.5 Analysis of patients who rolled over to Trial BI 1182.17 from the CPI/r arm of RESIST trials and died

As noted in Section 8.3, at the cut-off for the Safety Update, 43% of patients (316 out of 737) left the comparator arm of the RESIST trials due to virologic failure Of the 316 patients, 298 (94%) rolled over into the BI 1182.17 study and received TPV/r. Patients leaving the CPI/r arm of the trial due to virologic failure had lower CD4+ counts (117 cells/mm^3) and higher viral loads (4.8 $\log_{10}$ copies/mL) compared to patients remaining in the trial on CPI/r (CD4+ counts of 238 cells/mm^3 and viral load of 3.7 $\log_{10}$ copies/mL). Of the patients who rolled over into BI 1182.17 from the CPI/r arm of the RESIST trials, 14 patients died. This finding is consistent with the fact that the median CD4+ cell count of the CPI/r RESIST trial rollover patients who died in BI 1182.17 after receiving TPV/r was 10 cells/mm3. An overview of the cause of death for these patients is shown in Table 8.5.5: 1; details of each case are listed in Appendix 4.

Table 8.5.5: 1 Mortality in the CPI/r rollover patients from the RESIST trials

RESIST trials CPI/r (n=14)	Rollover Trial 1182.17 CPI/r to TPV/r (n=14)
AIDS / Infections (4)	AIDS / Infections (9)
Lymphoma (4)	
Neoplasm (2)	Neoplasm (1)
General medical:	General medical:
Cardiac (2)	Cardiopulmonary (2)
Multi-organ failure (1)	Hepatic failure (1)
	Renal failure (1)
Unknown (1)	

8.5.6 Contrast of deaths in the rollover study: patients from RESIST clinical program compared to patients from other TPV trials

Additional support of the advanced disease status of CPI/r patients with virologic failure who rolled into Trial BI 1182.17 is evidenced by comparing these patients to those who entered the rollover study from other trials. As of 30 September 2004, there were 27 deaths among 772 patients (3.5%) in Trial BI 1182.17. Of these deaths, 13 were among 474 patients who rolled over into BI 1182.17 from a prior study in which they had received TPV/r, and 14 were among 298 patients (4.7%) who were CPI/r virologic failures in the RESIST trials receiving TPV/r for the first time in BI 1182.17.

The difference in the duration of TPV/r therapy that patients received prior to their death in BI 1182.17 was notable, comparing those CPI/r patients who rolled over from RESIST studies and the remaining patients who have died in BI 1182.17 (Table 8.5.6: 1). 50% of the mortality in the CPI/r rollover patients occurred within 90 days of starting TPV/r therapy compared with no patients who had been receiving TPV/r in a previous study. The median days of therapy was 100 days for those patients who were CPI/r virologic failures receiving TPV/r in Trial BI 1182.17 compared with 335 days for patients who were receiving TPV/r in a previous study and are now in Trial BI 1182.17.

Table 8.5.6: 1 Summary of duration of therapy in days for patients that died in Trial BI 1182.17

Treatment	Median (days)	0-30 days	31-90 days	91-180 days	>180 days
Patient deaths (n=27)	205	2	5	6	14
CPI/r virologic failures from RESIST that have died in 1182.17 (n=14)	100	2 (14.3%)	5 (35.7%)	5 (35.7%)	2 (14.3%)
TPV/r patients that have died in 1182.17 that were previously on TPV/r in trials 1182.4, 1182.51 or 1182.52 (n=13)	335	0	0	1 (7.7%)	12 (92.3%)

8.5.7 Review of hepatic deaths

In the TPV clinical development program there have been a limited number of cases of clinical hepatitis or death due to hepatic failure; these have generally occurred in patients with advanced HIV disease taking multiple concomitant medications, often in the setting of underlying chronic hepatitis or cirrhosis. Through September 30, 2004, 5 fatal cases out of 131 total deaths (3.8%) had a hepatic event reported as part of the clinical course prior to the patient's death. All five fatal cases were reported in patients exposed to TPV/r, 3 from the RESIST trials and 2 rollover patients to BI 1182.17 (one patient from the RESIST trials and one patient from the dual boosted Trial BI 1182.51). Two of the five cases occurred in patients co-infected with Hepatitis B. The causes of death for the 5 cases were: liver failure, multi-organ failure, hepatorenal syndrome, AIDS and B-cell lymphoma.

During the three month period from 1 October 2004 through 31 December 2004, 2 additional fatal cases with a hepatic event were reported. During this same period, a total of 39 additional fatal cases were reported. Therefore, through 31 December 2004, a total of 7 fatal cases with liver events were reported out of a total of 170 fatal cases, (4.1%). The two additional cases occurred in patients treated with TPV/r, one patient rolled over from the RESIST trials to BI 1182.17 and one patient was entered into the Expanded Access Program. One of the two patients was co-infected with Hepatitis C. The cause of death for the patient who rolled over from the RESIST trials to BI 1182.17 was end stage multidrug-resistant HIV,

liver biopsy consistent with drug-induced hepatitis. The cause of death for the patient from the Expanded Access Program was Burkitt's lymphoma. This patient was co-infected with Hepatitis C. Table 8.5: 7 provides brief clinical synopses of each of the fatal cases with liver events.

Table 8.5: 7 Clinical Summary of Fatal Cases with a Hepatic Event

Trial - Patient number	**Age, gender, HIV Status**	**Hepatitis Co-infection**	**History**	**Intercurrent Events**	**Nearest CD4+ VL**	**Cause of Death** (Days on TPV and Days to Death)
RESIST Trials						
1182.12-2052	43 yo WM HIV+	HBsAg(+)	Wasting, ?lipids, pancreatitis, neuropathy	?liver/spleen, ?nodes, fever, dehydration, SOB, renal failure	14 3.4 $\log_{10}$	**Hepatorenal** (245 and 268 days)
1182.12-2272	36 yo BM HIV+	HBsAg(+)	Hyperbilirubinemia, End-AIDS, MAC, PCP, neuropathy, diabetes	Cholestasis (?itraconazole related), renal and liver failure	49 3.0 $\log_{10}$	**AIDS** (346 and 364 days)
1182.48-4168	63 yo WM HIV+		PCN Allergy, ?lipids, lipodystrophy, neuropathy	Fever, liver biopsy: B-cell lymphoma, intra-abdominal bleed; liver failure post-chemo	45 3.3 $\log_{10}$	**B-cell Lymphoma** (85 and 91 days)
Rollover and Expanded Access Trials						
1182.17-121025	39 yo WM HIV+		Steatohepatitis, AIDS, MAC, wasting	Hepatic Failure	34 4.6 $\log_{10}$	**Liver Failure** (143 and 143 days)
1182.17-482621	49 yo BM HIV+		Ischemic stroke, diabetes mellitus, herpes labialis	Drug-induced hepatitis	3 4.6 $\log_{10}$	**End stage HIV** (71 and 118 days)
1182.17-510361	58 yo M HIV+		Hyperbilirubinemia , allergy to saquinavir, diabetes mellitus, peripheral edema	Jaundice, knee pain, severe leg edema, mild ectasia bile ducts, no DVT, general worsening with lactic acid-190mg/mL	135 4.6 $\log_{10}$	**Multi-organ failure** (218 and 218 days)
1182.67-TAL	43 yo M HIV+	HCV RNA(+)	Cirrhosis, chronic HCV	Decompensation of Cirrhosis	140 2.9 $\log_{10}$	**Burkitt's Lymphoma** (67 and 74 days)

8.5.8 Summary of deaths

In all TPV studies from program inception to the 30 September 2004, 131 HIV-positive patients have died. Among these, 13 deaths have occurred pre-treatment prior to exposure to study medication which underlines the advanced disease status of patients in the TPV development program.

Patients who entered the RESIST trials were highly treatment-experienced with advanced HIV disease. As of 30 September 2004, there were 39 deaths in the RESIST trials: 25 (3.3%) in patients receiving TPV/r, and 14 (1.9%) in patients receiving CPI/r. The exposure adjusted mortality rates in the RESIST trials were 4.1 deaths per 100 years exposure for patients receiving TPV/r and 3.5 deaths per 100 years exposure for patients receiving a CPI/r. This difference was not statistically significant. The majority of the patients who died in the RESIST trials experienced progression of their HIV-disease or an HIV-related opportunistic infection as the underlying cause of death. The mortality rates in the RESIST trials are similar to the mortality rates seen in other treatment experienced patient populations, e.g. the mortality rates in the CPCRA 064 trials (6.1 and 6.5 per 100 patient years) and in the PLATO[23] cohort (overall mortality 5.5 per 100 patient years).

The majority (94%) of patients who experienced virologic failure in the CPI/r arm transferred to the TPV rollover study (BI 1182.17). Patients leaving the CPI/r arm of the trial due to virologic failure had lower CD4+ counts (117 cells/mm^3) and higher viral loads (4.8 $\log_{10}$ copies/mL) compared to patients remaining in the trial on CPI/r, CD4+ 238, viral load 3.7 $\log_{10}$ copies/mL. Of the patients who rolled over into BI 1182.17 from the CPI/r arm of the RESIST trials, 14 patients died. A comparison of the causes of death, as identified by investigators, for patients who died in the RESIST trials and the RESIST CPI/r rollover patients to 1187.17 were similar, HIV disease, AIDS-related illnesses or AIDS-related opportunistic infections. This is consistent with the low median CD4+ cell counts for the patients who died in the RESIST trials, 17

[23] The PLATO Collaboration. Predictors of trend in CD4-positive T cell counts and mortality among HIV-1 infected individuals with virological failure to all three antiretroviral-drug classes. Lance 2004;364:51-62.

cells/mm3 for TPV/r patients and 53 cells/mm3 for CPI/r patients or who died after rolling over from CPI/r into BI 1182.17, median CD4+ cell count 10 cells/mm3.

Across the various trials conducted as part of the TPV/r development program, including the EUP and EAP programs and the BI 1182.17 roll over trial, more than 80% of deaths were attributable to an AIDS-defining OI or an AIDS-related illness. This is consistent with the highly treatment experienced HIV-positive patient population treated with TPV/r.

8.6 SAFETY RESULTS IN SPECIAL POPULATIONS

8.6.1 Long-term safety from rollover Trial BI 1182.17

Long-term data in HIV-positive patients is provided from patients that entered Trial BI 1182.17 (rollover extension from Phase II/III trials). In the NDA submission, safety data for 570 patients who were exposed to TPV/r for >24 weeks, 372 at the intended market dose of TPV/r 500 mg/200 mg, were reported (Table 8.6.1: 1). Because the TPV treatment in the initial trials varied with respect to TPV/r dose, formulation and patient experience, 3 patient Groups were designated to evaluate long-term safety data.

- Group 1 (n = 518): Data from early TPV trials with various dose regimens and formulations) and data from dose-finding studies with multiple regimens;
- Group 2 (n = 308): Data from Trial BI 1182.51 in which most were receiving a dual-boosted PI regimen containing TPV/r 500 mg/200 mg;
- Group 3 (n = 284[24]): Patients who failed virologically on the comparator-PI arm during RESIST trials and began TPV/r 500 mg/200 mg in Trial BI 1182.17.

A total of 220 patients (47 at the 500 mg/200 mg dose) have >48 weeks exposure, and 39 patients (none at the 500 mg/200 mg dose) have been exposed to TPV for over 3 years. The maximum exposure to TPV/r was 259.9 weeks, or almost 5 years. It is noted that nearly all

[24] In the Safety Update, a total of 298 patients who failed virologically on CPI/r of the RESIST trials entered BI Trial 1182.17.

patients in the BI 1182.17 trial who were on doses other than the 500 mg/200 mg dose from their prior trial have been switched to the TPV/r 500 mg/200 mg dose as of March 2003.

Table 8.6.1: 1 Summary of long-term exposure to TPV by HIV-positive patients, by trial grouping, from Trials BI 1182.2, 1182.4, 1182.6, 1182.17, 1182.51 and 1182.52

	Number (%) of patients			
	Group 1[a]	Group 2[b]	Group 3[c]	Total
Total treated	518 (100.0)	308 (100.0)	284 (100.0)	1110 (100.0)
Exposure duration[d]				
≥1 day	518 (100.0)	308 (100.0)	284 (100.0)	1110 (100.0)
> 4 weeks	323 (62.4)	301 (97.7)	256 (90.1)	880 (79.3)
> 24 weeks	253 (48.8)	248 (80.5)	69 (24.3)	570 (51.4)
> 48 weeks	214 (41.3)	6 (1.9)	0 (0.0)	220 (19.8)
> 72 weeks	185 (35.7)	0 (0.0)	0 (0.0)	185 (16.7)
> 96 weeks	66 (12.7)	0 (0.0)	0 (0.0)	66 (5.9)
> 144 weeks	39 (7.5)	0 (0.0)	0 (0.0)	39 (3.5)
> 168 weeks	32 (6.2)	0 (0.0)	0 (0.0)	32 (2.9)

a Group 1 = Patients from Trials 1182.2, 1182.4, 1182.6 and 1182.52. Patient 1182_0004/003154 rolled over from the SQV arm into 1182.17. Two patients in the TPV/r arm of the RESIST trials who rolled over into 1182.17 are also included.
b Group 2 = Patients from Trial 1182.51.
c Group 3 = CPI/r virologic failure patients from Trials 1182.12 and 1182.48
d Total exposure is defined as exposure in the prior trial plus exposure from Trial 1182.17, when applicable.
Note: This table includes data on all patients from Trials 1182.2, 1182.4, 1182.6, 1182.51 and 1182.52 and data for patients in Trial 1182.17 entering from those patients who entered Trial 1182.17 and were receiving TPV/r for the first time in Trial 1182.17.

Evaluation of events over time revealed that patients experienced nausea and diarrhea more frequently in the 0-4 week time interval compared to later time intervals. No events appeared later in the course of therapy (>24 weeks) that were not present earlier during therapy (≤24 weeks). Lipodystrophy, an event known to be associated with chronic administration of NRTI agents and PIs, was present in Groups 1 and 2 in a higher percentage of patients during later exposure periods, although the overall frequency was small (<3%). For other events, there did not appear to be an association with time.

The frequency of discontinuation of study medication due to adverse events appeared highest in Group 1, the patients with longest exposure to TPV/r, followed by Group 3 and then Group 2. Overall, the most frequently reported adverse events leading to discontinuation were nausea,

diarrhea, and increased ALT. In Group 1, the only group that had exposure data beyond Week 48, gastrointestinal events leading to discontinuation of study medication occurred primarily in the first 24 weeks of exposure. Increased liver enzymes resulted in premature discontinuations of study medication at less than 3% per year across the different time intervals. While these long-term data may suggest that the risk of persistent Grade 3/4 ALT and/or AST elevations does not increase significantly over time, additional data are required before this conclusion may be reached.

The type and frequency of serious adverse events were similar across the 3 patient Groups. The most commonly experienced SAEs were anemia, abdominal pain, diarrhea and pyrexia. There were no SAEs predominantly seen during a certain interval of time during TPV/r exposure, although Group 3, who initiated therapy with TPV/r in BI Trial 1182.17, had a higher overall frequency of SAEs in the first 4 weeks of exposure to TPV/r.

To date, the data suggest that long-term exposure to TPV/r treatment presents no new safety concerns, and is consistent with the already established TPV safety profile at 24 weeks.

8.6.2 Pediatric Trial BI 1182.14

Initial safety data from a multicenter, multiple-dose, open-label, randomised, safety and pharmacokinetic study of TPV in combination with low-dose RTV in HIV-infected children and adolescent patients (ages 2-18 years) was reported in the NDA submission. This 48-week trial was initiated in early 2004, and was fully accrued with 100 HIV-infected pediatric patients in October 2004.

Of the data for 37 patients available for safety evaluation, 18 were randomised to the TPV/r low dose group (TPV/r 290 mg/m2/115 mg/m^2 BID), and 19 patients were randomised to the TPV/r high dose group (TPV/r 375 mg/m^2/150 mg/m^2 BID). Patients were receiving TPV as the liquid formulation and RTV, as either the liquid or capsule formulation.

Overall, 70.3 % (26/37) of patients reported at least 1 adverse event, with 66.1% (11/18) in the TPV/r low dose group and 78.9% (15/19) in TPV/r high dose group. As seen in trials in HIV-positive adult patients, the highest percentages of pediatric patients reported adverse events in the

gastrointestinal disorders SOC (43.2%, (16/37), with nausea and vomiting being the 2 most frequently reported adverse events: 27.0% of patients (10/37) and 21.6% (8/37) of patients, respectively. Both nausea and vomiting occurred more frequently in the TPV/r high dose group than in the TPV/r low dose group: nausea, 31.6% compared with 22.2%; and vomiting, 26.3% compared to 16.7%, respectively.

Three patients (8.1%) discontinued from the study due to adverse events, 2 in the TPV/r high dose group and 1 in the TPV/r low dose group. Adverse events leading to discontinuation consisted of: abdominal pain, nausea and vomiting in 1 patient; retching and vomiting in 1 patient; and gastrointestinal discomfort and retching in 1 patient.

There were 3 SAEs reported: abdominal pain and nausea considered related to the study drugs in 1 patient; pyrexia in 1 patient, and oesophageal candidiasis in 1 patient both considered not to be related to study drug. There were no significant adverse events reported, as defined in the protocol, and no patients have died during the study.

8.6.3 Emergency Use and Expanded Access Programs

The objective of the BI Open Label Emergency Use Program (EUP) is to provide highly treatment-experienced patients who were unable to participate in the RESIST clinical trial program access to TPV/r treatment. Overall, 15 countries are participating in the EUP. The information presented is from the period of 01 May 2003 to 04 May 2004.

With the exception of the United States and France, both conducting the EUP as an Open Label Safety Study (OLSS), all other participating countries are conducting the EUP on a Named Patient Use (NPU) basis. The EUP opened accrual in May 2003 (3 months after the first patients were entering RESIST-1 and 2) and will close recruitment for adult patients once the Expanded Access Program has opened in each particular country.

In order to be eligible for the program, patients initially had to fulfill the following key entry criteria: CD4+ cell count < 50 cells per mm^3 and HIV RNA count >10,000 copies/mL. In January 2004, the baseline CD4+ cell count was increased from < 50 cells/mm^3 to < 100 cells/mm^3 providing a larger number of patients access to the program. Safety collection varied

from program to program depending upon local collection/reporting requirements. Following local regulatory requirements to conduct a NPU Program, only in 6 (US, France, Denmark, Greece, Belgium, and Switzerland) of the 15 participating countries could CRFs be utilised for systematic data collection in the EUP.

A total of 451 patients have entered the EUP. A total of 450 patients received at least 1 dose of TPV/r 500 mg/200 mg. Overall, 51 patients discontinued TPV/r therapy; 19 patients died. A total patient exposure of 131 patient years was estimated.

Demographic characteristic data were available for 266 patients. The EUP/OLSS population was predominantly male (89.5%); the mean age was 43.7 years. The mean baseline HIV-1 RNA value was 5.2 $\log_{10}$ copies /mL. Of the 266 patients, 54.9% showed a baseline HIV-1 RNA concentration between 100,000 and 1,000,000 copies/mL, and 5.3% had a viral load >1,000,000 copies/mL. Baseline information for CD4+ cell count was available for 263 patients. The mean baseline CD4+ count was 27.3 cells/mm^3 (median 18 cells/mm^3), with 84.8% of the patients having a CD4+ cell count < 50 cells/mm^3.

Details on the ARV treatment history were available for 264 patients. The mean number of ARV drugs each patient previously had received who entered the EUP/OLSS was 5.0 PIs, 5.8 NRTIs and 1.6 NNRTI. Previous exposure to an average of 12 ARV agents indicates that the number of drugs left to construct a viable regimen in this patient population was very limited.

Overall, 87 case reports, including 150 adverse events, were received in the EUP program at the time of the Summary of Clinical Safety submission. Nineteen of the 87 patients had a fatal outcome. Of the 150 adverse events received, 137 were serious and 13 were non-serious. Within the EUP, only SAEs and drug discontinuations were systematically collected. In addition to the 87 cases received in the time period, 7 SAE reports that occurred during the pre-treatment phase of the program were reported.

The incidence, as well as the type of SAEs reported in the EUP for the individual SOCs, was comparable to that seen in other trials conducted to date. The higher proportion of SAEs reported in the EUP for infections and infestations mirrors the advanced clinical condition of the

patients enrolled in this program. This SOC includes preferred terms that are clearly markers of advanced HIV disease.

A total of 7 case reports have been received with at least 1 event judged to be related to TPV/r treatment. On a case by case basis or cumulatively, these cases do not change the present understanding of the safety profile of TPV/r.

In the EUP, all fatal events were considered unrelated to TPV/r treatment by the investigator. Consistent with the advanced nature of the disease, baseline CD4+ cell count of the patients who died during the treatment with a TPV/r-containing ARV regimen ranged from 0 to 190 cells/mm^3 (median 8 cells/mm^3). The baseline viral load ranged from 10,690 to 1,000,000 copies/mL.

8.6.4 Safety in Women and Minorities

In the RESIST trials, 15.6% (117 of 748) patients treated with TPV/r were women. Overall, 92.3% of women reported adverse events as compared to 88.3% of men. A higher percentage of female patients (>5 % difference) tended to experience nausea (28.2 vs. 17.6% among males), vomiting (18.8 vs. 9.4%), headache (20.5 vs. 11.6%), and anxiety (7.7 vs. 1.4%). A higher percentage of males tended to experience fatigue (12.8 vs 5.1% among females). Although rash was observed in women using estrogen, the percentage of male and female TPV/r recipients in RESIST who experienced rash were 6.5 and 8.5%, respectively. There was no difference between genders in the percentage of TPV/r recipients in RESIST who developed a Grade 3 or greater laboratory abnormality.

In the RESIST trials, 12.5% (94 of 748) patients were black, 76.4% (572 of 748) patients were white and the remaining patients primarily did not have race reported due to local country regulations. Overall, 93.6% of black patients reported adverse events as compared to 88.5% of white patients. A higher percentage of black patients (>5% difference) reported adverse events in the infections and infestations and respiratory disorders SOC.

Overall, the number of women and black patients in the RESIST trials is small and no signals for differences in safety are detected.

8.7 SAFETY CONCLUSIONS

- There have been 1,870 HIV-positive patients treated with the TPV/r 500/200 mg dose for a total of 1,760 patient-years of exposure; 47% were treated for >48 weeks with a maximum exposure of 5 years.
- Although the overall rates and types of adverse events and SAEs, including fatal outcomes, reported in the RESIST trials were similar for TPV/r and CPI/r, TPV/r treated patients experienced more hepatic and lipid associated events. The adverse events seen with TPV/r are those expected with a ritonavir-boosted PI.
- Grade 3/4 elevations in ALT/AST and hepatic adverse events were more common with TPV/r than CPI/r. These events were generally asymptomatic and most patients were successfully continued on treatment. Most patients can be managed with routine laboratory monitoring except for patients with chronic Hepatitis B or C co-infection or elevated baseline LFTs, where increased monitoring of LFTs is recommended.
- Grade 3/4 elevations in cholesterol and triglycerides and lipodystrophy were more common with TPV/r. The lipid abnormalities were not associated with an increased risk of pancreatitis. It is not possible to draw definitive conclusions regarding the risk of potential long term sequelae of elevated plasma lipids, e.g. ischemic heart disease, given the limited number of patients exposed to TPV/r for more than one year.
- Lipodystrophy was more common with TPV/r. Many of the patients in the RESIST trials had extensive ARV exposure and entered with lipodystrophy. The definitive assessment of lipodystrophy will occur in the metabolic substudy of the naïve patient trial BI 1182.33.

9. OVERALL CONCLUSIONS

The emergence of a large and growing population of individuals infected with broadly antiretroviral drug resistant HIV-1 is of continuing concern. Tipranavir, a novel non-peptidic protease inhibitor, was the first PI to be developed with the intent that it would have activity in these patients and thus improve their clinical status. The interim data reviewed in this application provides for an appropriate benefit/risk profile of TPV/r for the treatment of PI-experienced patients.

As of 30 September 2004, a total of 3,367 HIV-positive patients have been treated with TPV/r, representing over 1,760 patient-years of drug exposure. More than 900 patients have been treated for at least 48 weeks, and some patients have received TPV/r for over five years. 1,411 patients have been treated with the TPV/r 500/200 mg dose with 1,206 having received this to-be-marketed dose for at least 24 weeks.

Early in pre-clinical development, it was recognized that tipranavir had significant antiviral activity against viral isolates with resistance to other ARV drugs. Additional studies that tested TPV against clinical isolates from the Phase II and III program confirmed that TPV maintains significant *in vitro* antiviral activity (<3-fold resistance) against the majority of HIV-1 clinical isolates from PI-resistant treatment experienced patients that have reduced susceptibility to the following currently approved PIs: amprenavir, atazanavir, indinavir, lopinavir, ritonavir, nelfinavir and saquinavir.

The tipranavir development program is the first PI to be primarily studied for use in treatment experienced patients. The *in vitro* resistance profile of tipranavir has shown that TPV retains antiviral activity against many viral isolates that are resistant to existing PI options.

The TPV development program has included 39 clinical studies, ranging from small single-dose PK trials to large, multi-national, controlled Phase III pivotal studies. The combined data from these broadly variable trials demonstrates that TPV/r has potent antiviral activity in PI treatment-experienced patients and has a safety profile that is generally similar to that of other RTV-boosted PIs.

The primary focus of the development program has been to establish the efficacy of TPV in patients with PI treatment experience without other available treatment options. Based on the data from the Phase III RESIST studies, the antiviral activity—as demonstrated by multiple efficacy endpoints—is encouraging. Tipranavir has demonstrated statistical superiority to optimized standard of care regimens in multiple drug experienced patients.

The 24-week interim analysis of the RESIST program has succeeded in demonstrating efficacy of TPV across multiple efficacy endpoints (Table 9: 1). In short, these data show that TPV/r has potent antiviral activity in patients with PI-resistant virus who have previously been exposed to 2 or more PI-containing antiretroviral regimens and these data demonstrate that the difference between patients receiving TPV/r is statistically significantly superior to patients receiving an optimized standard of care regimen of currently marketed RTV-boosted PIs. In addition, patients using TPV/r had a statistically superior immunologic improvement and had fewer AIDS progression events than patients receiving the optimized standard of care comparator PI. The antiviral and immunologic benefits for patients receiving TPV/r were further enhanced in the presence of other active background drugs, such as enfuvirtide.

Table 9: 1 Overview of Week 24 efficacy endpoints - combined RESIST trials

	TPV/r + OBR N = 582	CPI/r + OBR N = 577
Median baseline viral load (range)	4.83 (2.34 - 6.52)	4.82 (2.01 - 6.76)
Median baseline CD4+ count (range)	155 (1 - 1893)	158 (1 - 1184)
Treatment Response	41 %	19 %
Median HIV VL change from baseline (log_{10} copies/mL)	-0.80	-0.25
HIV VL < 400 copies/mL	34 %	15 %
HIV VL < 50 copies/mL	24 %	9 %
Median increase in CD4+ cell count (cells/mm^3)	34	4
Reasons for treatment failure	59 %	81 %
Death	1 %	1 %
Discontinued or OBR change due to lack of efficacy	6 %	37 %
Virologic rebound	15 %	11 %
No confirmed virologic response	24 %	23 %
Discontinued due to any adverse event	8 %	3 %
Discontinued due to other reasons	4 %	5 %

The clinical efficacy results confirm what the *in vitro* resistance testing results have shown and extend what was known about the TPV resistance profile from the early pre-clinical development stage. Based on resistance analyses from the Phase II and III program, it is now known that: (1) It takes 3 key mutations and > 4 TPV-associated mutations to produce decreased TPV susceptibility ($\geq$ 3-fold wild-type) *in vitro* or decreased antiviral responses clinical isolates; (2) high level resistance (> 10-fold wild type) generally requires the presence of all 4 key mutations or > 7 TPV-associated mutations that are uncommon in clinical HIV-1 isolates from treatment-experienced patients; (3) many of the mutations that produce reduced TPV susceptibility are different than the mutations that produce drug resistance to currently available PIs (TPV mutation score vs. IAS mutation count). These *in vitro* and clinical data confirm earlier data demonstrating that there is a high genetic barrier to resistance with TPV. For patients considering the use of TPV/r, genotypic resistance testing may assist in the selection of drugs to

combine with TPV/r and in determination of which patients are most likely to benefit from a TPV/r-based regimen.

Despite the demonstrated efficacy and resistance benefits of TPV, these data must be balanced with the knowledge of the potential safety risks for patients who may receive the drug.

Based on the interim analyses of the RESIST studies and available longer term safety data from other trials, tipranavir is generally safe to administer to treatment-experienced patients. The rate and type of AEs reported by patients receiving TPV/r is similar to those reported in other patients receiving RTV-boosted PIs.

As might be expected for any PI, the most commonly reported AEs for patients receiving TPV/r involve the GI tract. These were generally mild to moderate in severity and resolved spontaneously without treatment interruption. Both SAEs and deaths reported in the TPV development program appear to reflect the advanced nature of the patients studied, and there were no commonly occurring events that suggest a pattern of possible treatment-relatedness.

Most laboratory tests were unaffected by treatment with TPV/r. However, both hepatic enzyme elevations and plasma lipid elevations were more common in patients receiving TPV/r than in patients on the CPI/r arms of the RESIST studies.

While most patients with hepatic enzyme elevations were asymptomatic and were able to safely continue on treatment without permanent discontinuation, the higher rate of ALT/AST elevations and the minority of patients who were symptomatic suggests that clinicians should be vigilant in monitoring their patients who begin treatment with TPV/r, especially in patients with increased hepatic risk factors at baseline. Specifically, the hepatic observations from the RESIST trials warrant that patients treated with TPV/r be monitored appropriately. LFT tests should be obtained prior to initiating therapy with TPV/r and during treatment. Increased monitoring is necessary when TPV/r is administered to patients with elevated baseline ALT or AST levels or chronic hepatitis B or C. As with any potentially hepatotoxic agent, patients with signs or symptoms of clinical hepatitis should discontinue TPV/r treatment and seek medical evaluation.

Given the limited number of hepatitis B or C co-infected patients in the TPV/r clinical development program, additional TPV/r studies, epidemiologic and clinical trials, will be conducted to better quantify the risks and benefits of TPV/r-containing antiretroviral regimens in hepatitis B or C co-infected HIV-1 patients. TPV/r is contraindicated in patients with severe liver diseases, i.e. Child-Pugh C cirrhosis. There have been a limited number of cases of clinical hepatitis or death due to hepatic failure in the TPV development program, primarily in patients with advanced HIV disease taking multiple concomitant medications and a causal relationship to TPV/r was not established.

Lipid elevations are challenging to fully understand because most patients who received TPV/r in the Phase II/III program were treatment-experienced and entered with variable levels of pre-existing lipid abnormalities or even lipodystrophy. Nonetheless, the rate of Grade 3 or 4 lipid elevations was higher in the TPV/r arms than in the CPI/r arms, though this may have also resulted from the higher dose of RTV given in the TPV arms. The ongoing study in treatment-naïve adult patients (BI 1182.33) will better define the risk of blood lipid abnormalities and lipodystrophy when those patients complete 48 weeks of treatment.

From a pharmacokinetic standpoint, tipranavir is a unique protease inhibitor with a potent inductive effect on the cytochrome P450 3A isoenzyme. TPV 500 mg must be given simultaneously with ritonavir 200 mg both given twice daily to obtain the desired therapeutic drug levels. When TPV is combined with 200 mg of ritonavir there is a net inhibition of CYP3A. Due to its metabolism through the CYP 3A4 pathway, clinicians should be aware of the potential drug-drug interactions that could occur when patients take TPV/r with other commonly co-administered drugs. In general, the pharmacokinetic drug interactions for most concomitant medications with TPV/r are consistent with other RTV-boosted PIs.

While reductions in plasma concentrations of abacavir and zidovudine have been observed when they are combined with TPV/r, the clinical relevance of these changes has not been established and no dose adjustment can be recommended at this time. In addition, drug levels for RTV-boosted lopinavir, saquinavir, and amprenavir were significantly reduced when combined with TPV/r, therefore these combinations are not recommended. PI levels for novel dual PI regimens

containing TPV/r cannot be predicted without formal drug interaction studies possibly due to the mixed patterns of inhibition and induction of CYP pathways seen with these drug combinations.

Additional information that will be forthcoming from the ongoing Phase III clinical development program involves the use of TPV/r in antiretroviral naïve adults and HIV-positive children (ages 2 to 18). The naïve adult study (BI 1182.33) is designed to help discern (1) whether a lower RTV dose (100 mg) to boost TPV provides sufficient antiviral activity in treatment-naïve patients; (2) the safety and tolerability profile of TPV/r, especially regarding elevations of ALT/AST and lipids, and whether it is different for naïve versus treatment-experienced individuals; (3) the resistance mutations that emerge in naïve patients and the effect of those mutations on susceptibility to the other available PIs. The ongoing pediatric study (BI 1182.14) will determine the safety, tolerability, pharmacokinetics, efficacy and optimal dose of tipranavir oral solution for children and adolescents.

Based on these short-term analyses of efficacy, safety, and pharmacokinetics, the benefit risk profile of tipranavir is clearly favorable for treatment experienced patients. The use of TPV/r based regimens in patients resistant to other treatment options meets a large unmet clinical need in the community. In summary, the balance of the benefits and risks of drug regimens containing TPV/r supports the indication for use in PI treatment-experienced patients with HIV-1 infection.

10. PLANS FOR COMPLETING REQUIREMENTS FOR TRADITIONAL APPROVAL

BI will provide 48-week data from the RESIST studies once the final analyses and clinical trial reports are completed; these 48-week data are intended to support the application for Traditional Approval.

APPENDIX 1 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

APPENDIX 1.1 OVERVIEW

General/safety pharmacology studies were performed following single administration to assess TPV's potential effects on a number of organ systems including: central nervous system, cardiovascular, pulmonary, renal and gastrointestinal. The cardiovascular assessment included both *in vitro* and *in vivo* evaluations of TPV for possible pro-arrhythmic risk potential. Owing to its targeted patient population, TPV was also evaluated for effects on immune function.

A number of single and repeated dose pharmacokinetic studies were conducted in several animal species (including CD-1 mouse, Sprague Dawley rat, New Zealand White rabbit, beagle dog and rhesus monkey) to derive pharmacokinetic parameters both with and without RTV co-administration. A number of formulations were evaluated in dogs to optimize systemic exposure. Studies using radiolabelled TPV were also conducted to assess the absorption, distribution, and excretion of TPV in mouse, rat, rabbit and dog. Metabolism studies in rat are also included. *In vivo* metabolism studies in mouse and dog are ongoing. Protein binding studies were performed with plasma of a number of species as well as FBS contained in media that was used in studies to determine *in vitro* potencies to inhibit viral proteases. Whole body autoradiography studies in rat were conducted to select the appropriate radiolabelled dose of TPV for the human ADME study. Studies in pregnant rats were conducted to assess placental transfer and lacteal secretion. *Ex vivo* analyses of induction in rats and dogs by TPV were performed.

In vitro metabolism studies were conducted using hepatic microsomes from a number of species and rat and human hepatocytes. Since these studies were conducted in the absence of RTV, the data is not expected to reflect what occurs *in vivo.* Studies to assess permeability and active transport of TPV were conducted *in vitro* using Caco 2 and MDCK cells transfected with Pgp. The stereochemical stability of TPV in plasma samples was confirmed by capillary electrophoresis. Most of these studies were not conducted under GLP.

Since TPV is a chronically administered drug, the nonclinical safety assessment strategy was designed to address repeated dose administration over an extended period of time. A battery of nonclinical studies has been performed with TPV to address toxicity in support of clinical trials and final registration. Repeat-dose toxicity of TPV has been addressed in both rats and beagle dogs by the oral route of administration for durations of up to 26 weeks and 39 weeks, respectively, and repeat-dose toxicity of TPV with RTV co-administration has been performed in rats and beagle dogs in studies up to 26 weeks of duration. Genotoxicity was evaluated in *in vitro* and *in vivo* assays. Traditional two-year carcinogenicity studies with TPV and TPV/RTV are on-going in mice and rats. The effects of TPV on reproduction, teratogenicity, and pre- and post-natal development were assessed in standard tests in rats and rabbits. Specific studies have been performed to address toxicity of drug substance (DS) and drug product (DP) impurities and degradation products. Finally, single- and repeat-dose studies have been performed to evaluate the toxicity of the TPV bulk fill solution formulation (i.e., for TPV capsules 250 mg). An

assessment of the safety of excipients in the TPV oral solution has been performed, based on information available in the literature, but no toxicity studies were performed to evaluate this formulation. Overall, the nonclinical pharmacokinetic and toxicology studies supported the use of tipranavir in Phase I, II, and III studies.

APPENDIX 1.2 GENERAL AND SAFETY PHARMACOLOGY

TPV was investigated in a number of general/safety pharmacology tests, a series of secondary pharmacodynamic immune function tests, and a biochemical receptor assay screen. TPV was well tolerated in most *in vivo* tests, with some effects seen in the renal and GI systems. TPV demonstrated an inhibitory effect *in vitro* on the HERG-associated potassium channel (I_{kr}). However, no effects were observed *in vitro* in action potential duration studies. TPV demonstrated no effects on QT prolongation in *in vivo* conscious dog ECG studies. Taken together, these *in vitro* and *in vivo* proarrhythmic risk studies suggest that TPV has little potential to prolong the QT interval; findings in the clinical support this view as no evidence of QT prolongation in humans has been shown. Finally, due to the targeted patient population, TPV was evaluated for effects on immune function, and slight to modest effects on T-cell activation in mice were observed.

In studies on renal function, TPV caused significant changes in sodium and potassium excretion following single oral doses of 62.5, 200 and 500 mg/kg in female rats and 62.5, 200 and 625 mg/kg in male rats. No relevant effects on water consumption, urine volume or chloride excretion were demonstrated. In studies on GI function at the same doses, TPV caused decreased gastric emptying and decreased GI propulsion in both female and male rats. In addition, gastric fluid volume was significantly increased in male rats at the high dose, and the acid concentration of the gastric fluid was significantly decreased in both female and male rats at the high dose levels studied. Acid output was not significantly altered.

TPV's potential to prolong QT interval was assessed both *in vitro* and *in vivo.* In HEK293 cells transfected with HERG cDNA to express the HERG-associated potassium channel (I_{kr}), TPV demonstrated an IC_{50} of 2.9 µM in a protein-free environment. Since TPV demonstrated no effects related to QT interval prolongation *in vitro* on action potential duration in the guinea pig papillary muscle assay at similar concentrations, or *in vivo* in conscious dog ECG studies following single administration, it is unlikely that the compound possesses a risk for causing cardiac arrhythmias, a finding supported by multiple clinical evaluations.

Due to the immunodeficient targeted patient population, TPV was evaluated for effects on immune function. In studies designed to assess effects on T-cell activation, TPV displayed some slight (25%) to modest (39%) effects in mice at a dose of 300 mg/kg (41µM, four hours post-administration). In other tests, TPV did not affect T-cell independent B-cell activation and did not exhibit immunogenic effects up to the limit of solubility.

APPENDIX 1.3 ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

The results of preclinical *in vitro* studies and *in vivo* pharmacokinetic/toxicokinetic studies in animals are summarized below:

Absorption

- Oral bioavailability after a single oral or intravenous dose of TPV in rats, dogs, mice, and rabbits was generally low to moderate (6.5 to 28%). Systemic exposure increased in a dose-dependent manner for all species administered repeated daily, oral doses of TPV. Levels in humans exceed levels achievable in animals.
- RTV boosted levels of TPV in all non-clinical species tested to various extents based on species and repeat dose toxicity studies.

Distribution

- Plasma protein binding was high with animal and human plasma. In human plasma at a TPV concentration of 20 µM, the unbound fraction was 0.032%. At 2 and 20 µM, the unbound fraction in cell culture was 0.12% and 3.7%, respectively.
- Following oral dosing, drug-related radioactivity was primarily associated with the liver and with the tissues and contents of the GI tract. Radioactivity did not readily cross the blood brain barrier. The pharmacokinetic parameters for radioactivity were similar for pigmented and non-pigmented rats. There was no apparent melanin binding. Partitioning of radioactivity into red blood cells was very low. The distribution of TPV with RTV co-administration was similar to that observed without RTV co-administration.
- Drug-related radioactivity was secreted in milk of lactating rats orally dosed with TPV and RTV. Radioactivity also crossed the placenta of pregnant rats.

Metabolism

- Since the onset of the Phase IIB development program, TPV is always co-administered with RTV in humans. With RTV co-administration, TPV accounted for most of the drug-related radioactivity in plasma, feces, and urine in the species studies to date, rat and human, with excreted metabolites accounting for only about 6% or less of the administered [14C]TPV. The observation of significantly decreased levels of metabolites is consistent with the mechanism of inhibition of metabolism by RTV. In vitro studies conducted in the absence of RTV do not reflect in vivo and are of limited significance.
- CYP3A is the predominant human isoform of CYP450 involved in TPV metabolism. TPV also appears to be a substrate for efflux transporter(s), in particular P-glycoprotein.

Elimination

- In mouse, rat, and dog, the main route of excretion of drug-related radioactivity following oral dosing of radiolabelled TPV (with RTV) was via feces (≥87%, ≥75 %, and ≥68%, respectively).
- Enterohepatic recirculation of TPV-related material was observed in rats

APPENDIX 1.4 TOXICOLOGY

Appendix 1.4.1 Single dose toxicity studies (acute toxicity)

In acute toxicity studies, the minimum lethal oral dose of TPV was 3000 mg/kg in mice, 1500 mg/kg in rats, and >500 mg/kg in dogs. Common findings among the species tested were gastrointestinal symptoms including emesis, soft stools and/or diarrhea. In rats, slight elevations of coagulation parameters were noted in females after single administration of 1500 to 3000 mg/kg.

Repeat dose toxicity studies

Primary target organs of TPV identified in mice, rats, dogs and/or monkeys in repeat-dose toxicity studies include the liver and gastrointestinal tract. Additional organs that were affected included the thyroid gland, testes, and to a lesser extent, the adrenal gland, kidneys, spleen, and heart. The changes in these organs are discussed below. None of the effects noted in target organs preclude use of TPV in humans.

Short-term Studies

Repeat dose toxicity studies of 2 to 13 weeks duration were conducted with TPV to identify target organs of toxicity in mice, rats, dogs, and cynomologus monkeys. TPV was administered by oral gavage (BID, 8 hours apart), 7 days per week. Selected studies were performed by TPV administered orally by diet or dermally via skin application. Identified target organs were the GI tract and liver in all species tested, and the thyroid gland in rodents.

Mice During 4 to 13 week oral gavage studies, TPV (≥80 mg/kg/day) reduced food consumption and body weight gains. Clinical pathology assessments revealed that ≥360 mg/kg/day increased activated partial thromboplastin time (aPTT), plasma fibrinogen concentrations and ALT, while daily doses of ≥400 mg/kg caused increased thyroxine and triiodothyronine (T4 and T3, respectively) concentrations with a trend to increased thyroid stimulating hormone (TSH). Doses of ≥300 mg/kg/day caused hepatocellular hypertrophy, vacuolation, and necrosis; and 800 mg/kg/day caused thyroid follicle cell hypertrophy.

Administration of TPV by dietary admixture for 13 weeks to mice at dose levels escalated up to 3240 mg/kg/day resulted in findings similar to those observed with oral gavage administration. Additional changes noted included heart changes of myocarditis and minimal to mild myocardial degeneration at =360 mg/kg/day and liver findings of cholangiohepatitis, Kupffer cell hyperplasia, and interstitial fibrosis at the escalated dose level. The heart was not noted as a target organ in any other studies with TPV in mice, nor in any other species tested. Dermal administration of TPV for 4 weeks in mice confirmed liver as a target organ, with similar changes as noted with organ gavage.

Rats During 2- and 4-weeks studies in rats, TPV (40 to 1,250 mg/kg/day) reduced food consumption and body weight gains and increased prothrombin and activated partial thromboplastin times. Thyroid effects included elevated plasma TSH and decreased plasma T3 and T4 concentrations, increased thyroid weights, and thyroid follicle cell hypertrophy. Liver weights were increased in a dose-related manner, and microscopic examination revealed hepatocellular hypertrophy. During the 4-week study, TPV was associated with increased adrenal gland weights, but histopathological correlates were not apparent.

Dogs During an 8-day study, TPV (75 to 300 mg/kg/day) caused emesis, soft stools, diarrhea, and increased alkaline phosphatase (AP). The highest dose increased liver weights, but histopathologic changes were absent. During a 4-week study with a 4-week recovery period, TPV (30 to 320 mg/kg/day) caused emesis, salivation, and soft stools/diarrhea. Doses =75 mg/kg/day caused decreases in body weights and decreased aPTT and increased AP both of which were reversible effects. Increased liver weights were observed with =160 mg/kg/day causing hepatocellular hypertrophy and 320 mg/kg/day causing hepatocellular hypertrophy associated with proliferation of smooth endoplasmic reticulum. Doses of =75 mg/kg/day increased adrenal weights, but there were no histopathologic correlates.

Non-human primates Male cynomologus monkeys had TPV-related emesis, diarrhea, and/or soft stools at all dose levels but most frequently at 320 mg/kg/day, the highest dose tested. At the conclusion of the 2-week study, there were elevated plasma fibrinogen concentrations in all dose groups. Histopathology data are not available because the animals were not sacrificed at the study conclusion. Studies in non-human primates have not been pursued beyond 2 weeks duration because of low systemic exposure to TPV in this species compared to that in rats and dogs.

Appendix 1.4.2 Chronic studies

Chronic studies in rats (26 weeks with 13 weeks of recovery) and dogs (39 weeks with 9 weeks of recovery) revealed target organ effects essentially identical to those observed during short-term studies. In addition, the dog testes and gallbladder were identified as target organs during the 39-week study, although further evaluation has determined that the former finding was without merit, as described below.

Rats TPV (0, 20, 40, 125, and 400 mg/kg/day) was administered for 26-weeks, and groups of Control and 400 mg/kg/day animals were afforded a 13-week recovery period after cessation of

dosing. The no observable toxic effect levels in this study were judged to be 40 and 20 mg/kg/day for males and females, respectively. TPV-associated changes consistent with earlier studies included dose-related increases in aPTT and PT (only in males), and hepatic and thyroid changes. Findings unique to the chronic study included decreases in red blood cell (RBC) parameters, increases in plasma total protein, globulin and albumin, urinary protein, and kidney weights and increased numbers of multinucleated hepatocytes, and increased incidences of chronic progressive nephropathy. Chronic progressive nephropathy is an age-related, rat-specific lesion; the increased incidence was considered to be a stress-related exacerbation of a naturally occurring disease and not a primary effect of TPV on the kidneys. Changes observed in 400 mg/kg/day rats afforded 13-weeks for recovery included increased urinary protein in females, increased liver weights in both sexes, slightly increased kidney weights, increased incidences of chronic progressive nephropathy and multinucleate hepatocytes in both sexes. The magnitude of these changes after recovery was small relative to changes observed at the time of cessation of dosing, suggesting reversibility of the findings.

Dogs TPV (0, 20, 75, and 320 mg/kg/day) was administered to dogs for 39 weeks, and reversibility of induced changes was assessed after a 9-week recovery period. The no observable toxic effect dose level was judged to be 20 mg/kg/day in both sexes. Consistent with short-term studies, TPV caused emesis, salivation and soft stools, increases in alkaline phosphatase, hepatomegaly, and hepatocellular hypertrophy during the chronic study. TPV-associated changes unique to the chronic study in dogs included 10-15% decreases in total plasma protein, albumin, and albumin/globulin ratio, RBC parameters and calcium. Microscopic changes, included hepatocellular hypertrophy, splenic hematopoiesis, cystic hyperplasia of the gallbladder, testicular degeneration/atrophy, and bile duct hyperplasia. Cystic hyperplasia of the gallbladder was present but less prominent in high-dose dogs afforded the 9-week recovery period. One of three recovery group males also exhibited degeneration of the seminiferous tubules and abnormal germ cells in the epididymis. Re-evaluation of testes changes by a group of experts revealed that the microscopic findings in the testes were within normal variation for beagle dogs. Consequently, testes were judged not to be a target organ in this study.

Appendix 1.4.3 TPV-ritonavir co-administration studies

Co-administration of TPV and RTV for 4 weeks in mice and for up to 26 weeks in rats and dogs revealed no target organs other than those already identified for each drug, nor did co-administration exacerbate the known toxicity of either drug. Toxicokinetic assessments revealed that co-administration of the drugs increased systemic exposure to TPV while decreasing exposure to RTV in both species.

Mice In a 4-week study in mice (15/sex/group), TPV was co-administered with RTV in a 3.75:1 ratio, the same dose ratio as the clinical dose of 750/200 TPV/r BID. Dose levels included 0, 150/40, 300/80, and 600/160 mg/kg/day TPV/RTV, 600 mg/kg/day TPV, or 160 mg/kg/day RTV. The principal organ of toxicity was the liver, and changes upon co-administration were the same as with TPV alone. Hypertrophy of the zona fasciculate of the adrenal was noted in males only at 600/160 mg/kg/day TPV/RTV and to a lesser extent at 600 mg/kg/day TPV. Secondary changes consisting of spontaneous changes in mice exacerbated

by treatment included mixed cell infiltrates and focal mineralization in the parenchyma of the liver, granulocytic hyperplasia in the bone marrow, extramedullary hematopoesis in the spleen, and lymphoid follicular hyperplasia in the spleen.

Rats In a 2-week dose range-finding (5/sex/group) and a 26-week study in rats (20/sex/group), TPV and RTV were co-administered in a consistent TPV: RTV ratio of 3.75:1. In the 26-week study, administered doses included 0, 120/32, 600/160, or 1200/320 mg/kg/day TPV/r, 1200 mg/kg/day TPV, or 160 mg/kg/day RTV. In both studies, co-administration of TPV and RTV resulted in toxicities common to the individual compounds administered separately. Target organs resulting from the gavage administration of TPV/r co-administration to rats for 26 weeks comprised effects seen previously on the thyroid gland and liver with TPV, with additional liver findings including an increased incidence in karyomegaly, a documented finding in rat studies with RTV. At high dose levels administered in this study, effects on aPTT and PT were augmented, with resultant observations of excessive hemorrhage and consequent increases in lethality, notably in males. Lymphoid depletion of multiple tissues, thymic lymphocytolysis, and subcutaneous fat depletion were observed at high dose levels. Bilateral testicular degeneration was noted in males administered the high-dose of TPV/r. When TPV was administered alone, target organs were similar to those of TPV/r at the same TPV dose level, with the exception that no hepatic karyomegaly was observed, and there were no testicular findings. Hepatic karyomegaly and testicular degeneration are findings associated with RTV administration, with the former finding observed in this study at the RTV alone dose level, but the latter finding not evident. Testes changes were re-evaluated by an expert panel. These testicular changes in rats, seen in only three animals at a high dose level, were morphologically and pathogenically unrelated and therefore not related to drug treatment. Consequently, testes are not considered to be a target organ of toxicity.

Dogs Two-week (1 dog/sex/group) and 26-week (3 dogs/sex/group) toxicity studies were conducted with co-administered dosage regimens of 15/4, 37.5/10, or 75/20 (escalated to 150/40) mg/kg/day TPV/r. Additional groups of dogs received TPV or RTV alone. Treatment-induced emesis was the dose-limiting factor during these studies. Co-administration of the drugs did not influence toxicity, although during the 26-week study a single female (75-150/20-40 TPV/r) exhibited mild, diffuse hypertrophy superficial transitional epithelium of the urinary bladder. Similar to studies with TPV alone, hepatocellular hypertrophy was observed in a dose-related fashion. Conversely, microscopic changes in the bone marrow, gallbladder, and spleen were seen in dogs dosed with TPV and RTV alone but not in animals administered both drugs. A no toxic effect level was not determined, due to the presence of hepatocellular hypertrophy at 15/4 mg/kg/day.

Repeated administration of TPV has been shown to increase activity of hepatic drug metabolizing enzymes CYP2B and CYP3A in rats and, to a lesser degree, in dogs. The toxicokinetics results of these drug-drug interaction studies most likely reflect a preferential metabolism of RTV by the induced CYP2A and CYP3A.

Summary of Effect on Target Organs

Effects on the GI System GI effects of TPV, observed in all species tested, may reflect local actions, although correlative macro- or microscopic changes have not been observed. Addition of RTV to TPV dosage regimens was without effect on either the incidence or severity of GI effects in rats and dogs.

Effects on the Liver Hepatic effects of TPV were dose-related, reversible, and likely reflective of hepatic enzyme induction. Increases in liver weights in rats and dogs were correlated with increased CYP3A and CYP2B content, and hepatocellular hypertrophy was characterized by small mitochondria in rats and proliferation of smooth endoplasmic reticulum in rats and dogs. At higher doses, rodents showed evidence of hepatocellular degeneration (including vacuolation), mineral deposition in mice, and multinucleated hepatocytes in rats. Karyomegaly, a well-documented effect of RTV in rats, was observed at a low incidence in rats administered TPV/r for 26 weeks. In mice, clinical chemistry evaluation revealed the presence of enzyme leakage (e.g., ALT, AST) at high dose levels, mirrored in the histopathologic evaluation as hepatocellular necrosis. Changes in coagulation indices, observed only in rodents, were judged secondary to hepatic enzyme induction and/or effects on vitamin K recycling. In contrast, no adverse effects on coagulation were noted in dogs receiving TPV alone up to 39 weeks or TPV/r up to 26 weeks.

Effects on the Testes Testicular effects consisting of decreased weights and bilateral seminiferous tubule degeneration and/or atrophy were observed in a 26-week TPV/r study in rats and a 39-week TPV study in dogs. Re-evaluation of these data by an expert panel indicated that the findings in the beagle dog were within normal limits of variation. The testicular changes in rats, seen in only three animals at a high dose level, were morphologically and pathogenically unrelated and therefore not related to drug treatment. Consequently, testes are not considered to be a target organ of toxicity.

Effects on the Thyroid Gland in Rodents Thyroid gland changes in TPV-dosed rodents are considered to reflect a rodent-specific increase in thyroid hormone metabolism secondary to induction of hepatic drug metabolizing enzymes. The primary clearance of thyroid hormone in rodents is via glucuronidation and biliary excretion, whereas humans readily deiodinate T4 and T3, making conjugation a minor elimination pathway.

Additional Effects Chronic progressive nephropathy (CPN) is a spontaneous, age- and stress-related change commonly observed in rats. Increased urinary protein observed in TPV-dosed rats was considered due to exacerbation of CPN by stress and therefore an action without predictive validity for humans.

Increased extramedullary hematopoiesis was observed in the spleen in mice, rats, and dogs. This finding was judged secondary to the mildly reduced red blood cell parameters in rats and dogs, and hemorrhage observed in the 26-week TPV/r rat study.

Adrenal gland effects consisted of increased adrenal weights without correlative microscopic changes, with the exception of one 4-week study in mice where hypertrophy of the zona fasciculata was observed at the highest TPV and TPV/RTV dose levels. Based on the high dose

levels that caused these findings, the minimal to mild effects noted, and the lack of biologically relevant changes in dogs, the effects on the adrenal gland in rodents were attributed to stress, and not a direct effect of TPV.

Minimal to mild myocardial degeneration was observed in one study in mice when TPV was administered by diet over 13 weeks. No heart changes were observed in any gavage administration study in mice up to 13-weeks, nor have heart changes been seen in any study in rats or dogs, up to 26- and 39-weeks, respectively. Consequently, the significance of this finding in relation to humans is unclear. However, it is judged that TPV, if it had any cardiotoxic liability, would have caused cardiac changes in multiple species, or consistently in one species, rather than showing evidence in only one study.

Appendix 1.4.4 Genotoxicity studies

TPV was neither mutagenic nor clastogenic in a battery of five *in vitro* and *in vivo* assays widely employed for the assessment of genotoxicity. *In vitro* tests included the Ames Assay, assessment of unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, and a chromosome aberration assay in human peripheral lymphocytes. The *in vivo* test was a micronucleus assay in mice.

Appendix 1.4.5 Reproduction toxicology

Fertility and Embryotoxicity

TPV administered at dose levels as high as 1000 mg/kg/day was without effects on spermatogenesis, estrous cycles, copulation, conception, fertility, implantation, or early embryonic development in rats. A dose of 1000 mg/kg/day produced a C_{max} of 258 µM in female rats.

Teratogenicity

Rats In both range-findings and definitive studies, TPV at oral dose levels of 40 to 1000 mg/kg/day showed no evidence of teratogenicity or embryolethality. However, maternal toxicity, as well as decreased fetal body weight and sternebrae ossification, was observed at dose levels of 400 mg/kg/day and above. Consequently, the no toxic effect level for maternal and developmental toxicity was 40 mg/kg/day, corresponding to a mean C_{max} and AUC of 30.4 µM and 304 µM·h, respectively.

Rabbits TPV was without teratogenic effect when administered to pregnant rabbits in daily (gestation Days 6 through 20) doses up to 150 mg/kg, although that dose caused maternal toxicity (abortion). During a dose range-finding study in pregnant rabbits, daily administration of up to 750 mg/kg was embryotoxic and produced maternal (e.g., deaths, abortions, decreased body weight) and developmental toxicity (i.e., decreased fetal weights), but neither external malformations nor variations. However, in a definitive study in rabbits, 375 mg/kg/day of TPV

caused maternal toxicity similar to that previously seen at 750 mg/kg/day in the range-finding study, as well as developmental toxicity (i.e., decreased fetal weight, increased gross malformations). Gross malformations included dome-shaped head (with associated hydrocephaly), omphalocele, carpal flexure, bent femurs, arthrogryposis, and wavy ribs. It is noteworthy that a single litter was responsible for 75–80% of fetuses with gross and visceral malformations and 50% with skeletal malformation. This suggests that anomalies may have been due to a litter effect rather than a TPV-induced teratogenesis. Consequently, the maternal no toxic effect level was determined to be 75 mg/kg/day, while the fetal no toxic effect level was 150 mg/kg/day. These dose levels were associated with steady state C_{max} values of 4.9 and 8.4 µM and AUC_{0-24} values of 66 and 120 µM·h/mL, respectively. Based on the lack of characteristics typical of known developmental toxicants coupled with the marked maternal toxicity observed, the results of these experiments in rabbits support a conclusion that TPV is not a selective developmental toxicant.

Pre-natal and Postnatal Studies

In a pre-natal and postnatal development study in rats, an oral dose of 40 mg/kg/day of TPV was considered a no toxic effect level in dams and pups if administered from Day 6 of gestation to Day 21 postpartum. Administration of 400 mg/kg/day and above caused dose-related maternal toxicity and retarded pup growth, but no post-weaning functions were affected nor was there any evidence of teratogenicity at any dose level.

Appendix 1.4.6 Other toxicity

Immunotoxicity

Daily exposure of female CD-1 mice (10/group) to TPV co-administered with RTV, TPV alone, or RTV alone for a period of 28 days did not result in alterations of the major organs of the immune system, the thymus or the spleen, or on the humoral immune response as evaluated in the IgM antibody-forming cell response to the T-dependent antigen, sheep red blood cells. TPV was co-administered with RTV at dose levels of 30/8, 100/26.7, or 300/80 mg/kg/day TPV/RTV. In addition, a Sham Control group, Vehicle Control group, Positive Control group, and TPV alone (300 mg/kg/day) and RTV alone (80 mg/kg/day) groups were included in this study. In TPV/RTV, TPV, or RTV-treated groups, there was no statistically significant effect on spleen cell number or IgM production when evaluated as either specific activity or as total spleen activity. The Positive Control (cyclophosphamide), behaved as expected, resulting in decreases in mean thymus and spleen weights as well as a 99% decrease in specific activity and 100% decrease in total spleen activity. Therefore, under the conditions of this study, TPV administered with or without RTV was considered to have no effect on the T-dependent immune response of CD-1 female mice.

Evaluation of Formulations

The toxicity of various TPV SEDDS formulations has been investigated in a series of toxicity studies in rats and dogs. In rats, acute to 13-week studies revealed no toxicities specific to the SEDDS formulation at up to 2 mL/kg/day or ~30-fold the equivalent human exposure on a body weight basis. The 26-week safety study in beagle dogs was designed to particularly address the toxicity of one excipient of the bulk fill solution, Cremophor EL (CrEL; polyoxyl castor oil 35). Dogs have been shown to be a species sensitive to effects of CrEL. To this end, this dog study employed a SEDDS formulation similar to the bulk fill solution in that the levels of excipients were in the same ratios, but volume of the SEDDS formulation administered was varied while the level of TPV/RTV present was fixed in the treatment groups. In this study, Control and High-dose dogs were exposed to approximately 30-fold the human exposure of CrEL at a TPV/RTV dose of 500/200 mg BID, based on body weight (mg/kg/day). Results of this study indicate leukocytosis with neutrophilia, as well as an increase in liver AP isoenzymes, related to exposure to the high-dose level of SEDDS vehicle. Mortality occurred in one Control female exposed to 30-fold the human exposure of CrEL. No changes in dogs were noted at 10-fold human exposure to SEDDS. Further, no CrEL was detectable during analysis of plasma samples from over 100 patients receiving TPV in the SEDDS formulation. The formulation at the proposed human dose of 500/200 mg BID TPV/RTV is considered safe for use in humans. The exposure to other excipients present in the TPV SEDDS formulation is considered within standards for pharmaceutical use of these materials.

The components of the TPV oral solution formulation are different than those of the TPV bulk fill solution used in TPV capsules 250 mg. This formulation has not been evaluated in toxicity tests in animals. However, an evaluation of its individual components has been performed, based on literature review. In this review, the addition of excipients contained in RTV oral solution have been taken into account, as this formulation contains propylene glycol (PG) as well as 43% ethanol.

The levels of the following excipients are above WHO acceptable limits when TPV and RTV oral solutions are co-administered: polyethylene glycol 400 (PEG 400), propylene glycol, and Vitamin E TPGS. All other excipients are within acceptable limits. Key issues relating to these excipients above WHO acceptable limits are discussed below. However, the levels of all excipients present are considered appropriate with the caveats described under the key issues.

The level of propylene glycol (PG), when TPV and RTV oral solutions are co-administered, is above WHO acceptable limits, but is considered safe, as toxicity of PG is very low. Review of potential PG exposure revealed that PG levels with RTV co administration are below that of currently marketed formulations (e.g., Norvir® oral solution). Consequently, no precautionary labeling is warranted. There are concerns regarding metabolism of this excipient in infants and children less than 2 years of age, due to the low levels of the PG-metabolizing enzyme alcohol dehydrogenase expressed by young livers. Consequently, caution must be exercised when administering this combination to infants or children less than 2 year of age when administering TPV oral and RTV oral solutions along with other prescription and/or non-prescription

medications containing propylene glycol and/or ethanol. Clinically, CNS effects similar to those of ethanol intoxication should be monitored for, e.g. stupor, ataxia.

PEG 400, at this dose level, may contribute somewhat to GI disturbances such as soft stool and/or diarrhea, but these effects may not be distinguishable from the GI side-effects of TPV itself. There are no systemic toxicity concerns regarding the level of PEG 400 in the TPV oral solution formulation, based on literature assessment.

Due to the presence of Vitamin E TPGS at 300 mg/mL in the TPV oral solution, it is recommended that the labeling state that Vitamin E supplementation should not be taken along with this medication since the Vitamin E content of this product exceeds the Reference Daily Intake (30 IU/day for adults and children over 4, 10 IU/day for children under 4, and 5 IU/day for infants). At the therapeutic dose level of 500/200 mg TPV/RTV BID, an individual would consume 1160 IU Vitamin E/day when taking the oral solution. Literature indicates a tendency for high doses of Vitamin E to cause an anticoagulant effect. A number of studies in rats with oral administration of high dose levels of tocopherols showed increases in prothrombin and partial thromboplastin times along with hemorrhages in the epididymis and other organs. The biochemical mechanism(s) of the reduction of blood coagulation factors II, VII, IX, and X by Vitamin E has not been studied, but are considered linked to Vitamin K cycling. Evidence from several large clinical trials in which human adults received 300-800 IU of Vitamin E daily for 1.4-4.5 years showed no increased risk of stroke, but at least one study (ATBC Cancer Prevention study) reported an increased mortality from hemorrhagic stroke in male smokers receiving 50 IU of Vitamin E daily. An increase in hemorrhagic stroke was not detected in a 2 year study in Alzheimer's patients receiving 2100 IU of Vitamin E daily. Oral Vitamin E, up to a daily intake of 600 IU for up to 3 years in healthy individuals, did not adversely affect blood coagulation. However, the possibility that the relatively high dosages of Vitamin E could exacerbate coagulation defects in individuals who are deficient in Vitamin K or are receiving anticoagulant therapy, suggests that caution is warranted.

APPENDIX 2 TPV CLINICAL TRIAL PROGRAM

APPENDIX 2.1 BIOPHARMACEUTIC STUDIES

Table 1 Listing of Biopharmaceutic Studies

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Biopharmaceutic Studies									
PK/Safety Phase I	No BI study number U00-3208	United States	• To assess the effect of RTV on the PK of TPV; • To assess the effect of TPV on the PK of RTV; • To assess PK of TPV given q 12 h; • To assess the short term safety and tolerance of TPV + RTV	Open-label, multiple-dose, single-treatment	TPV: 1350-mg dose BID: 150-mg HFC x 9 RTV: escalating doses: 100-mg capsules x 2, 3, 4, 5 – all BID, except as noted Day 1-7: TPV 1350 mg BID (AM dose only Day 7) Day 8-9: RTV 200 mg Day 10-11: RTV 300 mg Day 12-15: RTV 400 mg Day 16-31: RTV 500 mg (AM dose only on Day 31) Day 22-31: TPV 1350 mg BID (AM dose only on Day 31)	n = 14	HIV-1 negative, healthy male and female volunteers	31-day study period	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 1 (continued) Listing of Biopharmaceutic Studies (Page 2 of 3)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Biopharmaceutic Studies (continued)									
PK/Safety Phase I	1182.5 U01-3295	United States	• Determine the effects of TPV/r on the cytochrome P-450 activity; • Establish the dependency of the TPV M1 metabolite on RTV co-administration; • Evaluate the short term safety and tolerance of TPV/r.	Open label, parallel group	TPV 250 mg/RTV 200 mg BID; TPV 500 mg/RTV 100 mg BID; TPV 500 mg/RTV 200 mg BID; TPV 750 mg/RTV 100 mg BID; TPV 750 mg/RTV 200 mg BID; TPV 1000 mg/RTV 100 mg BID; TPV 1000 mg/RTV 200 mg BID; TPV 1250 mg/RTV 100 mg BID	n = 13 n = 13 n = 13 n = 12 n = 14 n = 14 n = 13 n = 21 Total = 113	Healthy HIV negative volunteers	10 days TPV monotherapy, then 21 days of TPV/r therapy: 31 days total	Complete; Final report
PK Phase I	1182.45 U04-1751	Germany	• Evaluate the bioavailability of TPV/r solution vs. TPV/r capsules • Evaluate the bioavailability of TPV/r solution with food vs. without food.	Open label, single-dose, three-way crossover trial	Liquid and SEDDS TPV formulations	n = 30	Healthy HIV negative volunteers	1 day (single dose) for each treatment, total 3 days	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 1 (continued) Listing of Biopharmaceutic Studies (Page 3 of 3)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Biopharmaceutic Studies (continued)									
PK/Safety Phase I	No BI study number U00-3267	United States	• To assess the bioavailability of three SEDDS TPV formulations relative to a 300-mg TPV HFC formulation • To assess the effect of a high-fat meal on the bioavailability of TPV SEDDS and HFC formulations • To assess short-term safety	Randomized, open-label, four-way crossover + fifth treatment period to assess food effect	TPV: single 1200-mg dose A) 4 x 300-mg HFC capsules B) 4 x 300-mg SEC (SEDDSno-base) C) 4 x 300-mg SEC (SEDDS, Tris with GDO/GMO) D) 5 x 240 mg HFC (SEDDS, Tris with Capmul MCM) Fifth period: Treatments A, B, C, D with high-fat meal	n = 16	HIV-1 negative, healthy male and female volunteers	31-day study period	Complete; Final report
PK/Safety Phase I	No BI study number U01-3056	United States	• To assess the bioavailability of two 300-mg SEDDS TPV formulations relative to a 300-mg TPV HFC formulation • To assess safety and tolerability	Randomized, open-label, parallel-group	TPV: 1200 mg BID: 300-mg SEDDS x 4 and 2400 mg BID: 300 mg HFC x 8 • 8 x 300-mg HFC • 4 x 300-mg SEC (SEDDS no-base) • 4 x 300-mg SEC (SEDDS, Tris with GDO/GMO)	n = 18	HIV-1 negative, healthy male and female volunteers	10-day study period	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

APPENDIX 2.2 HUMAN PHARMACOKINETIC STUDIES

Table 2 Listing of Human Pharmacokinetic Studies

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies									
PK Phase I	No BI study number U00-3265	United States	•Evaluate the safety and PK of multiple doses of TPV after an oral administration to normal healthy volunteers	Single-center, randomized, double-blind PBO-controlled escalating dose	PBO capsules TPV hand filled Capsules (free acid equivalent capsules): 100 mg and 300 mg Doses given: 300 mg 600 mg 900 mg 1200 mg 1600 mg 2000 mg	n = 12 n = 36 n = 6 n = 6 n = 6 n = 6 n = 6 n = 6 Total = 48	HIV-1 negative, healthy male and female volunteers	Single dose, followed by 2 days of no drug and then 9.3 days of multiple doses	Complete; Final report

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 2 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
Safety, Efficacy and PK Phase II	1182.1 U01-3010 U02-3090	United States	- Determine the safety, tolerance, maximum tolerated dose, and PK of TPV with two NRTIs in patients who have received the same two NRTIs for a minimum of 2 months and who have not previously been treated with PIs. - Determine the efficacy of TPV when administered in combination with two NRTIs to PI-naïve patients.	Open label, non randomized	PI naive: TPV 900 mg TID; TPV 1200 mg TID; TPV 1500 mg TID PI experienced (Exp): TPV 1500 mg TID Hard filled capsules (HFC) Optional Extension TPV 1200 mg TID TPV 1500 mg TID (up to 184 weeks) HFC then SEDDS	 n = 8 n = 8 n = 8 naïve = 24 Exp = 16 Trial total = 40 n = 1 n = 1 Total = 2	HIV positive patients; PI-naïve and PI-experienced	PI-naïve: 24 weeks with optional extension; PI-experienced: 4 weeks with optional extension	Complete; Final report
PK (ADME mass balance) Phase I	1182.24 U03-3605-01	United States	- To characterize the excretion balance and metabolite profile of ^{14}C-radiolabelled TPV in healthy male subjects.	Open label, single dose ^{14}C TPV 500 mg labelled with RTV 200 mg	TPV 500 mg/RTV 200 mg BID for 7 days followed by a single dose ^{14}C TPV 500 mg /RTV 200 mg , followed by TPV 500 mg/RTV 200 mg BID for 7-14 additional days as specified	n = 12	Healthy HIV negative male volunteers	Up to 3 weeks	Complete; Final report

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 3 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK (hepatic insufficiency) Phase I	1182.32 U04-3373	Canada	- To provide dosage recommendations in patients with different severities of hepatic impairment.	Open label	TPV 500 mg/RTV 200 mg single dose oral	n = 20 in SCS n = 24 in final report 9 mild/ 9 controls; 3 moderate /3 controls	Hepatic impaired, HIV negative patients with matching controls	1 week for mild hepatic insufficiency; single-dose for moderate hepatic insufficiency	Complete; Final Report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 4 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK Phase I-IIa	1182.6 U03-3131-01	Belgium, Germany, Denmark, Spain, France, United States	- Determine the effects of three dose combinations of TPV/r on the steady state of zidovudine, lamivudine, stavudine, abacavir, didanosine, nevirapine and efavirenz.	Open label, sequential PK	TPV 250 mg/RTV 200 mg BID; TPV 750 mg/RTV 100 mg BID; TPV 1250 mg/RTV 100 mg BID with zidovudine, lamivudine, stavudine, abacavir, didanosine, nevirapine and efavirenz.	n = 87 n = 63 n = 58 Total = 208	HIV positive patients	PK exposure 22 days, with optional safety extension of 20 weeks	Complete; Final report
PK Phase I	1182.37 U03-3120-01	United States	- Characterize the effects of two dose combinations of TPV/r administered BID on the PK of zidovudine (ZDV) and ZDV-glucuronide and the effects of ZDV on the PK of TPV and RTV.	Randomized, open label, parallel group	TPV 500 mg/RTV 100 mg BID; TPV 750 mg/RTV 200 mg BID and ZDV 300 mg on Days 1 and 13	n = 30 n = 30 Total = 60	Healthy HIV negative volunteers	13 days (12 days TPV/r)	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 5 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK Phase I	1182.42 U03-1070	Germany	- Evaluate the PK interaction between two doses of TPV/r administered BID at steady state with single-dose didanosine.	Randomized, open label, parallel group	TPV 500 mg/RTV 100 mg BID; TPV 750 mg/RTV 200 mg BID and ddI 400 mg on Days 1 and 15.	n = 11 n = 12 Total = 23	Healthy HIV negative volunteers	15 days (14 days TPV/r)	Discontinued; Final report
PK Phase I	1182.46 U04-1249-01	United Kingdom	- Evaluate the PK interaction between two doses of TPV/r administered BID with single-dose tenofovir capsules	Randomized, open label, parallel group	TPV 500 mg/RTV 100 mg BID; TPV 750 mg/RTV 200 mg BID And tenofovir 300 mg on Days 1 and 13	n = 24 n = 25 Total = 49	Healthy HIV negative volunteers	13 days (12 days TPV/r)	Complete; Final report
PK Phase I	1182.41 U03-3217-01	United States	- Characterize the PK interaction between two doses of TPV/r administered BID with efavirenz[2].	Randomized, open label, parallel group	TPV 500 mg/RTV 100 mg BID; TPV 750 mg/RTV 200 mg BID and EFV 600 mg	n = 34 n = 34 (32 TPV treated) Total = 68 (66 TPV treated)	Healthy HIV negative volunteers	19 days (10 days TPV/r)	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 6 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK Phase IIb	1182.51 U04-1726	Australia, Belgium, Canada, Germany, Denmark, France, Greece, Italy, Netherlands, Switzerland, United Kingdom, United States	- To evaluate the PK of TPV/r alone or with SQV, APV or LPV plus an OBR	Randomized, open label, parallel group	TPV 500 mg/RTV 200 mg BID alone or with SQV, APV or LPV plus an OBR	Total = 315 TPV treated = 308 CPI only = 7	HIV positive patients	24 weeks	Complete; Final report
PK Phase I	1182.10 U04-3100	Canada	- Drug interaction potential of fluconazole and TPV/r	Open label, (A) fluconazole; (B) TPV/r A + B	Fluconazole 200 mg TPV 500 mg/RTV 200 mg single oral doses	n = 20	Healthy HIV negative volunteers	13 days (7 days TPV/r)	Complete; Final report
PK Phase I	1182.44 U04-3198	Canada	- To characterize the drug interaction potential of rifabutin and TPV/r (including metabolites)	Open label (A) rifabutin; (B) TPV/r A + B	TPV 500 mg/RTV 200 mg Rifabutin 300 mg on Days 1 and 15	n = 24	Healthy HIV negative volunteers	14 days (13 days TPV/r)	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 7 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK Phase I	1182.11 U04-1257	Canada	- To characterize the drug interaction potential of clarithromycin and TPV/r (including metabolites)	Open label (A) clarithromycin; (B) TPV/r A + B	Clarithromycin 500 mg TPV 500 mg/RTV 200 mg single oral doses	n = 24	Healthy HIV negative volunteers	13 days (8 days TPV/r)	Complete; Final report
PK Phase I	1182.21 U04-3216	Canada	- To characterize the drug interaction potential of atorvastatin and TPV/r (including metabolites)	Open label, (A) atorvastatin; (B) TPV/r A + B	Atorvastatin 20 mg TPV 500 mg/RTV 200 mg single oral doses	n = 23	Healthy HIV negative volunteers	11 days (10 days TPV/r)	Complete; Final report
PK Phase I	1182.22 U03-3408	Canada	- Characterize the PK interaction between two doses of TPV/r administered BID on the PK characteristics of norethindrone-ethinyl estradiol (NET/EE Ortho® 1/35).	Open label, Randomized, parallel group	TPV 500 mg/RTV 100 mg BID; TPV 750mg/RTV 200 mg BID TPV/r on Days 4–16 and NET/EE Ortho® 1/35 on Days 1 and 15	n = 26 n = 26 Total = 52	Healthy HIV negative, female volunteers	16 days (13 days TPV/r)	Discontinued ; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 2 (continued) Listing of Human Pharmacokinetic Studies (Page 8 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacokinetic Studies (continued)									
PK/PD drug interaction Phase I	1182.55 U04-3125	United States	-To determine if the co-administration of loperamide with TPV or RTV or with the combination of TPV/r causes a clinically significant change in respiratory response to carbon dioxide.	Open label, randomized, parallel group	TPV 750 mg/RTV 200 mg BID TPV 500 mg/RTV 200 mg BID and loperamide 16 mg on Days 1, 9 and 22 TPV 750 mg or RTV 200 mg and loperamide 16 mg on specified study days, then TPV 750 mg/RTV 200 mg BID and loperamide 16 mg daily on specified study days[3]	n = 12 n = 12 n = 24 Total = 24	Healthy HIV negative volunteers	TPV or RTV for 5.5 consecutive days. Subsequent to this, all subjects received TPV/ r for 10.5 consecutive days. All subjects received loperamide on Days 1, 9, and 22.	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

APPENDIX 2.3 HUMAN PHARMACODYNAMIC STUDIES

Table 3 Listing of Human Pharmacodynamic Studies

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective (s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacodynamic Studies (continued)									
Safety, Efficacy and PK Phase II	1182.3 U01-3009 U01-3352	Puerto Rico, United States, South Africa	- To evaluate the effectiveness and the safety and tolerability of TPV alone and two TPV/r dose combinations.	Open label, Randomized, parallel group	TPV 1200 mg BID; TPV 300 mg/RTV 200 mg BID; TPV 1200 mg/RTV 200 mg BID (all SEDDS)	n = 10 n = 10 n = 11 Total = 31	HIV positive patients; ARV naïve	14 days with TPV alone or in combination with RTV; Optional extension with DLV, ZDV, and 3TC for additional 46 weeks with no TPV	Complete; Final report on 14-day portion; Safety Summary of 18 patients on 46 week optional extension (no TPV).

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 3 (continued) Listing of Human Pharmacodynamic Studies (Page 2 of 2)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Human Pharmacodynamic Studies (continued)									
PK and Safety Pediatrics Phase I/IIA	1182.14 U04-3384	Argentina, Brazil, Canada, France, Germany, Italy, Spain, Mexico, United States	- To obtain information concerning the safety, tolerability, and PK of TPV together with low-dose RTV in subjects 2-18 years old that will provide a systemic exposure similar to adults.	Open label, randomized, dose finding	TPV 290 mg/m^2 BID /RTV 115 mg/m^2 BID + OBR or TPV 375 mg/m^2 BID /RTV 150 mg/m^2 BID + OBR Liquid TPV formulation = 100 mg per mL Liquid RTV formulation = 80 mg per mL All subjects take TPV liquid formulation for the initial 4 weeks. After that adolescents will be offered the option to cross over to an equivalent TPV dose using the SEDDS 500 mg BID	57 randomized and treated with at least one dose of study drug; however, only 37 patients had CRFs entered in the database at the time of data cut-off.	HIV positive patients: PI experienced and naïve children between 2-18 years of age	48 weeks with optimal safety extension	Ongoing; Summary Report , up to 4-week data

NOTE: Footnotes and translations of abbreviations for this table follow below.

APPENDIX 2.4 CLINICAL EFFICACY AND SAFETY STUDIES

Table 4 Listing of Phase II and III Efficacy and Safety Studies (Page 1 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies									
Safety and Efficacy Phase II	1182.2 U03-3006	United States	- To evaluate the antiviral activity and safety of two regimens of TPV/r given with one new NRTI + one new NNRTI (efavirenz) in multiple PI-experienced HIV positive patients.	Open label, randomized, parallel group	TPV 1200 mg HFC (hard filled capsules)/ RTV 100 mg BID, subsequently: TPV 500 mg (SEDDS)/RTV 100 mg BID TPV 2400 mg HFC/RTV 200 mg BID, subsequently: TPV 1000 mg (SEDDS)/RTV 100 mg BID EFV 600 mg QD	n = 19 n = 22 Total = 41	HIV positive patients: multiple PI-experienced with clinical virological failure; NNRTI naïve	24 weeks with an optional extension period up to 112 weeks	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 2 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies									
Safety and Efficacy Phase II	1182.4 U03-3207-01	France, Italy, United States	- To evaluate the safety and efficacy of two TPV/r doses compared with that of a standard dual PI combination and to evaluate the dose response of the two TPV/r doses.	Open label, randomized, active control	TPV 500 mg /RTV100 mg BID; TPV 1250 mg /RTV 100 mg BID; Saquinavir 400 mg / RTV 400 mg BID	n = 25 n =25 n = 29 Total = 79 2 additional patients entered but were not treated.	HIV positive patients: single PI-experienced with clinical virological failure; NNRTI experienced	24 weeks with an optional extension period up to 96 weeks	Complete; Final report
Safety, Efficacy and PK Phase IIb	1182.52 U03-3236-03	Australia, Canada, Germany, Spain, France, Italy, Netherlands, United Kingdom, United States	- To demonstrate the most tolerable and effective dose of TPV/r for use in Phase III studies.	Randomized, double-blind, dose optimization	TPV 500 mg/RTV 100 mg BID; TPV 500 mg/RTV 200 mg BID; TPV 750 mg/RTV 200 mg BID	n = 73 n = 72 n = 71 Total = 216	HIV positive patients; multiple PI-experienced with primary PI resistance mutations on TRUGENE® testing; NNRTI experienced.	2 weeks functional monotherapy (TPV/r + current ARV therapy); then 10-30 weeks TPV/r + optimized ARV; up to 32 weeks total	Complete; Final report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 3 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies (continued)									
Safety, Efficacy and PK Phase III	1182.12 U04-3339	Australia, Canada, United States	- Determine the safety and efficacy of TPV/r versus an active control arm in highly treatment experienced HIV positive patients.	Open label, randomized, active control	TPV 500 mg/RTV 200 mg BID or CPI/RTV, stratified according to pre-selected PI.	n = 313 entered, 311 treated n = 317 entered, 309 treated Total = 630 entered, 620 treated	HIV positive patients	96 weeks	Ongoing; Interim report, up to 24-week data

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 4 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies (continued)									
Safety, Efficacy and PK Phase III	1182.48 U04-1526	Argentina, Austria, Belgium, Brazil, Germany, Denmark, Spain, France, Greece, Ireland, Italy, Luxembourg, Mexico, Netherlands, Portugal, Sweden, Switzerland, United Kingdom	- Determine the safety and efficacy of TPV/r versus an active control group in highly treatment-experienced HIV positive patients.	Open label, randomized, active control	TPV 500 mg/RTV 200 mg BID or CPI/RTV, stratified according to pre-selected PI.	n = 442 entered, 435 treated n = 437 entered, 428 treated Total = 879 entered, 863 treated	HIV positive patients	96 weeks	Ongoing; Interim report, up to 24-week data

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 5 of 8)

Type of Study	Study No. and BI Report No. (P& U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies (continued)									
Safety Phase IV	1182.58 U04-0094	Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States	- To evaluate the safety of TPV/r when used in combination with other agents for the treatment of HIV positive patients.	Open-label	TPV 500 mg/RTV 200 mg BID	n = 451 (as per report cut-off date); 450 of the 451 were treated; 448 of the 450 are newly exposed patients to TPV	HIV positive patients	24 months	Ongoing; Summary Report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 6 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Safety Phase II	1182.17 U04-3360	All countries of RESIST-1 and 2	- To determine the long term safety and tolerance of multiple oral doses of TPV and RTV alone or in combination with one or more marketed anti-retroviral therapies.[4]	Open-label long-term, rollover trial-subjects from trials: M3342/0004 (1182.1), 1182.2, 1182.4, 1182.6, 1182.12, 1182.48, 1182.51, 1182.52	Early patients were on various TPV or TPV/r doses; as of March 2003, nearly all patients have been switched to the TPV/r 500 mg/ 200 mg BID dose	n = 748 (as per report cut-off); with 286 CPI/r virologic failures from 1182.12 or 1182.48 included in the report	HIV positive patients who have successfully completed participation in combination TPV/r studies or failed the comparator PI in Trials 1182.12 or 1182.48.	Until TPV is licensed	Ongoing; Interim report

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 7 of 8)

Type of Study	Study No. and BI Report No. (P&U Protocol Number, if applicable)	Countries Study Conducted	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen	Number of Human Subjects Entered	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Safety and Efficacy Phase IIb	1182.33 U04-1642	Argentina, Australia, Brazil, Caribbean Canada, Columbia, France, Germany, Mexico, Poland, Romania, Russia, Spain, UK, Thailand, Uganda	- Determine the safety and efficacy of TPV/RTV in naïve HIV positive patients	Open label (Data are currently blinded to the sponsor)	TPV 500 mg plus 100 mg or 200 mg RTV in combination with TDF + 3TC versus Kaletra® in combination with TDF + 3 TC	n = 16 (as per report cut-off date); 15 treated with either TPV/r or LPV/r	Naïve HIV positive patients	48 weeks (with extension up to 156 weeks)	Ongoing; Summary report

NOTE: Footnotes and translations of abbreviations for this table follow below.

Table 4 (continued) Listing of Phase II and III Efficacy and Safety Studies (Page 8 of 8)

Footnotes to Table 2.4: 1:

1 All doses were administered orally. All doses were administered BID, with the exception of Trial 1182.1, a Phase I trial in 24 HIV-positive patients, in which TPV monotherapy was administered by using the Hard Filled Capsule (HFC) formulation of tipranavir at doses of 900 mg, 1200 mg and 1500 mg, all TID.
Prior to acquisition of TPV by BI in 2000, P&U conducted 14 trials with several different formulations. For the BI trials, all subjects/patients received the Self-Emulsifying Drug Delivery System (SEDDS) formulation of tipranavir with the exception of those in the 1182.1 trial and patients in the 1182.2 trial, who received the HFC formulation initially and then were switched to the SEDDS formulation. Pediatric patients in Trial 1182.14 received a liquid formulation of tipranavir. Bioequivalence/bioavailability Trial 1182.45 used both the SEDDS and liquid formulations. 147 of all treated subjects/patients received TPV monotherapy: 113 in Trial 1182.5 (TPV 250 mg, 500 mg, 750 mg, 1000 mg, or 1250 mg BID), for the first 10 days of the study, 24 in Trial 1182.1 monotherapy (TPV 900 mg, 1200 mg or 1500 mg TID), and 10 in Trial 1182.3 (TPV 1200 mg BID).

2 In Trial 1182.41, subjects were scheduled to take TPV/r for 10 days (3 days as a single dose - trial Days 3, 5, and 14), and 7 days BID (Trial Days 15-21). Subjects were scheduled to take EFV as a single daily dose on 17 days (Trial Days 1, 5, and 7-21).

3 In Trial 1182.55, loperamide (16 mg) was administered on Days 1, 9 and 22. On Days 4-9 (5.5 days), subjects received either TPV 750 mg BID or RTV 200 mg BID. From Days 12-22 (10.5 days), subjects received TPV 750 mg and RTV 200 mg BID. No drugs were administered on Days 2 and 3 and Days 10 and 11.

4 Nearly all patients in Trial 1182.17 were transitioned to the standard TPV/r dose of 500 mg/200 mg BID as of January 20, 2003

APPENDIX 3 DRUG INTERACTIONS

Table 1 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs

Coadministered Drug	Coadministered Drug Dose (Schedule)	TPV/r Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 Cmax	AUC	Cmin
Atorvastatin	10 mg (1 dose)	500/200 mg bid (14 doses)	22	↔	0.96 (0.86, 1.07)	1.08 (1.00, 1.15)	1.04 (0.89, 1.22)
Clarithromycin	500 mg BID (25 doses)	500/200 BID*	24/68	↑	1.40 (1.24 – 1.47)	1.66 (1.43 – 1.73)	2.00 (1.58 – 2.47)
Didanosine	400 mg (1 dose)	500/100 mg bid (27 doses)	5	↓	1.32 (1.09, 1.60)	1.08 (0.82, 1.42)	0.66 (0.31, 1.43)
Efavirenz	600 mg (1 dose)	500/100 mg	24	↔	0.93 (0.82, 1.06)	0.92 (0.81, 1.04)	0.90 (0.78, 1.04)
		750/200 mg (1 dose)	26	↔	0.91 (0.81, 1.03)	0.93 (0.79, 1.10)	0.88 (0.69, 1.11)
	600 mg qd (8 doses)	500/100 mg	21	↓	0.61 (0.51, 0.72)	0.43 (0.35, 0.52)	0.23 (0.16, 0.33)
		750/200 mg (1 dose)	25	↓	0.69 (0.58, 0.83)	0.66 (0.56, 0.79)	0.64 (0.52, 0.79)
		500/100 mg*	21/89	↓	0.79 (0.69 – 0.89)	0.69 (0.57 – 0.83)	0.58 (0.36 – 0.86)
		750/200 mg*	25/100	↔	0.97 (0.85 – 1.09)	1.01 (0.85 – 1.18)	0.97 (0.69 – 1.28)
Ethinyl estradiol / Norethindrone	0.035/1.0 mg (1 dose)	500/100 mg bid (21 doses)	21	↓	1.10 (0.98, 1.24)	0.98 (0.88, 1.11)	0.73 (0.59, 0.90)
		750/200 mg bid (21 doses)	13	↔	1.01 (0.96, 1.06)	0.98 (0.90, 1.07)	0.91 (0.69, 1.20)
Fluconazole	100 mg QD (12 dose)	500/200 BID*	20/68	↑	1.32 (1.18 – 1.47)	1.50 (1.29 – 1.73)	1.69 (1.33 – 2.09)
Loperamide	16 mg (1 dose)	750/200 mg bid (21 doses)	24	↓	1.03 (0.92, 1.17)	0.98 (0.86, 1.12)	0.74 (0.62, 0.88)
Rifabutin	150 mg (1 dose)	500/200 mg bid (15 doses)	21	↔	0.99 (0.93, 1.07)	1.00 (0.96, 1.04)	1.16 (1.07, 1.27)
Tenofovir	300 mg (1 dose)	500/100 mg bid	22	↓	0.83 (0.74, 0.94)	0.82 (0.75, 0.91)	0.79 (0.70, 0.90)
		750/200 mg bid (23 doses)	20	↔	0.89 (0.84, 0.96)	0.91 (0.85, 0.97)	0.88 (0.78, 1.00)
Zidovudine	300 mg (1 dose)	500/100 mg bid	29	↓	0.87 (0.80, 0.94)	0.82 (0.76, 0.89)	0.77 (0.68, 0.87)
		750/200 mg bid (23 doses)	25	↔	1.02 (0.94, 1.10)	1.02 (0.92, 1.13)	1.07 (0.86, 1.34)

*steady state comparison to historical data

Table 2 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tipranavir/Ritonavir

Coadministered Drug	Coadministered Drug Dose (Schedule)	TPV/r Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without TPV/r; No Effect = 1.00		
					Cmax	AUC	Cmin
Amprenavir/RTV†	600/100 mg bid (27 doses)	500/200 mg bid (28 doses)	16 74	↓ ↓	0.61 (0.51, 0.73)* -	0.56 (0.49, 0.64)* -	0.45 (0.38, 0.53)* 0.44 (0.39, 0.49)**
Abacavir†	300 mg bid (43 doses)	250/200 mg bid 750/100 mg bid 1250/100 mg bid	28 14 11	↓ ↓ ↓	0.56 (0.48, 0.66) 0.54 (0.47, 0.63) 0.48 (0.42, 0.53)	0.56 (0.49, 0.63) 0.64 (0.55, 0.74) 0.65 (0.55, 0.76)	- - -
Atorvastatin	10 mg (1 dose)	500/200 mg bid (17 doses)	22	↑	8.61 (7.25, 10.21)	9.36 (8.02, 10.94)	5.19 (4.21, 6.40)
Orthohydroxy-atorvastatin			21, 12, 17	↓	0.02 (0.02, 0.03)	0.11 (0.08, 0.17)	0.07 (0.06, 0.08)
Parahydroxy-atorvastatin			13, 22, 1	↓	1.04 (0.87, 1.25)	0.18 (0.14, 0.24)	0.33 (NA)
Clarithromycin	500 mg bid (11 doses)	500/200 mg (1 dose)	24	↑	0.88 (0.78, 1.00)	1.00 (0.91, 1.11)	1.50 (1.31, 1.71)
14-OH-clarithromycin			24	↓	0.75 (0.68, 0.83)	0.54 (0.48, 0.59)	0.39 (0.35, 0.44)
Clarithromycin	500 mg bid (25 doses)	500/200 mg bid (15 doses)	21	↑	0.95 (0.83, 1.09)	1.19 (1.04, 1.37)	1.68 (1.42, 1.98)
14-OH-clarithromycin			21	↓	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
Didanosine††	200 mg bid, ≥60 Kg 125 mg bid, <60 Kg (43 doses)	250/200 mg bid 750/100 mg bid 1250/100 mg bid (42 doses)	10 8 9	↓ ↔ ↔	0.57 (0.42, 0.79) 0.76 (0.49, 1.17) 0.77 (0.47,1.26)	0.67 (0.51, 0.88) 0.97 (0.64, 1.47) 0.87 (0.47, 1.65)	- - -
	400 mg (1 dose)	500/100 mg bid (27 doses)	5	↔	0.80 (0.63, 1.02)	0.90 (0.72, 1.11)	1.17 (0.62, 2.20)
Efavirenz††	600 mg qd (22 doses)	250/200 mg bid 750/100 mg bid 1250/100 mg bid (42 doses)	23 19 15	↔ ↔ ↔	1.13 (0.99, 1.28) 0.95 (0.83, 1.08) 0.95 (0.81, 1.12)	1.12 (1.02, 1.24) 0.91 (0.80, 1.03) 0.92 (0.75, 1.12)	1.01 (0.84, 1.20) 0.92 (0.80, 1.07) 1.02 (0.79, 1.31)
	600 mg (1 dose)	500/100 mg 750/200 mg (1 dose)	30 26	↑ ↑	1.37 (1.24, 1.50) 1.19 (1.08, 1.32)	1.04 (0.91, 1.18) 0.92 (0.81, 1.05)	1.01 (0.90, 1.12) 0.95 (0.84, 1.07)
	600 mg qd (8 doses)	500/100 mg 750/200 mg (1 dose)	28 28	↔ ↔	1.18 (1.12, 1.25) 1.22 (1.15, 1.29)	1.11 (1.08, 1.15) 1.15 (1.11, 1.20)	1.04 (1.00, 1.08) 1.07 (0.99, 1.14)
	600 mg qd (15 doses)	500/100 mg bid 750/200 mg bid (15 doses)	24 22	↔ ↔	1.09 (0.99, 1.19) 1.12 (0.98, 1.28)	1.04 (0.97, 1.12) 1.00 (0.93, 1.09)	1.02 (0.92, 1.12) 0.94 (0.84, 1.04)
Ethinyl estradiol	0.035 mg (1 dose)	500/100 mg bid 750/200 mg bid (21 doses)	21 13	↓ ↓	0.52 (0.47, 0.57) 0.48 (0.42, 0.57)	0.52 (0.48, 0.56) 0.57 (0.54, 0.60)	- -
Fluconazole	200 mg (Day 1) then 100 mg qd (6 or 12 doses)	500/200 mg bid (2 or 14 doses)	19 19	↔ ↔	0.97 (0.94, 1.01) 0.94 (0.91, 0.98)	0.99 (0.97, 1.02) 0.92 (0.88, 0.95)	0.98 (0.94, 1.02) 0.89 (0.85, 0.92)
Lopinavir/RTV†	400/100 mg bid (27 doses)	500/200 mg bid (28 doses)	21 69	↓ ↓	0.53 (0.40, 0.69)* -	0.45 (0.32, 0.63)* -	0.30 (0.17, 0.51)* 0.48 (0.40, 0.58)**
Loperamide	16 mg (1 dose)	750/200 mg bid (21 doses)	24	↓	0.39 (0.31, 0.48)	0.49 (0.40, 0.61)	-
N-Demethyl-Loperamide			24	↓	0.21 (0.17, 0.25)	0.23 (0.19, 0.27)	

†HIV+ patients; ††HIV+ patients (TPV/r 250 mg/200 mg, 750mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/r 500 mg/100 mg and 750 mg/200 mg)

[a]Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)

*Intensive PK analysis

**Therapeutic Drug Monitoring 8-16 hrs post-dose

Table 2 (continued) Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tipranavir/Ritonavir (Page 2 of 2)

Coadministered Drug	Coadministered Drug Dose (Schedule)	TPV/r Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without TPV/r; No Effect = 1.00 Cmax	AUC	Cmin
Lamivudine†	150 mg bid (43 doses)	250/200 mg bid	64	↔	0.96 (0.89, 1.03)	0.95 (0.89, 1.02)	-
		750/100 mg bid	46	↔	0.86 (0.78, 0.94)	0.96 (0.90, 1.03)	-
		1250/100 mg bid (42 doses)	35	↔	0.71 (0.62, 0.81)	0.82 (0.66, 1.00)	-
Nevirapine†	200 mg bid (43 doses)	250/200 mg bid	26	↔	0.97 (0.90, 1.04)	0.97 (0.91, 1.04)	0.96 (0.87, 1.05)
		750/100 mg bid	22	↔	0.86 (0.76, 0.97)	0.89 (0.78, 1.01)	0.93 (0.80, 1.08)
		1250/100 mg bid (42 doses)	17	↔	0.71 (0.62, 0.82)	0.76 (0.63, 0.91)	0.77 (0.64, 0.92)
Norethindrone	1.0 mg (1 dose)	500/100 mg bid	21	↔	1.03 (0.94, 1.13)	1.14 (1.06,1.22)	-
		750/200 mg bid (21 doses)	13	↔	1.08 (0.97, 1.20)	1.27 (1.13,1.43)	-
Rifabutin	150 mg (1 dose)	500/200 mg bid (15 doses)	20	↑	1.70 (1.49, 1.94)	2.90 (2.59, 3.26)	2.14 (1.90, 2.41)
25-0-desacetyl-rifabutin			20	↑	3.20 (2.78, 3.68)	20.71 (17.66, 24.28)	7.83 (6.70, 9.14)
Rifabutin + 25-O-desacety-lrifabutin [a]			20	↑	1.86 (1.63, 2.12)	4.33 (3.86, 4.86)	2.76 (2.44, 3.12)
Saquinavir/RTV†	600/100 mg bid (27 doses)	500/2 00 mg bid (28 doses)	20	↓	0.30 (0.23, 0.40)*	0.24 (0.19, 0.32)*	0.18(0.13,0.26)*
			68	↓	-	-	0.20(0.16,0.25)**
Stavudine†	40 mg bid, ≥60 Kg 30 mg bid, <60 Kg (43 doses)	250/200 mg bid	26	↔	0.90 (0.81, 1.02)	1.00 (0.91, 1.11)	-
		750/100 mg bid	22	↔	0.76 (0.66, 0.89)	0.84 (0.74, 0.96)	-
		1250/100 mg bid (42 doses)	19	↔	0.74 (0.69, 0.80)	0.93 (0.83, 1.05)	-
Tenofovir	300 mg (1 dose)	500/100 mg bid	22	↓	0.77 (0.68, 0.87)	0.98 (0.91, 1.05)	1.07 (0.98, 1.17)
		750/200 mg bid (23 doses)	20	↓	0.62 (0.54, 0.71)	1.02 (0.94, 1.10)	1.14 (1.01, 1.27)
Zidovudine††	300 mg bid (43 doses)	250/200 mg bid	48	↓	0.54 (0.47, 0.62)	0.58 (0.51, 0.66)	-
		750/100 mg bid	31	↓	0.51 (0.44, 0.60)	0.64 (0.55, 0.75)	-
		1250/100 mg bid (42 doses)	23	↓	0.49 (0.40, 0.59)	0.69 (0.49, 0.97)	-
	300 mg (1 dose)	500/100 mg bid	29	↓	0.39 (0.33, 0.45)	0.57 (0.52, 0.63)	0.89 (0.81, 0.99)
		750/200 mg bid (23 doses)	25	↓,↑	0.44 (0.36, 0.54)	0.67 (0.62, 0.73)	1.25 (1.08, 1.44)
Zidovudine glucuronide		500/100 mg bid	29	↑	0.82 (0.74, 0.90)	1.02 (0.97, 1.06)	1.52 (1.34, 1.71)
		750/200 mg bid (23 doses)	25	↑	0.82 (0.73, 0.92)	1.09 (1.05, 1.14)	1.94 (1.62, 2.31)

†HIV+ patients
††HIV+ patients (TPV/r 250 mg/200 mg, 750mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/r 500 mg/100 mg and 750 mg/200 mg)
[a]Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacety-lrifabutin)
*Intensive PK analysis
**Therapeutic Drug Monitoring 8-16 hrs post-dose

APPENDIX 4 FATAL EVENTS IN RESIST TRIALS

Table 1 Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2003-BP-10111BP	12	1029	43 M	5.8	27	TPV/r	Renal failure, PCP, COPD	Persistent PCP, bacterial pneumonia	End stage AIDS	31.0
2003-BP-09677BP	12	1341	46 M	5.0	2	TPV/r	Wasting, CMV retinitis, MAC, adrenal insufficiency, DM, seizure disorder, depression, transient ischemic attacks	HIV/AIDS, cellulitis, anemia, progressive CMV infection, progressive wasting, progressive IDDM, progressive electrolyte imbalance	AIDS related complex	22.0
2003-BP-05935BP	12	1568	47 M	5.6	13	TPV/r	No significant or relevant past medical history	Shingles, diarrhea, mental status changes, MRI of the head which showed increased atrophy	Acquired immunodeficiency syndrome	23.3
2004-BP-06918BP	12	2272	36 M	5.3	4	TPV/r	MAC, PCP, chronic hepatitis, hyperbilirubinemia, CHF, CNS bacterial abscess, DM, pneumothorax, COPD, acute renal failure, hypokalemia	Liver failure (total bilirubin 4.2), renal failure	Acquired immunodeficiency syndrome	52.1
2003-BP-09673BP	12	2374	47 M	4.9	1	TPV/r	Disseminated cryptococcal infection, wasting, diarrhea, pancreatic enzyme insufficiency	Left upper extremity weakness, pseudomonas sinusitis, acute demyelinating sensorimotor polyneuropathy, necrotizing stomatitis,	Asthenia	8.3

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 2 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2003-DE-03576GB	48	5061	44 M	4.7	96	TPV/r	HIV encephalopathy, HIV cachexia, dehydration of unknown duration, esophageal candidiasis, mycobacterium tuberculosis, anemia	Cachexia	Cachexia	3.0
2004-BP-00953BR	48	9137	43 F	5.2	18	TPV/r	Hemiparesis, toxoplasmosis, aspiration pneumonia, dyspnea, chronic bronchitis, convulsive disorder	Urinary tract infection, pruritus, hypertension	Acquired immunodeficiency syndrome	18.4
2003-BP-04975BP	12	2060	34 M	5.1	3	TPV/r	PCP, pancytopenia, IDDM, pancreatitis	CNS lymphoma, PML, cryptococcal meningitis, ARDS, sepsis	Sepsis	1.3
2004-BP-07328BP	12	1884	61 M	3.7	152	TPV/r	PCP, hypothyroidism, non Hodgkin's lymphoma, oral candidiasis	Malignant lymphoma, dehydration, hypotension, chronic hypothyroidism	Disseminated lymphoma	58.9
2003-BP-04600BP	12	1917	49 M	5.3	4	TPV/r	Anemia, neutropenia, PCP, MAC, mental retardation, HIV encephalopathy, Kaposi's sarcoma, wasting, depression, hypothyroidism, pancreatitis	Febrile neutropenia, CNS lymphoma, profound weakness, mental status deficiency, brain herniation	Central nervous system lymphoma	1.4

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 3 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2003-BP-08944BP	12	2280	43 M	4.7	31	TPV/r	Intermittent FUO, splenomegaly, periportal lymphadenopathy, candida esophagitis, CMV retinitis, PCP, MAC, toxoplasmosis of the brain, wasting, depression, renal insufficiency	Splenectomy, pancreatitis, iliac vein thrombosis, hyperglycemia, urinary tract infection, anemia, candidiasis, catheter-related infection, abnormal hepatic function, Hodgkin's lymphoma, post-surgical pancreatitis, peritonitis status post laparotomy, PICC line had a positive culture for acinetobacter	Hodgkin's disease	10.9
2003-DE-03351DE	48	4168	63 M	5.3	15	TPV/r	Squamous cell carcinoma, hepatic failure, intra-abdominal hemorrhage, esophageal candidiasis, PCP, wasting	Depression, diarrhea, hypertension, neutropenia, multiple pulmonary lesions, suspicious liver lesions, squamous cell carcinoma, FUO, hepatic biopsy demonstrating B-cell lymphoma, hepatic failure	B-cell lymphoma	13.1
2004-BP-03860BP	12	1050	52 M	4.7	15	TPV/r	Melanoma of chest wall, squamous cell carcinoma of the eye lid	Squamous cell neoplasm of the oral cavity, radiation therapy, metastatic malignant melanoma, chemotherapy	Metastatic malignant melanoma	58.4
2003-BP-10241BP	12	1308	73 M	4.8	103	TPV/r	No significant past medical history	Anemia, oral thrush, metastatic rectal cancer	Rectal cancer metastatic	49.7
2003-FF-00518FF	48	3305	45 M	4.9	14	TPV/r	Kaposi's sarcoma, alcoholism, myocardial infarction, dyspnea, angioma	Diarrhea, epilepsy, anal abscess, pulmonary Kaposi sarcoma, sepsis	Kaposi's sarcoma	14.3

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 4 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2004-BP-02646BP	58	181	41 M	2.3	86	TPV/r	Liver lymphoma	Hypertriglyceridemia, DM, CNS lymphoma, sepsis due to lymphoma chemotherapy	Sepsis	10.3
2004-BP-04366BP	12	1441	43 M	5.4	3	TPV/r	PCP	PCP, atrial fibrillation, intubated for respiratory distress, pneumomediastinum, progressive respiratory failure	Respiratory distress	47.9
2004-BP-01447BP	12	1550	55 M	3.8	318	TPV/r	Emphysema, cholinergic urticaria secondary to agent orange, right bundle branch block, atrial dilatation	COPD	Chronic obstructive airways disease	18.4
2003-BP-06839BP	12	1647	42 M	5.5	18	TPV/r	Aspergillosis, anemia, HTN, cardiomyopathy, CHF, CMV retinitis, wasting	Kaposi's sarcoma, bilateral pneumonia, renal failure, severe respiratory insufficiency	Respiratory failure	15.6
2003-BP-08880BP	12	1878	44 M	5.7	5	TPV/r	Anemia, history of seizures, cardiac arrhythmias, HTN, PCP, wasting	CVA, UTI, sepsis, neck mass, spinal cord compression, lymphoma, MI	Myocardial infarction	11.7
2004-BP-06332BP	12	1886	42 M	4.8	58	TPV/r	Lactic acidosis, nephrolithiasis, wasting	Wasting, elevated creatinine, hematuria, HIV nephropathy, hyperbilirubinemia, weakness, difficulty walking, HTN ASHD, cardiomegaly, atherosclerosis, cortical infract of kidney	Cardiac death	51.3

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 5 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2004-BP-03640BP	12	2052	43 M	4.9	34	TPV/r	Pancreatitis, hepatitis B, esophageal candidiasis, anemia, neuropathy, wasting	Renal insufficiency, hepatosplenomegaly	Hepatorenal syndrome	38.4
2004-CN-00310CN	12	3083	39 M	4.8	254	TPV/r	Asthma, pulmonary congestion	Urosepsis treated with piperacillin and tobramycin, Hodgkin's lymphoma	Urosepsis	62.6
2004-BP-07236BR	48	9030	42 M	5.5	28	TPV/r	PCP	Disorientation, renal insufficiency, lactic acidosis, respiratory infection	Respiratory failure	49.0
2004-BP-04500RA	48	1097	46 M	5.1	5	TPV/r	Toxoplasmosis	Patient found dead at home	Not reported	39.3
2004-BP-07623BP	12	2048	37 M	5.2	7	TPV/r	PCP	Parasite infection, GERD, dehydration, hypotension, HIV encephalopathy, pneumonia, progressive weakness, difficulty swallowing, slow slurred speech, worsening confusion, presumptive MAC, presumptive TB	Not reported	52.6
2003-FF-00378FF	48	3150	37 M	5.1	27	CPI/r	Injection drug user, anorexia, esophageal candidiasis, PCP	Anorexia, esophageal candidiasis, walking disorders, upper limbs tremor, asthenia, insomnia, cerebellous syndrome, PML, HIV encephalopathy	Progressive multifocal leukoencephalopathy	8.7

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 6 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2004-FF-00058FF	48	3270	50 M	4.8	18	CPI/r	Hypertriglyceridemia, renal artery stenosis with renal insufficiency, hypertension, non insulin dependent diabetes	Upper limb weakness, speech disorders, progressive multifocal Leukoencephalopathy (PML), left hemiplegia, consciousness disorders, neurologic disorders were related to aggravation of PML	Progressive multifocal leukoencephalopathy	28.4
2003-BP-02218AU	12	4073	44 M	5.1	150	CPI/r	CMV retinitis, MAI, AIDS dementia, lipodystrophy, peripheral neuropathy	PML, severe ataxia, end stage AIDS	Acquired immunodeficiency syndrome	8.9
2004-BP-00677BP	12	2091	43 M	5.5	6	CPI/r	Candida esophagitis, CMV retinitis, PCP, wasting	Anemia, pancytopenia, diarrhea, nausea and gastritis, rectal hemorrhage, CMV pneumonia	Pneumonia cytomegaloviral	24.7
2003-BP-02067BP	12	1199	50 M	5.2	55	CPI/r	MAC	Non-Hodgkin's lymphoma, radiculopathy, decreased level of consciousness and intelligible speech, multiple sites of presumed lymphoma, bone marrow lymphoma, anemia	Lymphoma	6.6
2003-BP-07278BP	12	1219	42 F	5.5	26	CPI/r	No conditions which may be considered relevant to the fatal event.	Imbalance, headaches, CNS lymphoma	Central nervous system lymphoma	20.9
2003-BP-10433BP	12	2087	43 M	3.0	545	CPI/r	No past medical history has been reported	Progressive central neurologic symptoms, brain lymphoma	Central nervous system lymphoma	24.6

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 7 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2003-DE-03239PO	48	2211	33 M	4.8	658	CPI/r	No relevant past medical history noted	Burkitt's Lymphoma, renal insufficiency and edema to be caused by chemotherapy	Burkitt's lymphoma	6.6
2003-BP-10341AU	12	4006	57 M	3.2	725	CPI/r	Cryptosporidiosis	Bone marrow infiltration with acute myeloblastic leukemia	Acute myeloid leukaemia	62.3
2003-ES-00310ES	48.58	7135	52 M	3.7	234	CPI/r	No significant or relevant past medical history reported	Neutropenic fever, acute lymphoblastic leukaemia	Acute lymphocytic leukaemia	27.9
2003-FF-00246FF	48	3033	51 M	6.6	13	CPI/r	Kaposi's syndrome, diffuse digestive candidiasis, MAC pulmonary infection	Fever, dry cough, severe dyspnea and severe anemia, diarrhea, suspected mycobacterium avium or tuberculosis, loss of consciousness and hypercapnia, cardio-respiratory arrest for which cardiac massage was performed unsuccessfully	Cardio-respiratory arrest	5.0
2003-UK-00670UK	48	8032	46 M	5.7	17	CPI/r	No significant relevant past medical history reported	Suspected PCP, multi organ failure	Ventricular fibrillation	11.7
2004-BP-03614BR	48	9328	44 M	4.8	51	CPI/r	Diabetes, candidiasis, herpes, hypertriglyceridemia	Lymphoma	Multi-organ failure	25.7
2003-BP-10569BP	12	2090	44 M	4.8	165	CPI/r	Candidiasis, COPD	Found dead at home	Death	15.6
2004-BP-00736BP	17	121783	40 M	5.2	3	C to TPV/r	MAC infection, renal failure amikacin-related	Renal failure, anemia, hospice	Disease progression	16.4

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 8 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2004-BP-01767BP	17	121888	48 M	5.1	4	C to TPV/r	No relevant past medical history noted	Cryptosporidium infection, hospice, chronic wasting syndrome	Failure to thrive	13.6
2003-BP-10274BP	17	122062	59 M	5.1	74	C to TPV/r	Cardiomyopathy, atrial fibrillation	MI, congestive heart failure, pulmonary edema, hypersensitive autoimmune reaction to HIV medications	Immune reconstitution syndrome	8.3
2003-BP-06681BP	17	121093	46 M	5.2	12	C to TPV/r	No relevant past medical history noted	Septic shock, pneumococcal bacteremia	Septic shock	9.3
2004-BP-02871BP	17	121262	58 M	6.0	3	C to TPV/r	No relevant past medical history noted	Aspergillus infection, dehydration, lung abscess, anemia	Aspergillosis	46.3
2004-BP-05859BP	17	121476	43 M	6.3	1	C to TPV/r	No relevant past medical history noted	HIV encephalopathy, dementia, hospice	Pneumonia	31.9
2004-BP-07134BP	17	121479	48 M	5.2	7	C to TPV/r	No relevant past medical history noted	Candida esophagitis, CMV retinitis, neutropenia, thrombocytopenia, severe febrile illness, splenomegaly, pulmonary infiltrates, AIDS	Febrile neutropenia	44.4
2004-DE-00489GB	17	485007	40 M	2.0	8	C to TPV/r	No relevant past medical history noted	Esophagitis, cachexia, herpes encephalitis, wasting,	Encephalitis herpes	27.0
2003-DE-03806DE	58	None	57 M			C to TPV/r	Intestinal cryptosporidiosis	Diarrhea, vomiting, non-specified drug allergy	Gastroenteritis cryptosporidial	
2004-BP-00114BP	17	121025	39 M	4.7	69	C to TPV/r	AIDS, wasting, Cryptococcus, steatohepatitis, MAC	Herpes zoster, cachexia, abdominal tenderness, dysarthria, arthralgias, myalgias, liver failure, multiple organ failure	Hepatic failure	20.7

Table 1 (continued) Summaries of Fatal Outcomes from RESIST trials including CPI/r rollover patients to 1182.17 (Pg 9 of 9)

Pt Case Number	Trial	Pt	Age	Bsl VL	Bsl CD4	Treatment	Medical history	Intercurrent / Concurrent Illnesses	Cause of death	Death Week
2003-BP-04672BP	17	121244	39 M	4.8	6	C to TPV/r	Cryptosporidiosis, Kaposi's' sarcoma	Colitis, hypovolemia, renal impairment, wasting, cryptosporidiosis, acute renal insufficiency, metabolic acidosis, volume depletion, staphylococcus aureus, resulting in bacteremia, worsening renal failure secondary to vancomycin , septic shock	Renal failure acute	18.7
2003-BP-07277BP	17	121543	40 M	4.4	253	C to TPV/r	Kaposi's, anemia	Splenomegaly, cardiopulmonary failure, lymphoma, AIDS	Cardiopulmonary failure	1.0
2004-NL-00039NL	17	482017	62 M	1.4	146	C to TPV/r	Lung cancer	Fatigue, liver metastases, anorexia, weight loss	Liver scan abnormal	21.1
2004-IT-00012IT	17	486039	40 M	2.3	16	C to TPV/r	Mycobacteriosis infection, pneumonia, CMV, retinitis, chronic hepatitis, DM	Pneumonia, cardio-circulatory arrest	Cardiac arrest	21.7
2004-BP-04244BR	17	489318	41 M	5.4	27	C to TPV/r	Mycobacterium infection	Aspiration pneumonia, neurotoxoplasmosis, headache, vomiting, mental confusion, psychomotor agitation	Respiratory failure	