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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-814

Microbiology Review(s)

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21814 **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 21814 (capsules) **Serial #:** 000
Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Sponsor's Name and Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
Ridgefield, CT 06877

Initial Submission Dates:

Correspondence Date:	12/21/2004
CDER Receipt Date:	12/22/2004
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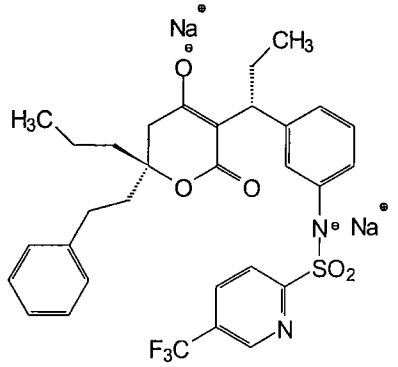
Review Complete Date:	6/15/2005
PDUFA Date:	6/22/2005

Amendments:
Related/Supporting Documents: IND51979

Product Name(s)
Proprietary: Aptivus
Non-Proprietary/USAN: tipranavir (TPV)
Code Name/Number: PNU-140690

Empirical formula: $C_{31}H_{31}F_3N_2O_5SNa_2$
Chemical Name: [R-R(*,R*)]-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-y1]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide disodium salt
Molecular mass: 646.63

Structural Formula:



TIPRANAVIR

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21814 **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

Drug category: antiviral
Dosage Form(s): 250-mg soft elastic capsules/Oral; co-administration of ritonavir as 100-mg soft gelatin capsules; 500 TPV/200 RTV mg BID
Route(s) of Administration: Oral
Indication(s): Combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Dispensed: Rx _X_ **OTC**___

Abbreviations: ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; CPI, comparator protease inhibitor; ddI, didanosine; d4T, stavudine; DLV, delavirdine; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus-1; IC, inhibitory concentration; IDV, indinavir; LOCF, last observation carried forward; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; /r, ritonavir boosted; RT, reverse transcriptase; SQV, saquinavir; T20, enfuvirtide; TNF, tenofovir; TPV, tipranavir; 3TC, lamivudine;

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Executive Summary

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

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

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

Clinical TPV Resistance
The efficacy of ritonavir boosted tipranavir (TPV/r) was examined in treatment-experienced HIV-infected subjects in two pivotal phase III trials, study 012 (RESIST 1) and study 048 (RESIST 2). Genotypes from 1482 isolates and 454 phenotypes from both studies were submitted for review. In the comparator PI arm (CPI/r), most patients received LPV/r (n=358) followed by APV/r (n=194), SQV/r (n=162) and IDV/r (n=23). The patient populations in RESIST 1 and 2 were highly treatment-experienced with a median number of 4 (range 1-7) PIs received prior to study. In the combined RESIST trials at baseline, 97% of the isolates were resistant to at least one PI, 95% of the isolates were resistant to at least one NRTI, and >75% of the isolates were resistant to at least one NNRTI. The treatment arms from both studies were balanced with respect to baseline

genotypic and phenotypic resistance. Baseline phenotypic resistance was equivalent between the TPV/r arm (n=745) and the CPI/r arm (n=737) with 30% of the isolates resistant to TPV at baseline and 80-90% of the isolates resistant to the other PIs - APV, ATV, IDV, LPV, NFV, RTV or SQV. The number of PI-resistance mutations was equivalent between the TPV/r and CPI/r arms in RESIST 1 and 2 and the median number of baseline PI, NRTI and NNRTI mutations was equivalent between arms in both studies.

Mutations Developing on TPV Treatment
TPV/r-resistant isolates were analyzed from treatment-experienced patients in the phase II study 052 (n=32) and the phase III studies RESIST 1 and 2 (n =59) who experienced virologic failure. The most common mutations that developed in greater than 20% of these TPV/r virologic failure isolates were L33V/I/F, V82T and I84V. Other mutations that developed in 10 to 20% of the TPV/r virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L and L89V/M/W. In RESIST 1 and 2, TPV/r resistance developed in the virologic failures (n=59) at an average of 38 weeks with a median decrease of >14-fold in TPV susceptibility from baseline. The resistance profile in treatment-naive subjects has not been characterized.

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

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

Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. In these analyses, any changes at protease amino acid positions -

D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 and L90 were counted if present at baseline. These PI mutations were used based on their association with reduced susceptibility to currently approved PIs, as reported in various publications.

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

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

Proportion of Responders by Baseline TPV Phenotype
TPV/r response rates were also assessed by baseline TPV phenotype. Again, we focused on the No T20 group in order to more accurately assess the effect of baseline phenotype on virologic success for TPV/r. With no T20 use, the proportion of responders was 45% if the shift in IC_{50} value from reference of TPV susceptibility was 3-fold or less at baseline. The proportion of responders decreased to 21% when the TPV baseline phenotype values were >3- to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

Conclusions

TPV is a novel protease inhibitor with antiviral activity against multi PI-resistant clinical HIV-1 isolates. The most common protease amino acid substitutions that developed in >20% of isolates from treatment-experienced subjects who failed on TPV/r treatment were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V. The resistance profile in treatment-naive subjects has not been characterized. Both the number and type of baseline PI mutations affected response rates to TPV/r in RESIST 1 and 2. Virologic response rates in TPV/r-treated subjects were reduced when isolates with substitutions at

amino acid positions I13, V32, M36, I47, Q58, D60 or I84 and substitutions V82S/F/I/L were present at baseline. Virologic responses to TPV/r at week 24 decreased when the number of baseline PI mutations was 5 or more. Subjects taking enfuvirtide with TPV/r were able to achieve >1.5 $\log_{10}$ reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations. Virologic responses to TPV/r in RESIST 1 and 2 decreased when the baseline phenotype for TPV was a >3 shift in susceptibility with respect to wild-type reference virus.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA for is approvable with respect to microbiology for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

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

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

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

2. Summary of OND Microbiology Assessments

2.1. Brief Overview of the Microbiological Program

2.1.1. Non-clinical

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combination with other antiviral drugs was determined in cell culture to assess the impact of potential in vitro drug interactions on overall antiviral activity. Additive to antagonistic relationships were seen with combinations of TPV with other PIs. Combinations of TPV with the NRTIs were generally additive, but additive to antagonistic for TPV in combination with ddI and 3TC. Combinations of TPV with the NNRTIs DLV and NVP were additive and with EFV were additive to antagonistic. Activity of TPV with the fusion inhibitor enfuvirtide (T20) was synergistic.

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2.1.2. Clinical Microbiology

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3. Administrative

3.1. Reviewer's Signature(s)

_____
Lisa K. Naeger, Ph.D.
Sr. Microbiologist, HFD-530

3.2. Concurrence

HFD-530/Signatory Authority _____ Signature _____ Date
HFD-530/Micro TL _____ Signature _____ Date

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814 **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

OND Microbiology Review

1. Introduction and Background

1.1. Important Milestones in Product Development

1.1.1. Methodology

Genotypic Methods
Genotypes from 1482 isolates were submitted for review. Genotypes were determined by two different methods in RESIST 1 and 2. In RESIST 1, the TruGene assay version 1.0 was used. If a sample could not be amplified and genotyped, version 1.5 was used. In RESIST 2, the Virco Virtual Phenotype assay was used for samples from Europe and the TruGene assay was used for samples from Latin America and Australia. Genotypic resistance testing was used to stratify patients according to pre-selected protease inhibitors (APV/r, IDV/r, LPV/r, SQV/r). For the purpose of stratification, protease inhibitor sensitivity was interpreted from genotypic reports as not resistant, possibly resistant or resistant. Differences in interpretation between the two studies could be attributed to the different algorithms used in the TruGene and Virtual Phenotype assays. In addition, phenotypic cut-offs used to determine the resistance strata are largely based on unboosted PI data, whereas ritonavir-boosted PIs were used in the RESIST trials.

Phenotypic Methods
Phenotypes (n= 454) were submitted for review with 361 from the TPV/r arm and 93 from the CPI/r arm. Both the Virco Antivirogram® and the Virologic Phenosense™ assays were used to determine phenotypes. The Antivirogram assay was used for the randomly selected baseline samples from the phase III trials. Baseline TPV phenotypes were measured with both assays in the Phase II studies. In study 051, the Antivirogram was used for baseline samples and the Phenosense assay was used for 80 randomly selected baseline samples. In study 052, both assays were used for all the baseline samples and the Phenosense assay was used for selected on-treatment samples. The fold change in IC_{50} values for TPV and the other PIs was similar whether assayed by the VIRCO Antivirogram or Virologic Phenosense assay ($r = 0.83$ and $r = 0.92$, respectively).

1.1.2. Major microbiological issues that arose during product development.
In vitro combination studies were requested because of the drug interactions between TPV and other PIs seen in study 051. Data examining the activity of TPV against different clades of HIV-1 and HIV-2 was also requested.

We requested analyses of on-treatment samples from virologic failures on TPV treatment because the applicant did not intend to submit this data until traditional approval.

1.2. State of antimicrobials used for the indication (s) sought:

An estimated 40 million people worldwide were infected with HIV in 2001 and 3 million died from AIDS. Since HAART regimens have been introduced, the number of AIDS cases has decreased dramatically. HAART does not eradicate HIV from patients completely and even though the number of HIV RNA copies is reduced to undetectable levels, HIV re-emerges quickly after discontinuation of HAART. Therefore, with the currently available regimens, it is likely that most HIV-infected patients will require antiretroviral therapy throughout their lives.

There are currently twenty FDA-approved anti-HIV drugs including seven PIs (amprenavir/fosamprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), eight NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), three NNRTIs (delavirdine, efavirenz, nevirapine) and the fusion inhibitor T-20 (enfuvirtide). PIs work at the late stage of viral replication to prevent virus production from infected cells. They block the HIV protease enzyme, which is necessary for the production of mature virions, resulting in defective particles that are unable to infect new cells. NRTIs mimic nucleosides and target HIV-1 RT by competing with natural deoxynucleoside triphosphates for binding to RT and by incorporating into newly synthesized viral DNA resulting in chain-termination. NNRTIs inhibit HIV-1 RT by binding near the catalytic site of RT and acting as noncompetitive inhibitors. Enfuvirtide (T-20) is a gp41 fusion inhibitor preventing the joining of the viral and cellular membranes necessary for virus entry.

Unfortunately, HIV develops resistance to antiretroviral drugs over time usually from the accumulation of multiple mutations. HAART regimens are also associated with acute toxicities such as diarrhea, kidney stones, rash, CNS toxicities and hepatotoxicity. Long-term toxicities from antiretroviral therapies include mitochondrial toxicities associated with NRTIs (lactic acidosis, myopathy, neuropathy, pancreatitis), and disorders of lipid metabolism (dyslipidemia) and glucose metabolism (lipodystophy, hypercholesterolemia, hypertriglyceridemia) associated with PIs. These tolerability issues make compliance to therapy more challenging. Compliance is an important determinant of successful virologic suppression for patients on HAART. Regimens that are well-tolerated and easy to administer with a few pills once daily are likely to aid in patient compliance and improve clinical outcomes. There is a need for new anti-HIV drugs that are well-tolerated and easy to use with new modes of action and low likelihood of viral resistance development. Additionally, drugs that are effective against viruses resistant to all currently approved drugs are needed for the heavily treatment-experienced population.

2. Non-clinical Microbiology

Mechanism of Action

Tipranavir is a non-peptidic protease inhibitor of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. In enzymatic assays, TPV demonstrates inhibition of the cleavage of a peptidic substrate by the HIV-1 protease with an inhibition constant (K_i) of 8.9 + 6.8 pM. Using the same assay, TPV also inhibits the activities of HIV-2 protease (K_i <1 μM) and of mutant HIV-1 proteases carrying the mutations V82A (K_i = 0.003 μM) or V82F/184V (K_i = 0.25 μM). Selectivity for the HIV protease was demonstrated by high K_i values against the human aspartyl proteases pepsin (K_i = 2 μM), cathepsin D (K_i = 15 μM), and cathepsin F (K_i = 9 μM).

Antiviral Activity In Vitro

The in vitro antiviral activity of TPV against laboratory HIV strains and clinical HIV isolates was evaluated in acutely and chronically infected lymphoblastic and monocytic cell lines and peripheral blood lymphocytes (PBMC). Cell culture toxicity was determined using a MTT assay. The activity of TPV against laboratory strains of wild type HIV is shown in Table 1 (Report U04-3215, page 52).

Table 1. Antiviral activity of TPV against wild type laboratory HIV strains in acute and chronic models of infection using PBMC and different cell lines

Assay[1]	IC_{50}[2]	IC_{90}[2]	$CCTD_{50}$[3]	$CCTD_{90}$[3]	Selectivity Index[4]
Acute H9/HIV-1 $_{IIIB}$	0.04 ± 0.01	0.16 ± 0.07	21.1	38.7	528
Acute PBMC/HIV-1 $_{JR-CSF}$	0.05	0.18	17.5 ± 0.05	34.8 ± 7.4	350
Acute U397/HIV-1 $_{IIIB}$	0.11	0.55	7.4	16.8	67
Chronic H9/HIV-1 $_{IIIB}$	0.39	1.9	Not done	Not done	Not done

1 Results represent means and standard errors of at least two repeated experiments. Concentrations expressed in μM.

2 Compound concentration required to inhibit 50% or 90% of HIV-1 p24 antigen production compared with drug free controls.

3 Cell culture toxicity dose (CCTD) required to inhibit 50 or 90% of metabolism as determined by an MTT assay.

4 Calculated by dividing $CCTD_{50}$ by IC_{50}.

Since one of the target populations for TPV is treatment-experienced HIV positive patients, the antiviral activity of TPV has been tested against HIV-1 isolates resistant to currently available protease inhibitors. The average IC_{90} value for multidrug resistant clinical HIV-1 isolates was 619 nM (range 31 to 860 nM) and the average IC_{50} value for multi PI-resistant clinical HIV-1 isolates was 240 nM (range 50 to 380 nM). The isolates shown in Table 2 (Report U04-3215, page 53) had an IC_{50} value of >0.1 μM for indinavir or nelfinavir and had been obtained from patients who had increasing viral loads while taking these drugs.

Table 2. Phenotypic susceptibility to tipranavir of HIV-l isolates resistant to IDV and/or NFV

Clinical isolate[1]	IC_{50}	IC_{90}
006	0.191 ± 0.01	0.860 ± 0.04
003	0.280 ± 0.02	0.560 ± 0.05
007	0.046 ± 0.01	0.310 ± 0.02
008	0.097 ± 0.04	0.650 ± 0.01
004	0.315 ± 0.01	0.740 ± 0.07
010	0.103 ± 0.07	0.340 ± 0.02
001	0.355 ± 0.05	0.670 ± 0.01
002	0.363 ± 0.03	0.660 ± 0.08
009	0.301 ± 0.09	0.668 ± 0.04
005	0.383 ± 0.05	0.730 ± 0.07

1 Results (mean ± standard error) of three experiments are presented.

In addition, the TPV susceptibility of 134 isolates obtained from multiple PI-experienced HIV-positive patients (127 different subjects) were tested using the VIRCO Antivirogram method. Identified were 105 variants resistant (10-fold or greater increase in IC_{50} value) to at least three protease inhibitors and 29 variants resistant (10-fold or greater increase in IC_{50} value) to a single protease inhibitor. Of the 105 highly cross-resistant variants, 98% had less than a 10-fold decrease in susceptibility to TPV and 90% had less than a 4-fold decrease in susceptibility to TPV.

TPV demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF) with EC_{50} values ranging from 28 to 116 nM with the mean EC_{50} values for each clade shown in Table 3. The mean fold change in TPV susceptibility for each clade compared to the reference strain never exceeded 1.6-fold. Group O and HIV-2 isolates have reduced susceptibility in vitro to TPV with EC_{50} values ranging from 164 -1,000 nM and 233-522 nM, respectively (Table 4).

Table 3. Mean TPV EC_{50} values for HIV-1 Clades

HIV-1 Clade	Mean TPV EC_{50} Value (nM)
Ref NL4-3 (clade B)	62
A/A2	57
B	52
C	62
D	80
F/F1	97
G	41
H	81
CRF01 AE	61
CRF02 AG	77
CRF12 BF	33

Table 4. TPV EC_{50} Values for HIV-2 and Group O Viruses

Strain	HIV-1 Clade	TPV EC_{50} value (nM)
5512	B	125
BCF01 (+Y181C)	O	>333 (100% inhibition at 1000 nM)
BCF11	O	164
MVP5180	O	>333 (50% inhibition at 1000 nM)
CBL-20	HIV-2	548
CBL-23	HIV-2	246
MVP 15132	HIV-2	45

Serum Binding

Most protease inhibitors are highly protein bound, and this binding can limit antiviral activity. To determine a target TPV trough concentration to be achieved during clinical trials, the degree of change in the IC_{90} value caused by protein binding was determined (serum shift). The target trough TPV concentration was assumed to represent the product of the average TPV IC_{90} value for resistant HIV-1 isolates (approximately 600 nM) multiplied by the serum shift and a "safety factor" of 10. In equilibrium dialysis experiments using whole human plasma, the fraction of TPV (assayed at 20 μM) bound to plasma protein was 99.97%. In cell culture medium (60% fetal bovine serum), the fraction of TPV bound to proteins was dependent on the concentration of TPV used, with saturation above 2 μM. In antiviral activity assays, it was determined that the addition of 33% or 75% human plasma resulted in a 1.6-fold and 4-fold shift in the in vitro antiviral activity of TPV. A serum shift of 3.75 was used. The estimated target TPV trough concentration would be: 0.6 μM X 3.75 X 10, giving a result of 22.5 μM. Therefore, an initial TPV target trough of 20 μM was chosen.

In vitro Anti-HIV Activity of Drug Combinations

Because TPV will be administered to HIV-positive patients as part of a HAART regimen comprising several antiretroviral agents, the activity of TPV in combination with other agents was determined in cell culture. A panel of antiviral agents including seven NRTIs (3TC, ABC, AZT, d4T, ddI, FTC, TNF), three NNRTIs (DLV, EFV, NVP), seven PIs (APV, ATV, IDV, LPV, NFV, RTV, SQV), one fusion inhibitor enfuvirtide (T20), the anti-HCV drug ribavirin (RBV), and the anti-HBV drug adefovir (PMEA) were tested alone or in combination with TPV to assess the impact of potential in vitro drug interactions on the overall antiviral activity against wild-type HIV-1 in cell culture. The degree of drug interactions was determined by the median-effect principle using the combination index (CI) calculation and the "mutually exclusive" drug interaction condition.

The majority of combinations showed less than 5% toxicity. Only the combinations TPV:TNF and TPV:FTC showed toxicity levels between 5% to 14% at the highest

concentration of the ratios tested while TPV:RBV showed 26% toxicity at the highest concentration of the 1:100 ratio only. The toxicity levels greater than 5% observed when TPV was combined with TNF, FTC, or RBV are consistent with the observed toxicities of these agents when tested alone.

The combination index (CI) values at the EC_{50} and EC_{75} values for the various TPV:drug combination ratios corresponding to equipotent amounts of both drugs were determined. The interpretation of the CI values was based on the system recommended by Chou and Hayball (Calcusyn Windows software, User manual, Biosoft 1996) but with fewer descriptive levels in order to be consistent with the observed intrinsic variability of the antiviral replication assay used. Thus a CI value of 0.8-1.2 indicates an additive effect. CI values incrementally larger than 1.2 suggest increasing level of antagonism while CI values incrementally smaller than 0.8 suggest increasing level of synergy.

The AZT:ddI combination at a ratio 1:100 (i.e., closely corresponding to equipotent amounts of both drugs) has been reported to show synergistic interactions in cell culture and was selected as a control for synergy. When AZT was combined with ddI at the ratio 1:100, the CI values at the EC_{50} and EC_{75} values ranged from 0.12 to 0.42 consistent with synergistic combination of the two drugs. Other drug combinations have been reported to act antagonistically such as AZT:RBV, LPV:APV, IDV:SQV and AZT:d4T. The combination of AZT:d4T was used as a control for antagonism. The antagonism between AZT:d4T is mechanistically interpreted in terms of a competition between these two structurally related nucleosides for the same phosphorylation pathway in cells and has been confirmed in the clinic. However, conflicting results showing evidence of synergy, additivity or slight antagonism for the AZT:d4T combination have also been reported in cell culture against wild type HIV-1. In the experiments in this report, the AZT:d4T combination showed a level of synergy even after expanding the range to high drug ratios. None of the combinations cited above as antagonistic showed clear evidence of antagonism in this report. The sponsor states that they are trying to identify a clear positive control for antagonism in their laboratory.

Eqipotent combinations of TPV with PIs generally ranged from additive to antagonistic at the 50% and 75% inhibition endpoint (Table 5). The highest level of antagonism (CI = 1.47) was observed with TPV:ATV at a 10:1 ratio and at 75% inhibition. This ratio approaches the ratio of 11:1 calculated based on the C_{max} values of 80 μM and 7 μM independently observed in patients treated with TPV and ATV respectively (at the recommended doses of 500 mg TPV/200 mg RTV bid and at 300 mg ATV/100 mg RTV qd). The combinations of TPV with NRTIs were generally additive at the 50% inhibition and the 75% inhibition level (Table 5). The pairs TPV:3TC and TPV:ddI showed additive to antagonistic effects (at 50% and 75% inhibition) depending on the ratio tested. A mean CI of 1.38 (antagonism) was observed at the TPV:ddI ratio of 10:1 and mean CI of 1.31 (antagonism) was observed at the TPV:3TC ratio of 3:1. The combinations of TPV with the two NNRTIs were additive with NVP and additive to antagonistic with EFV.

The combination of TPV with the HIV fusion inhibitor enfuvirtide was clearly indicative of synergy at all ratios at both 50% and 75% inhibition. This combination is the most synergistic observed in this study. The combination of TPV with ribavirin was additive to synergistic at both 50% and 75% inhibition while the combination with PMEA (adefovir) was additive.

Table 5. Summary of In Vitro Drug Combination Studies with TPV

Drugs	Ratio (Equipotent of both drugs)	Mean CI at 50% inhibition	Mean CI at 75% inhibition	Assessment
TPV:APV	3:1	1.13	1.33	Additive/antagonistic
TPV:ATV	10:1	0.84	1.47	Additive/antagonistic
TPV:IDV	3:1	0.82	1.13	Additive/antagonistic
TPV:LPV	10:1	1.24	0.76	Additive/antagonistic
TPV:NFV	10:1	0.88	0.77	Additive
TPV:RTV	3:1	1.06	0.89	Additive/antagonistic
TPV:SQV	10:1	1.01	1.34	Additive/antagonistic
TPV:3TC	3:1	1.00	1.31	Additive/antagonistic
TPV:ABC	1:10	0.53	0.59	Additive
TPV:AZT	3:1	0.98	0.91	Additive
TPV:d4T	1:10	0.76	0.96	Additive
TPV:ddI	1:10	0.98	0.72	Additive/antagonistic
TPV:FTC	3:1	1.01	0.84	Additive
TPV:TNF	1:10	0.70	0.85	Additive
TPV:EFV	100:1	1.09	1.19	Additive/antagonistic
TPV:NVP	5:1	0.78	0.88	Additive
TPV:DLV	10:1	0.56	0.65	Additive/synergistic
TPV:T20	1:3	0.46	0.62	synergistic
TPV:RBV	1:100	0.54	0.85	Additive/synergistic
TPV:PMEA	1:10	1.20	0.78	Additive

Range of CI	
<0.3	strongly synergistic
0.3-0.8	synergistic
0.8-1.2	additive
1.2-1.7	antagonistic
>1.7	strongly antagonistic

Overall, the results of in vitro combination activity assessments suggest that additive to antagonistic relationships were seen with combinations of TPV with the PIs. The combinations of TPV with the NRTIs were generally additive and additive to antagonistic for TPV in combination with 3TC and ddI. The combinations of TPV with the NNRTIs DLV and NVP were additive and additive to antagonistic with EFV. The combination of

TPV with the HIV fusion inhibitor enfuvirtide was synergistic. The combination of TPV with ribavirin was additive to synergistic and the combination with adefovir was additive.

After discussions with the applicant, the following was concluded for the in vitro combinations with TPV. The combination of tipranavir was additive to antagonistic with the PIs (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and generally additive with the NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine), and the NNRTIs (delavirdine, efavirenz, and nevirapine). The combination of TPV was synergistic with the HIV fusion inhibitor enfuvirtide and additive to synergistic with the two compounds used in the treatment of viral hepatitis, adefovir and ribavirin.

Development of Resistance In Vitro

HIV- 1 isolates NL4-3 (WT) and P37 (drug resistant) were evaluated in serial passage in MT-2 cells in the presence of TPV. The NL4-3 virus showed a 3.5-fold decrease in TPV susceptibility at passages 14 and 26. The P37 virus showed a decrease in TPV susceptibility of up to 2.9-fold at passages 7, 13, and 22 in another in vitro study. No viruses with >10-fold decrease in TPV susceptibility were detected in this study.

HIV-l isolate NL4-3 (WT) was passaged in C8166 cells in the presence of increasing concentrations of TPV in tissue culture for 9 months. Following each viral breakthrough, the HIV-l protease gene and adjacent cleavage sites were sequenced. Viral breakthroughs were detected as sudden increases in the cytopathic effect. To determine the contribution of the mutations found to resistance, molecular clones containing emerging mutations were constructed and tested in antiviral activity assays against TPV (Table 6).

Table 6. Tipranavir susceptibility of molecularly cloned breakthrough viruses obtained by serial passage in the presence of increasing concentrations of TPV

Passage Number	Mutations	IC_{50} Value (nM)	Fold WT	TPV Conc (nM)
16	**L33F, I84V**	100	1.7	800
33	L33F, **K45I**, I84V	167	2.8	1000
39	**I13V, V32I**, L33F, K45I, I84V	407	6.9	2000
49	I13V, V32I, L33F, K45I, **V82L**, I84V	967	16.0	5000
68	I13V, V32I, L33F, **M36I**, K45I, **A71V**, V82L, I84V	1687	29.0	20000
70	**L10F**, I13V, V32I, L33F, M36I, K45I, **I54T/V**, A71V, V82L, I84V	4156	70.0	20000

New Mutations appearing at a given passage are in bold.

Mutations emerged initially at positions L33F and I84V, producing a 1.7-fold decrease in TPV susceptibility. Viruses with >10-fold decreased susceptibility were not detected until virus broke through drug concentrations of 5 μM at passage 49, when six mutations were detected. After 70 passages (9 months), HIV- 1 variants capable of growing in the presence of >20 μM of TPV were selected; this population showed a 70-fold decrease in susceptibility to TPV. A mutation in the CA/P2 protease cleavage site, a valine to isoleucine substitution at the P2 residue, was observed first in variants from passage 39 (2/10 clones sequenced) and it was present in all clones sequenced at later passages. In addition, a serine to proline substitution in the transframe region, 17 amino acids upstream of the protease sequence was also observed. This mutation was also observed first at passage 39 and was maintained in all subsequent passages. Neither the CA/P2 nor the transframe region mutations contributed to the phenotypic resistance of reconstituted molecular clones as demonstrated by mutagenesis. Finally, the genotype of passage 70 viruses (10 mutations in the protease, a CA/P2 cleavage site mutation and a transframe region mutation) was stable for at least 12 passages in vitro in the absence of TPV.

These in vitro data provide the best indication of the emergence of TPV resistance when starting with a drug sensitive wild-type HIV isolate. These results demonstrate that the development of TPV resistance in vitro is complex and involves the sequential accumulation in the protease gene of up to 10 mutations, each contributing an increase in resistance. TPV resistance development in treatment-naïve patients has not been evaluated at this time.

In Vitro Cross-Resistance

The susceptibility to TPV of isolates resistant to currently available protease inhibitors was analyzed in multiple studies. Results from a study by Larder *et al.* showed that TPV had <4-fold decreased susceptibility against 90% (94/105) of HIV-1 isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, or SQV (Larder *et al.*, 2000). The mean fold decrease in the TPV IC_{50} value was 3. Most (>90%) of these PI-resistant isolates had a 10-fold or greater decrease in susceptibility to protease inhibitors. The mean IC_{50} value increase for these isolates was 35-fold for IDV, 57-fold for RTV, 37-fold for NFV, and 51-fold for SQV. Interestingly, G48V and V82A were mutations frequently observed among the isolates with increased susceptibility to TPV. In contrast, isolates resistant to TPV had a high frequency of the mutations V82T and I84V or I84V and L90M with numerous other PI mutations.

The susceptibility to currently available protease inhibitors of HIV isolates resistant to TPV has been investigated using two molecular clones selected by in vitro passage of wild-type virus containing 6 and 10 protease mutations. TPV-resistant viral molecular clones showed decreased susceptibility to all currently available protease inhibitors except SQV (Table 7) (Report U04-3215, page 57).

Table 7. In vitro susceptibility of TPV-resistant viral molecular clones to various protease inhibitors

	IC_{50} (μM), (fold change over WT)		
	WT	13, 32, 33, 45, 82, 84	10, 13, 32, 33, 36, 45, 54, 71, 82, 84
Amprenavir	13	1189 (91)	431 (33)
Atazanavir	4	130 (33)	472 (118)
Indinavir	6	169 (28)	540 (90)
Lopinavir	7	196 (28)	473 (68)
Nelfinavir	5	48 (10)	195 (39)
Ritonavir	26	1580 (61)	4148 (159)
Saquinavir	4	2 (0.5)	10 (2.5)
Tipranavir	60	967 (16)	4156 (69)

1 WT virus as well as viral molecular clones representing passage 49 (genotype I13V, V32I, L33F, K45I, I82L, I84V in column 3) and 70 (genotype L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V, V82L, I84V in column 4) of the TPV selection experiment were tested in viral replication assays for their susceptibility to a panel of protease inhibitors. Values in parenthesis represent the fold over WT median effective dose (EC_{50}) values. Each value represents the mean of at least two independent experiments.

3. Clinical Studies

The two identically designed RESIST trials, RESIST 1 (1182.12) and RESIST 2 (1182.48), were multi-center, multi-national, randomized and controlled, open-label 96-week studies in highly treatment-experienced HIV-infected patients with triple antiretroviral class (NRTI, NNRTI, and PI) and dual protease inhibitor (dual PI)–drug regimen experience. RESIST 1 was conducted in the United States, Canada and Australia, while RESIST 2 was conducted in Europe and Latin America. Tipranavir boosted with ritonavir (TPV/r 500 mg/200 mg) was compared with respect to safety and efficacy through 24 weeks of treatment against a control group of other protease inhibitors boosted with ritonavir (CPI/r) where the control PIs were genotypically determined.

Genotypic resistance testing was done at screening to enroll patients with at least one primary PI mutation at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and no more than two protease mutations at positions 33, 82, 84, or 90. Patients were randomized equally to either TPV/r or CPI/r arm and stratified with respect to pre-selected protease inhibitor (PI) as well as use of enfuvirtide (T-20). Both treatment groups (TPV/r versus CPI/r) were designed to receive optimized background regimen based on genotypic resistance testing prior to randomization. Due to the complex comparator treatment group containing various protease inhibitors with varying degrees of resistance profiles of the drugs, the studies had to be designed as open-label trials. It is noteworthy that the comparator protease inhibitor control arm was a partially active control in this highly treatment-experienced group of patients. Therefore, the FDA review team strongly recommended to the Applicant that the studies be tested for superiority of efficacy of TPV/r versus CPI/r.

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814 **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

Safety

A safety concern throughout the TPV drug development program has been hepatotoxicity. Initial signals were observed throughout the 18 Phase 1 studies in healthy volunteers. Detailed exposure response analysis on Study 1182.52 indicated that the ALT abnormality was associated with TPV exposure. The likelihood that RTV contributed to the ALT abnormality was small. In the RESIST trials, 10% of subjects on the TPV/r arm compared to 3% on the CPI/r arm developed treatment-emergent grade 3 or 4 ALT or AST elevations. The relationship (and time-course) of these liver enzyme elevations with symptomatic clinical disease manifestation was difficult to ascertain.

Analyses of RESIST 1 laboratory data showed that the time to first Grade 3 or 4 in total cholesterol ($p=0.0007$) and triglycerides ($p=0.0186$) were significantly different between the two arms. Analyses of RESIST 2 laboratory data showed that the time to first Grade 3 or 4 in total cholesterol ($p=0.0255$) and triglycerides ($p<0.0001$) were significantly shorter for subjects in the TPV/r arm. More subjects in the TPV/r arm developed Grade 3 or 4 total cholesterol and triglycerides than those in the CPI/r arm and at a significantly faster pace. For combined RESIST 1 and 2 datasets, 21% of subjects developed treatment emergent grade 3 or 4 triglycerides compared to 11% of subjects on the CPI/r arm. At the 24 week time-point, 1 of 5 subjects with documented clinical pancreatitis also had hypertriglyceridemia as a laboratory abnormality. The lipid abnormalities measured in the RESIST trials for TPV/r is consistent with what has been generally observed as an important safety concern regarding the PI class.

Cutaneous reactions (rash) was another safety event of special interest in this review due to a substantial Phase 1 signal from an oral contraceptive study in healthy HIV negative women (study 1182.22). Seventeen subjects (33%) developed a rash while receiving TPV and 20% had musculoskeletal pain. In the phase 3 RESIST trials, the overall incidence of rash was similar on both arms (11% TPV/r versus 10% CPI/r). The severity and need for treatment were also similar between the two arms. Three subjects on the TPV/r arm compared to zero on the CPI/r arm ended up discontinuing study treatment due to their rash. Since the RESIST trial population was a clinically advanced and immunologically depleted, examination of immunologically-mediated rash (or drug hypersensitivity) adverse reactions was limited. Sulfa-allergic subjects were not excluded in RESIST trials resulting in 5% of subjects on each arm having a documented sulfa allergy. Of these subjects, 6% (n=5/80) on the TPV/r and 7% (n=6/84) on the CPI/r arm had rash as a treatment emergent adverse event. A subgroup analysis of the females in the RESIST trials (n=118 TPV/r; n=90 CPI/r) did show that the females on the TPV/r arm had a higher incidence of rash (14%) as compared to the females on the CPI/r arm (9%). However, 7 of the 17 subjects on the TPV/r had no baseline CD4+ cell count recorded, so DAVDP could not make an accurate assessment of the immunologic status of these women.

A total of 103 death cases representing 102 patients died during the entire TPV clinical development program. In total, 12 subjects died during the pretreatment phase and 90

subjects died after being exposed to at least one dose of drug (post-drug exposure). Three of the 90 post-drug exposure subject deaths were considered to be possibly TPV/r treatment related by the applicant. For most death cases, subjects had advanced HIV disease and multiple concomitant medications. Although only these three cases are described here, relatedness or possible contribution of the effects of TPV to the death events could not be ruled out by the FDA reviewers for almost all death cases. This unclear ascertainment of study drug's relationship to mortality (and to morbidity) is due to the nature of the population under study, and in many cases, was due to the lack of available information surrounding the death cases. Please see Medical Officer Andrea James' review for a full analysis of safety.

Efficacy

The primary efficacy endpoint in the RESIST trials is the proportion of patients with a treatment response at 48 weeks ($\geq$ 1 $\log_{10}$ reduction from baseline HIV RNA in two consecutive measurements without prior evidence of treatment failure). The efficacy endpoint for the 24-week data submitted in this application is the proportion of patients with a treatment response at 24 weeks. Multiple secondary analyses were performed for each study. In each RESIST trial, the proportion of treatment responders were significantly higher in the TPV/r treated group versus the patients in the CPI/r treated group (RESIST 1: 36% TPV/r versus 16% CPI/r; RESIST 2: 32% TPV/r versus 13% CPI/r). TPV/r had a net treatment effect of 20% over CPI/r in this patient population. These results do not show that tipranavir is superior to other comparator protease inhibitors in other patient populations. Please see Statistical Review Rafia Bhore's review for a full analysis of efficacy.

HIV RNA Results according to Stratification Criteria

In the RESIST trials, randomizations were stratified according to the pre-selected protease inhibitors (APV/r, IDV/r, LPV/r, SQV/r) based on genotypic resistance testing and according to the use of enfuvirtide (T-20). FDA conducted subgroup analyses based on these stratification factors in order to determine if differences existed between RESIST 1 and 2. The results of the subgroup analyses are summarized in Tables 4 and 5 below

T-20 strata:

The treatment difference between the TPV/r (500 mg/200 mg) group and the low-dose ritonavir boosted comparator protease inhibitor group (CPI/r) was statistically significant in both subgroups of the enfuvirtide-use strata (used T-20 or did not use T-20). These results were consistent between RESIST 1 and RESIST 2 studies. In addition, FDA conducted statistical tests to examine interaction between the subgroups on T-20 use and treatment group. A statistically significant treatment interaction was observed for the subgroup of patients who actually used T-20 versus did not use T-20 (p-value = 0.02 significant at α=0.15 level). In this highly treatment-experienced patient population, the net proportion of patients with confirmed 1 $\log_{10}$ reduction in HIV-RNA using TPV/r in

combination with T-20 had a net treatment effect of 29.4% vs. 15.6% if TPV/r was used alone without T-20.

Pre-selected PI strata:
Genotypic resistance testing was used to stratify patients according to pre-selected protease inhibitors (APV/r, IDV/r, LPV/r, SQV/r). For the purpose of stratification, protease inhibitor sensitivity was interpreted from genotypic reports as not resistant, possibly resistant or resistant. Determinations of resistance differed between RESIST 1 and 2 and are based on two different methods. In RESIST 1, the TruGene assay was used whereas for RESIST 2 the Virtual Phenotype assay was used. Differences between the two studies could be attributed to the algorithms used. In addition, the Virtual Phenotype cut-offs used to determine the resistance strata are largely based on unboosted PI data and the interpretation of possibly resistant to individual RTV-boosted PIs is controversial. Therefore, these analyses were conducted for the purpose of evaluating stratification variables and not to evaluate outcomes by baseline resistance as shown in section III.

In RESIST 1, only 8% were interpreted as not resistant to the pre-selected PI, 35% were interpreted as possibly resistant and 58% were interpreted as resistant to the pre-selected PIs. In comparison, 20% were interpreted as not resistant, 6% as possibly resistance and 74% as resistance to the pre-selected protease inhibitors in RESIST 2. The explanation for the differences between the two studies could be explained by use of the different assays for the interpretation. The FDA does not believe that this interpretation of resistance by genotype for this highly experienced patient population is optimal and thus did not use these stratification criteria for resistance analyses. Efficacy conclusions also cannot be determined for this subgroup analysis because of the limited number of patients in the "not resistant" group. In the subgroup of patients for whom the pre-selected PI was not resistant to the HIV, the treatment difference between TPV/r and CPI/r was not consistent between RESIST 1 (-4.8%) versus RESIST 2 (15.4%). However, the result of the subgroup of patients with possible/definite resistance to PIs was consistent with the overall results on the primary efficacy endpoint (treatment effect of 19% to 20%). Please see Medical Officer Andrea James' and Statistician Rafia Bhore's reviews for a full analysis of efficacy.

4. Clinical Microbiology

The efficacy of TPV/r was examined in treatment-experienced HIV-infected subjects in two pivotal phase III trials, study 012 (RESIST 1) and study 048 (RESIST 2). Genotypes from 1482 isolates (Table 8) and 454 phenotypes (Table 9) from both studies were submitted for review.

Table 8. Number of Isolates with Genotypes

Study	TPV/r	APV/r	IDV/r	LPV/r	SQV/r
RESIST 1	310	45	13	187	64
RESIST 2	435	149	10	171	98
Total	745	194	23	358	162

Table 9. Number of Isolates with Phenotypes

Study	TPV/r	APV/r	IDV/r	LPV/r	SQV/r
RESIST 1	182	8	2	27	10
RESIST 2	179	19	1	18	8
Total	361	27	3	45	18

There 745 patient isolates in the TPV/r arm. In the comparator arm (CPI), most patients received LPV/r (n=358) followed by APV/r (n=194), SQV/r (n=162) and IDV/r (n=23) (Table 10).

Table 10. Patients in Each Arm

Study	TPV/r	APV/r	IDV/r	LPV/r	SQV/r
RESIST 1	310	45	13	187	64
RESIST 2	435	149	10	171	98
Total	745	194	23	358	162

Baseline Analysis

The patient populations in RESIST 1 and 2 were highly treatment-experienced with a median number of 4 (range 1-7) PIs received prior to study. In the combined RESIST trials at baseline, 97% of the isolates were resistant to at least one PI, 95% of the isolates were resistant to at least one NRTI, and >75% of the isolates were resistant to at least one NNRTI (Tables 11 and 12). The treatment arms from both studies were balanced with respect to baseline genotypic and phenotypic resistance. Baseline phenotypic resistance was equivalent between the TPV/r arm (n= 361) and the CPI/r arm (n=93) with 30% of the isolates resistant to TPV at baseline and 80-90% of the isolates resistant to the other PIs - APV, ATV, IDV, LPV, NFV, RTV or SQV (Table 13).

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Table 11. Number of Isolates Resistant to Anti-HIV Classes in RESIST 1 and 2 Arms

	APV/r (n=27)	IDV/r (n=3)	LPV/r (n=46)	SQV/r (n=18)	CPI/r (n=94)	TPV/r (n=367)
PI-R	26	3	45	18	92	357
NRTI-R	25	3	43	18	89	351
NNRTI-R	23	3	34	11	71	309

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Table 12. Percent Resistant to Anti-HIV Classes in RESIST 1 and 2

	CPI/r (n=94)	TPV/r (n=367)
PI-R	98%	97%
NRTI-R	95%	96%
NNRTI-R	76%	84%

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Table 13. Percent Resistant to Protease Inhibitors by Arm in RESIST 1 and 2

	TPV	APV	IDV	LPV	NFV	RTV	SQV	ATV
CPI/r n = 94	34	81	86	84	90	94	78	83
TPV/r n = 367	33	80	81	84	91	92	75	87

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

The number of PI-resistance mutations was equivalent between the TPV/r and CPI/r arms in RESIST 1 and 2 and the median number of baseline PI, NRTI and NNRTI mutations was equivalent between arms in both studies (Table 14 and 15).

Table 14. Proportion of Subjects with Baseline PI mutations by Study Arm in RESIST 1 and 2

	>3 TPV mut	>3 FDA mut	≥6 LPV mut
CPI/r n = 737	45%	64%	89%
TPV/r n = 745	46%	64%	88%

FDA PI mut - Number of amino acid substitutions at D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, or L90 at baseline
TPV PI mut - Number of protease mutations from 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, or 84V at baseline

LPV mut - Number of protease mutations from 10F/I/R/V, 20M/R, 24I, 46I/L, 53L, 54V/T/L, 63P, 71T/V/L, 82F/A/T, 84V, or 90M at baseline

Table 15. Median Number of Mutations at Baseline in RESIST 1 and 2

	FDA PI mut	TPV PI mut	Key PI mut	Primary PI mut	IAS PI mut	NRTI mut	NNRTI mut
TPV/r n = 745	4	3	2	3	9	5	1
CPI/r n = 737	4	3	2	3	9	5	1

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

Baseline Genotype and Virologic Outcome Analyses

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

For the resistance analyses, the FDA used a censored dataset or "as-treated" population. For the primary endpoint analysis, we included subjects who were responders, virologic failures, subjects who discontinued before they achieved viral suppression, subjects with HIV RNA data through week 16 and/or 24, subjects with HIV RNA data only through week 8 and who did not achieve at least 0.5 $\log_{10}$ decrease in HIV RNA, and subjects who added a new ARV that was a NRTI in class substitution. We censored subjects who did not reach week 24 and had only week 16 data available, subjects who discontinued while suppressed or discontinued before they achieved confirmed viral suppression because of an adverse event or other reasons, subjects who added a new ARV which included a change in PI, including a change to TPV or added a therapeutic dose of RTV,

and subjects who had no or unconfirmed virologic response (See Appendix B and C). This approach for analyzing baseline resistance data is consistent with the FDA Draft Guidance for Industry: Role of HIV Drug Resistance Testing in Antiretroviral Drug Development and FDA analyses for other antiviral drugs.

For the DAVG24 analyses, the FDA included responders, virologic failures, subjects from RESIST 2 who did not reach week 24 with only week 16 data available, subjects who discontinued while suppressed, and subjects who discontinued before achieving viral suppression. We censored discontinued before achieving viral suppression, subjects who added new ARV which was a change in PI, including a change to TPV or added a therapeutic dose of RTV.

Both the number and type of baseline PI mutations affected response rates in RESIST 1 and 2. Virologic responses were analyzed by the presence at baseline of each of 25 different protease amino acids using both the primary endpoint (>1 $\log_{10}$ decrease from baseline) and DAVG24. Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline substitution at amino acid position I13, V32, M36, I47, Q58, D60 or I84 (Table 16). The reduction in virologic responses for these baseline substitutions was most prominent in the No T20 subgroup. Virologic responses were similar or greater than the overall responses for each subgroup (All, No T20, +T20) when these amino acid positions were wild-type. In addition, virologic responses to substitutions at position V82 varied depending on the substitution. Interestingly, substitutions V82S or F or I or L, but not V82A or T or C, had reduced virologic responses compared to the overall.

Table 16. Effect of Type of Baseline PI Mutation on the Primary Endpoint in RESIST 1 and 2.

	TPV/r Arm (n=513)			CPI/r Arm (n=502)		
Mutation	**All**	**No T20**	**+T20**	**All**	**No T20**	**+T20**
Overall	47% (240/513)	40% (147/369)	65% (93/144)	22% (109/502)	19% (75/389)	30% (34/113)
I13V/A/L/S	40% (69/171)	27% (32/119)	69% (37/54)	20% (35/178)	15% (20/133)	33% (15/45)
V32I/L	39% (29/74)	26% (12/46)	61% (17/28)	15% (9/59)	14% (6/43)	19% (3/16)
M36I/A/V/L/N	40% (124/310)	29% (60/208)	63% (64/102)	20% (65/318)	18% (45/345)	27% (20/73)
I47V/A	31% (29/93)	18% (11/62)	58% (18/31)	11% (9/82)	10% (6/63)	16% (3/19)
Q58E	38% (28/74)	27% (14/52)	64% (14/22)	18% (17/93)	18% (14/79)	21% (3/14)
G48V/M	63% (50/80)	79% (19/24)	55% (31/56)	22% (20/90)	42% (10/24)	15% (10/66)
D60E/K/A/N	39% (43/110)	30% (24/79)	61% (19/31)	12% (8/66)	11% (6/53)	15% (2/13)
V82 any change	48% (149/311)	41% (90/222)	66% (59/89)	18% (54/202)	14% (33/236)	32% (21/66)

V82A/T/C	50% (133/264)	45% (85/189)	64% (48/75)	18% (46/259)	13% (27/202)	33% (19/57)
V82S/F/I/L	34% (16/47)	15% (5/33)	79% (11/14)	21% (9/43)	21% (7/34)	22% (2/9)
I84V/A	41% (64/155)	31% (32/103)	62% (32/52)	20% (32/162)	20% (23/115)	19% (9/47)

An additional analysis was done looking at the applicants 4 "key" positions L33, V82, I84 and L90. The applicant has determined that changes at these 4 positions affect the response to TPV and used the number of these key mutations (≤2) as entry criteria into the RESIST trials. Our analysis of the effect on response rates of changes versus WT at these key positions is shown in Table 17 and effect on response rates of combinations of the key mutations is shown in Table 18.

Table 17. Effect of TPV "Key" Mutations

	TPV/r Arm (n=513)			CPI/r Arm (n=502)		
Mutation	**All**	**-T20**	**+T20**	**All**	**-T20**	**+T20**
	47% (240/513)	**40%** (147/369)	**65%** (93/144)	**22%** (109/502)	**19%** (75/389)	**30%** (34/113)
L90L	49% (113/231)	42% 70/168	68% 43/63	22% (50/230)	20% (36/183)	30% (14/47)
L90M/I/F	45% 127/282	38% 77/201	62% 50/81	22% (59/272)	19% (39/206)	30% (20/66)
V82V	45% 91/202	39% (57/147)	62% (34/55)	28% (55/200)	27% (42/153)	28% (13/47)
V82 any change	48% (149/311)	41% (90/222)	66% (59/89)	18% (54/202)	14% (33/236)	32% (21/66)
V82A	50% (116/230)	45% (76/170)	67% (40/60)	17% (38/222)	13% (23/176)	33% (15/46)
V82T	44% (12/27)	47% (7/15)	42% (5/12)	19% (5/27)	10% (2/20)	43% (3/7)
V82C/I/F/M/S/G	39% (22/56)	21% (8/39)	82% (14/17)	20% (11/56)	19% (8/42)	21% (3/14)
L33L	47% (183/394)	40% (118/393)	64% (65/101)	22% (86/385)	21% (63/303)	28% (23/82)
L33F/I/M/V/E	48% (57/119)	38% (29/76)	65% (28/43)	20% (23/117)	14% (12/86)	35% (11/31)
I84I	49% (176/358)	43% (115/266)	66% (61/92)	23% (77/340)	19% (52/274)	38% (25/66)
I84V/A	41% (64/155)	31% (32/103)	62% (32/52)	20% (32/162)	20% (23/115)	19% (9/47)

Table 18. Proportion of Responders at Week 24 by Combinations of TPV Key Mutations (33, 82, 94 and 90)

Number of Key Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
33 + 82	40/78 (51)	21/51 (41)	19/27 (70)	14/90 (16)	5/64 (8)	9/26 (35)
33 + 84	9/22 (41)	3/11 (27)	6/11 (54)	3/13 (25)	2/9 (22)	1/3 (33)
33 + 90	11/30 (37)	5/17 (29)	6/13 (46)	7/25 (28)	4/19 (21)	3/6 (50)
82 + 84	12/33 (36)	6/24 (25)	6/9 (67)	6/34 (18)	4/22 (18)	2/12 (17)
82 + 90	59/128 (46)	34/89 (38)	25/39 (64)	20/115 (17)	11/89 (12)	9/26 (35)
84 + 90	40/96 (42)	20/63 (31)	20/33 (61)	21/109 (19)	14/77 (18)	7/32 (22)

The summary points of the analysis of response by type of PI mutations are:

- Virologic responses were analyzed by the presence at baseline of substitutions at each of 25 different protease amino acid positions using both the primary endpoint (>1 $\log_{10}$ decrease from baseline) and DAVG24.

- The reduction in virologic responses for these baseline substitutions was most prominent in the No T20 subgroup. These mutations that decrease the response to TPV are included in the mutations that Boëhringer Ingelheim uses to determine its TPV score.

- Reduced virologic responses were seen in TPV/r-treated subjects when isolates had a baseline amino acid substitution at position I13, V32, M36, I47, Q58, or D60.

- TPV/r-treated subjects did better than the overall response (63% vs 47%) if their isolates had G48 substitutions even with 4+ mutations.

- Reduced virologic responses were seen in TPV/r-treated subjects when isolates had the baseline mutation I84V or A.

- In addition, virologic responses to substitutions at position V82 varied depending on the substitution.

- Substitutions V82S or F or I or L, but not V82A or T or C had reduced virologic responses compared to the overall.

- Interestingly, subjects with substitutions at V82 including V82A or T and I84V had lower response rates than the overall response (20-30%) (Table 19 and 20).

Table 19. Proportion of Responders at Week 24 by Combinations of I84V and V82 Mutations

Baseline PI mutations	TPV/r		
	All	No T20 Use	T20 Use
Overall	47%* (240/513)	40% (147/369)	65% (93/144)
V82 any change +I84V	36%* (12/33)	25% (2/24)	67% (6/9)
V82T + I84V	29% (2/7)	20% (1/5)	50% (1/2)
V82A + I84V	33% (6/18)	29% (4/14)	50% (2/4)
V82C/F/I/S + I84V	50% (4/8)	20% (1/5)	100% (3/3)

* p value = 0.017

Table 20. DAVG24 by Combination of I84V and V82 Mutations

Baseline PI mutations	TPV/r		
	All	No T20 Use	T20 Use
Overall	-1.31	-1.03	-1.89
V82 any change + I84V	-0.77 (37)	-0.70 (26)	-1.79 (11)
V82T + I84V	-0.48 (8)	-0.66 (5)	-0.17 (3)
V82A + I84V	-0.93 (20)	-0.72 (15)	-1.45 (5)
V82C/F/I/S + I84V	-0.77 (9)	-0.56 (6)	-2.82 (3)

The lower response rates in subjects with V82S/F/I/L at baseline does not appear to be explained by an increased incidence of the presence of I84V (Table 21) or lower T20 use [V82S/F/I/L +T20=30%; -T20=70%; V82A/T +T20 = 31%; - T20 = 69%].

Table 21. The Number of V82-containing Isolates with the I84V Mutation

	# with I84V	% R with I84V
V82 any change	11% (33/311)	
V82A/T/C	10%* (26/264)	31% (8/26)
V82S/F/I/L	15%* (7/47)	57% (4/7)

*p value = 0.30

The lower response rates of subjects with the V82S/F/I/L substitution in their HIV at baseline does not appear to be explained by an increased combination with another mutation that decreases TPV response (Table 22).

Table 22. Number of V82F/I/L/S isolates with Different Substitution Combinations

Substitution	% (#) V82F/I/L/S (n=47)	% (#) V82A/T/C (n=264)
L33	17% (8)	27% (70)
L90	45% (21)	41% (107)
M36	72% (34)	67% (177)
M46	74% (35)	73% (192)
I47	9% (4)	14% (37)
G48	19% (9)	25% (67)
I54	83% (39)	91% (240)
Q58	15% (7)	17% (46)
G73	9% (4)	16% (41)
I84	15% (7)	10% (26)
L89	11% (5)	16% (42)

Analyses were also conducted to assess virologic outcome by the number of PI mutations present at baseline. In these analyses, any changes at protease amino acid positions - D30, V32, M36, M46, I47, G48, I50, I54, F53, V82, I84, N88 and L90 were counted if present at baseline. These PI mutations were used based on their association with reduced susceptibility to currently approved PIs, as reported in various publications. The results of these analyses are shown in Tables 23 and 24.

Regardless of the endpoint used for these analyses, the response rates were greater for the TPV/r treatment arm compared to the CPI/r arm. In both the TPV/r and CPI/r arms of RESIST 1 and 2, response rates were similar to or greater than the overall response rates for the respective treatment groups for subjects with one to four PI mutations at baseline. Response rates were reduced if five or more PI-associated mutations were present at baseline. For subjects who did not use T20, 28% in the TPV/r arm and 11% in the CPI/r

arm had a confirmed 1 $\log_{10}$ decrease at Week 24 if they had five or more PI mutations in their HIV at baseline (Table 23). The subjects with five or more PI mutations in their HIV at baseline and not receiving T20 in their OBT achieved a 0.86 $\log_{10}$ median DAVG24 decrease in viral load on TPV/r treatment compared to a 0.23 $\log_{10}$ median DAVG24 decrease in viral load on CPI/r treatment (Table 24). In general, regardless of the number of baseline PI mutations or T20 use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 $\log_{10}$ decrease at Week 24) (Table 23) and greater declines in viral load by median DAVG24 (Table 24) than the CPI/r arm.

Table 23. Proportion of Responders (confirmed 1 $\log_{10}$ decrease at Week 24) by Number of Baseline PI Mutations

# Baseline FDA PI Mutations	TPV/r N=513			CPI/r N=502		
	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/513)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)
1-2	70% (30/43)	69% (27/39)	75% (3/4)	44% (19/43)	41% (17/41)	100% (2/2)
3-4	50% (117/236)	44% (78/176)	65% (39/60)	27% (60/221)	23% (39/169)	40% (21/52)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)

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

Table 24. Median DAVG24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations	TPV/r N=704			CPI/r N=705		
	All	No T20	+ T20	All	No T20	+ T20
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)
1-2	-1.43 (76)	-1.44 (69)	-1.42 (7)	-1.13 (65)	-1.01 (63)	-1.90 (2)
3-4	-1.36 (322)	-1.29 (259)	-1.96 (63)	-0.53 (316)	-0.44 (252)	-0.89 (64)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)

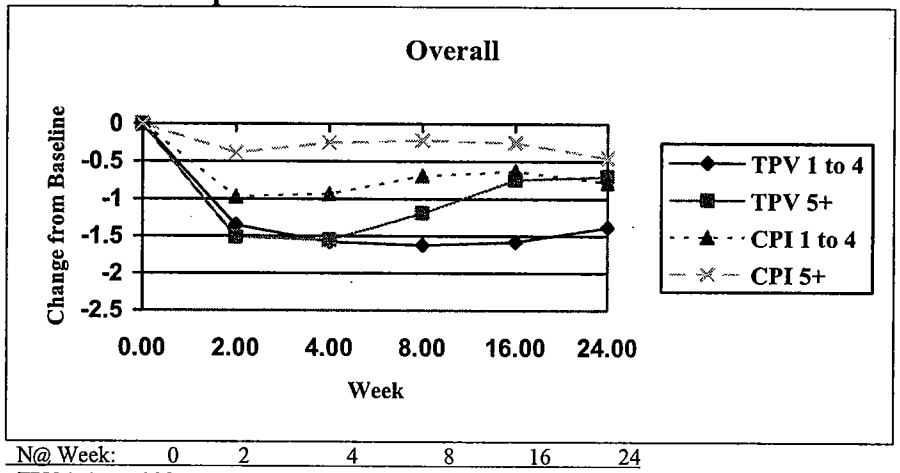
Any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

An examination of the median change from baseline of HIV RNA at weeks 2, 4, 8, 16 and 24 by number of baseline PI mutations (1-4 and 5+) showed the largest decline in viral load by Week 2 for all groups with the greatest decline observed in the TPV/r arms

(Figure 1). A 1.5 $\log_{10}$ decrease in viral load at Week 2 was observed for subjects receiving TPV/r regardless of the number of baseline PI mutations (1-4 or 5+). Sustained viral load decreases (1.5 – 2 $\log_{10}$) through Week 24 were observed in subjects receiving TPV/r and T20 (Figure 1C). However, subjects who received TPV/r without T20 and who had five or more baseline PI mutations group began to lose their antiviral response between Weeks 4 and 8 (Figure 1B).

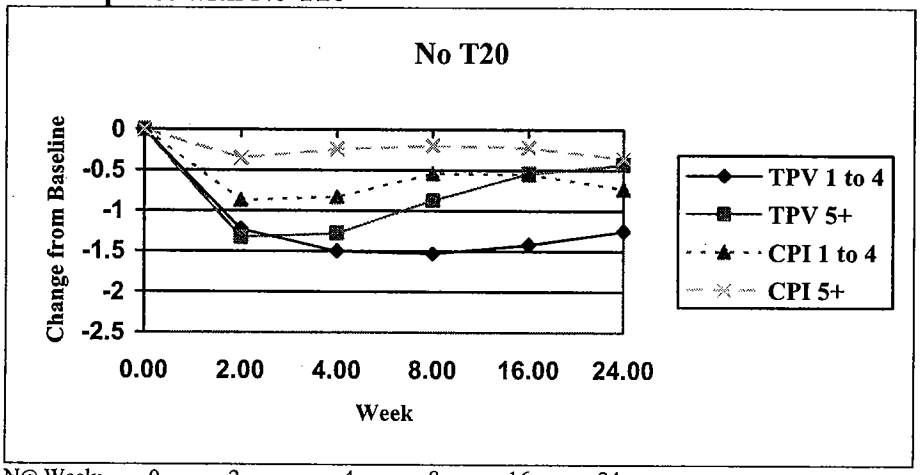
'Figure 1. Median Change from Baseline by Number of Baseline PI Mutations

1A. Overall Response



N@ Week:	0	2	4	8	16	24
TPV 1-4	398	378	384	387	365	262
TPV 5+	303	288	289	297	284	211
CPI 1-4	381	352	358	363	308	173
CPI 5+	322	304	312	311	242	110

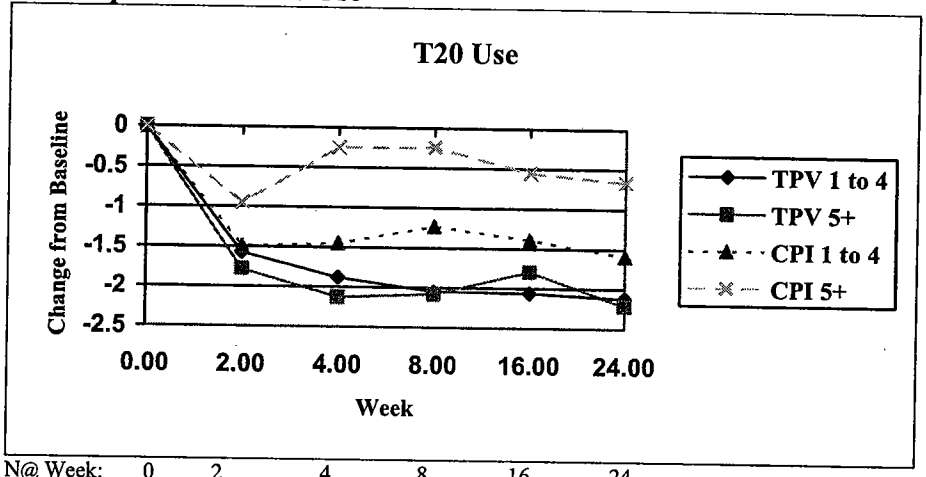
1B. Response with No T20



N@ Week:	0	2	4	8	16	24
TPV 1-4	328	311	315	318	297	199
TPV 5+	215	204	201	211	201	136

CPI 1-4	315	291	294	298	254	131
CPI 5+	258	244	252	249	194	82

1C. Response with T20 Use



N@ Week:	0	2	4	8	16	24
TPV 1-4	70	67	69	69	68	63
TPV 5+	88	84	85	86	83	75
CPI 1-4	66	61	64	65	54	42
CPI 5+	64	60	60	62	48	28

Baseline Genotypic Sensitivity Score

Analyses by baseline genotypic sensitivity score (GSS) for the optimized background regimens (OBR) were also conducted. BI included a GSS for each patient in the resistance dataset. A number was assigned for each agent in the OBR. Agents in the OBR interpreted as not resistant or possibly resistant were given a score of one and agents interpreted as resistant were given a score of zero. A score of one was always assigned if T20 was part of the OBR regardless if T20 use was new or ongoing at the start of the study. The number assigned to each agent in the OBR were added to determine a patients individual GSS such that higher the GSS, the more active drugs present in the regimen. The limitation of this analysis is how the GSS was determined. Agents interpreted as possibly resistant were given the same score (1) as agents not resistant. In previous trials susceptible agents are assigned a score of 1, possibly resistant agents are assigned a score of 0.5. As shown in Table 25, virologic response was greater as the number of active drugs in the regimen increased.

Table 25. Proportion of Responders (confirmed 1 log_{10} decrease at Week 24) by Baseline Genotypic Sensitivity Score

# Baseline FDA PI Mutations	TPV/r N=513			CPI/r N=502			LPV/r N=263		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/513)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0	15% (8/53)	15% (8/53)	None	10% (7/71)	10% (7/71)	None	14% (5/37)	14% (5/37)	None
1	43% (71/164)	33% (37/111)	64% (34/61)	15% (25/162)	15% (19/125)	16% (6/23)	16% (15/92)	19% (13/70)	9% (2/22)
2	52% (110/211)	48% (72/150)	62% (38/61)	23% (41/178)	23% (31/137)	24% (10/41)	24% (21/87)	27% (17/63)	17% (4/24)
3	61% (45/74)	55% (28/51)	74% (17/23)	41% (32/79)	37% (19/51)	46% (13/28)	44% (18/41)	40% (10/25)	50% (8/16)
4+	64% (7/11)	75% (3/4)	57% (4/11)	42% (5/12)	0% (0/5)	71% (5/6)	50% (3/6)	0% (0/2)	75% (3/4)

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

Baseline Phenotype and Virologic Outcome Analyses

TPV/r response rates were also assessed by baseline TPV phenotype. Again, we focused on the No T20 group in order to more accurately assess the effect of baseline phenotype on virologic success for TPV/r. With no T20 use, the proportion of responders was 45% if the shifts in the IC_{50} value from wild-type reference of TPV susceptibility was 3-fold or less at baseline (Table 26). The proportion of responders decreased to 21% when the TPV baseline phenotype values were >3- to 10-fold and 0% when TPV baseline phenotype values were >10-fold. The effect of baseline TPV phenotype on the DAVG24 endpoint is shown in Table 27.

Table 26. Proportion of Responders by Baseline TPV Phenotype

Baseline TPV Phenotype	All	No T20 Use	T20 Use
Overall	47% (146/313)	39% (84/218)	65% (62/95)
0-3	54% (120/223)	45% (74/163)	77% (46/60)
>3-10	29% (22/75)	21% (10/47)	43% (12/28)
>10	27% (4/15)	0% (0/8)	57% (4/7)

Table 27. Baseline TPV Phenotype and DAVG24

Baseline TPV Phenotype	All	No T20 Use	T20 Use
Overall	-1.29 (336)	-0.93 (236)	-1.97 (100)
0-3	-1.55 (237)	-1.31 (176)	-2.23 (61)
>3-10	-0.53 (79)	-0.41 (49)	-1.30 (30)
>10	-0.84 (20)	-0.24 (11)	-1.87 (9)

Virologic Outcome by Number of TPV "Key" Mutations

The applicant has determined and we have shown earlier in this review that the four positions L33, V82, I84 and L90 have an effect on response outcomes to TPV. An analysis of response by the number of these key mutations is shown in Tables 28 and 29. Response rates decrease when three or four of these key mutations are present at baseline.

Table 28. Proportion of Responders at Week 24 by Number of Substitutions at Amino Acid Positions 33, 82, 94 and 90

Number of Key Baseline PI mutations	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
0	8/16 (50)	6/14 (43)	2/2	7/17 (41)	7/16 (44)	0/1
1	74/144 (51)	57/116 (49)	17/28 (61)	40/133 (30)	29/112 (26)	11/21 (52)
2	153/336 (46)	83/231 (36)	70/105 (67)	59/335 (18)	40/251 (16)	19/84 (23)
3	6/17 (35)	2/9 (22)	4/9 (44)	4/17 (24)	0/10	4/7 (57)

Table 29. Median TPV Fold Change and DAVG by Number of Substitutions at Amino Acid Positions 33, 82, 94 and 90

Key Mutation Score	N	MEDIAN TPV FOLD CHANGE (Q25, Q75)	TPV ALL	TPV NO T20	TPV + T20
0	11	0.5 (0.3 – 2.3)	-1.55	-1.55 (9)	-2.20 (2)
1	97	1.2 (0.7, 2.05)	-1.42	-1.35 (78)	-2.26 (19)
2	217	2 (1, 4.45)	-1.22	-0.84 (143)	-2.05 (74)
3	10	7.75 (4.77, 13.92)	-0.32	-0.33 (5)	-0.31 (5)
4	1	4.7	-0.77	-0.77	None

Mutations Developing on TPV Treatment

TPV/r-resistant isolates were analyzed from treatment-experienced patients in Phase 2 Study 052 (n=32) and Phase 3 trials RESIST 1 and 2 (n =59) who experienced virologic failure. Study 052 was a study of 216 multiple PI-experienced triple ARV class-experienced subjects on 2-week functional monotherapy (three different dosages of TPV/r) followed by 30 weeks of TPV/r plus optimized ARV. The most common mutations that developed in greater than 20% of these TPV/r virologic failure isolates were L33V/I/F, V82T and I84V. Other mutations that developed in 10 to 20% of the TPV/r virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L and L89V/M/W (Table 30 and 31, Appendix L). These protease mutations that developed in clinical isolates from TPV/r-treated subjects are the same mutations that arose in serial in vitro passage experiments: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V. In RESIST 1 and 2, TPV/r resistance developed in the virologic failures (n=59) at an average of 38 weeks with a median decrease of 14-fold in TPV susceptibility (10-fold change from a baseline mean of 3.3 fold). The V82T mutation developed frequently (34%) in the failure especially when the V82A mutation was present at baseline, whereas isolates with wild-type V82 most often developed V82L. An alanine codon (GCX) at position 82 requires only one change to become threonine (ACX) whereas the wild-type valine codon (GUX) would require two changes to become threonine but only one for leucine (CUX). The possible pathways and codon changes at position 82 are shown in Table 32. The isolates that developed changes at V82 also frequently developed the I84V mutation because 20% (12/59) of the virologic failures developed both a change at V82 and an I84V mutation. The resistance profile in treatment-naive subjects has not been characterized.

Table 30. Mutations Developing on TPV Treatment in Phase II Trial 52

Mutation	Number Developing (%) (Total patients = 32)
L10I/V/F	6 (18%)
I13V	7 (22%)
L33F/I/V	3 (9%)
E34D/A/K/T/N/Q	5 (16%)
E35D/G	8 (25%)
M36V/L/I	9 (28%)
K43T/I	3 (9%)
K45I	1 (3%)
F53L	1 (3%)
I54V/A/M	4 (13%)
K70E	3 (9%)
V82T	21 (66%)
V82A/L	5 (16%)
I84V	7 (22%)
L89M/V	5 (16%)

Table 31. Mutations Developing In RESIST 1 and 2

Mutation	Resist 1 and 2 (n = 59)
L10S/I/V	17 (29%)
I13V	9 (15%)
I15V	5 (8.5%)
L23I/M	2 (3.3%)
L24M	2 (3.3%)
V32L/I/M	3 (5%)
L33F/V/I	**15 (25%)**
E34D/R/Q/H	6 (10%)
E35D/N/G	9 (15%)
M36V/I/A	9 (15%)
M46I/L	4 (7%)
I47V	7 (12%)
I54V/A/M	9 (15%)
K55R	8 (14%)
Q58E	1 (2%)
D60E	6 (10%)
I66V/L/F	3 (5%)
H69R/Q	2 (3.3%)
A71V/I/L/F	6 (10%)
V82T	**20 (34%)**
V82C	1 (2%)
V82S	2 (3.3%)
V82L	7 (12%)
V82L/C/S	10 (17%)
I84V	**15 (25%)**
N83D	2 (3.3%)
I85L	1 (2%)
N88D	1 (2%)
L89V/M/W	7 (12%)

Table 32. Codon Changes at Position 82

Amino Acid at position 82	Codon
Valine (V)	GUX
Leucine (L)	CUX
Alanine (A)	GCX
Threonine (T)	ACX
Serine (S)	UCX
Cysteine (C)	UGU/C

Possible Pathways	
V to L	
V to A to T	
V to A to T to I	
V to A to S to C	

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Conclusions:

- TPV is a protease inhibitor with antiviral activity against multi PI-resistant clinical HIV-1 isolates.

- The most common protease mutations that developed in >20% of isolates from treatment-experienced subjects who failed on TPV/r treatment were L33V/I/F, V82T and I84V. The resistance profile in treatment-naive subjects has not been characterized.

- Both the number and type of baseline PI mutations affected response rates to TPV/r in RESIST 1 and 2. Virologic response rates in TPV/r-treated subjects were reduced when isolates with amino acid substitutions at positions I13, V32, M36, I47, Q58, D60 or I84 were present at baseline. Virologic response rates in TPV/r-treated subjects were also reduced when substitutions V82S/F/I/L were present at baseline.

- Virologic responses to TPV/r at week 24 decreased when the number of baseline PI mutations was 5 or more.

- Subjects taking enfuvirtide with TPV/r were able to achieve >1.5 $\log_{10}$ reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations.

- Virologic responses to TPV/r decreased in RESIST 1 and 2 when the baseline phenotype for TPV was >3.

This NDA is approvable with respect to microbiology for the treatment of HIV-1 in highly PI-experienced patients. It is indicated for use as combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6. References

Larder BA, K Hertogs, S Bloor, C van den Eynde, W DeCian, Y Wang, W Freimuth, and G Tarpley, 2000, "Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples" AIDS 14: 1943-1948.

7. APPENDICES

Appendix A. Baseline Analyses of Study 012 and 048

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Percent Resistant of Study 012 Arms to Anti-HIV Classes

	APV/r (n=8)	IDV/r (n=2)	LPV/r (n=28)	SQV/r (n=10)	TPV/r (n=183)
PI-R	88	100	100	100	98
NRTI-R	88	100	100	100	95
NNRTI-R	63	100	81	40	84

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Percent Resistant to Protease Inhibitors by Arm in Study 012

	TPV	APV	IDV	LPV	NFV	RTV	SQV	ATV
APV/r n = 8	38	75	75	50	75	88	75	88
IDV/r n = 2	0	100	100	100	100	100	50	100
LPV/r n = 28	44	89	100	93	89	96	89	89
SQV/r n = 10	40	80	80	100	90	90	90	80
TPV/r n = 183	36	82	89	86	93	95	79	90

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Median Number of Mutations by Study Arm in 012

	NP mut	TPV mut	FDA mut	LPV mut	Key mut	PP mut	IAS mut	NRTI mut	NNRTI mut
APV/r n = 45	14	3	3	6	2	3	9	4	1
IDV/r n = 13	16	3	3	6	2	2	8	5	1
LPV/r	15	3	3	6	2	3	9	5	1

n = 187									
SQV/r n = 64	16	4	3	6	2	3	9.5	5	1
TPV/r n = 310	15	3	3	6	2	3	9	5	1

- Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

NP mut – Total number of PI mutations at baseline
TPV mut - Number of protease mutations from 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, or 84V at baseline
FDA mut - Number of protease mutations from 30N, 32I, 46I/L, 47V, 48V, 50V, 53L, 54V, 82A/F/T/S, 84V, 88D/S, or 90M at baseline
LPV mut - Number of protease mutations from 10F/I/R/V, 20M/R, 24I, 46I/L, 53L, 54V/T/L, 63P, 71T/V/L, 82F/A/T, 84V, or 90M at baseline
Key mut - Number of protease mutations at amino acid positions 33, 82, 84, or 90 at baseline
PP mut - Number of primary protease mutations at amino acid positions 30, 33, 46, 48, 50, 82, 84, or 90 at baseline
IAS mut - Number of protease mutations at amino acid positions 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, or 90 at baseline
NRTI mut - Number of RT mutations at amino acid positions 41, 44, 65, 67, 69, 70, 74, 115, 118, 184, 210, or 215 at baseline
NNRTI mut - Number of RT mutations at amino acid positions 98, 100, 103, 106, 108, 181, 188, 190, 225, 230, or 236 at the time of the isolate

Number of Mutations by Study Arm in 012

	>3 TPV mut	>3 FDA mut	≥6 LPV mut
APV/r n = 45	24%	49%	73%
IDV/r n = 13	31%	38%	54%
LPV/r n = 187	40%	45%	61%
SQV/r n = 64	53%	48%	63%
TPV/r n = 310	46%	46%	63%

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Baseline Phenotypic Analysis of Study 048

Percent Resistant of Study 048 Arms to Anti-HIV Classes

	APV/r (n=19)	IDV/r (n=1)	LPV/r (n=18)	SQV/r (n=8)	TPV/r (n=184)
PI-R	100	100	94	100	97
NRTI-R	95	100	83	100	96

NNRTI-R	95	100	67	88	84

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Percent Resistant to Protease Inhibitors by Arm in Study 048

	TPV	APV	IDV	LPV	NFV	RTV	SQV	ATV
APV/r n=19	32	83	100	89	95	95	79	78
IDV/r n=1	100	100	100	100	100	100	0	100
LPV/r n=18	22	61	71	61	89	94	67	78
SQV/r n=8	38	100	100	100	100	100	63	88
TPV/r n=184	31	84	90	87	94	95	76	87

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Median Number of Mutations by Study Arm in 048

	NP mut	TPV mut	FDA mut	LPV mut	Key mut	PP mut	IAS mut	NRTI mut	NNRTI mut
APV/r n=149	17	3	3	6	2	3	9	5	2
IDV/r n=10	19	4	4.5	7	2	4	10	6	19
LPV/r n=171	16	3	3	6	2	3	9	5	1
SQV/r n=98	16	4	3	6	1	3	9	5	1
TPV/r n=435	16	3	3	6	2	3	9	5	1

- Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

NP mut – Total number of PI mutations at baseline
TPV mut - Number of protease mutations from 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, or 84V at baseline
FDA mut - Number of protease mutations from 30N, 32I, 46I/L, 47V, 48V, 50V, 53L, 54V, 82A/F/T/S, 84V, 88D/S, or 90M at baseline
LPV mut - Number of protease mutations from 10F/I/R/V, 20M/R, 24I, 46I/L, 53L, 54V/T/L, 63P, 71T/V/L, 82F/A/T, 84V, or 90M at baseline
Key mut - Number of protease mutations amino acid positions 33, 82, 84, or 90 at baseline
PP mut - Number of primary protease mutations at amino acid positions 30, 33, 46, 48, 50, 82, 84, or 90 at baseline

IAS mut - Number of protease mutations at amino acid positions 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, or 90 at baseline
NRTI mut - Number of RT mutations at amino acid positions 41, 44, 65, 67, 69, 70, 74, 115, 118, 184, 210, or 215 at baseline
NNRTI mut - Number of RT mutations at amino acid positions 98, 100, 103, 106, 108, 181, 188, 190, 225, 230, or 236 at the time of the isolate

Number of Mutations by Study Arm in 048

	>3 TPV mut	>3 FDA mut	≥6 LPV mut
APV/r n=149	49%	39%	66%
IDV/r n=10	60%	60%	80%
LPV/r n=171	42%	49%	56%
SQV/r n=98	54%	36%	58%
TPV/r n=435	47%	44%	63%

Virco biological cutoffs for each PI were used to determine resistance: 2.5 for APV, ATV, TPV and SQV; 3 for IDV; 3.5 for RTV; 4 for NFV; 10 for LPV

Appendix B. Disposition of Censored Primary Endpoint Dataset

Censoring Rules for primary endpoint

Included the following in the analyses (did NOT censor) -

- Responder
- Virologic Failure
- D/C Before Achieve Viral Suppression
  - Subjects with HIV RNA data through week 16 and/or 24
  - Subjects with HIV RNA data only through week 8 and did not achieve at least 0.5 $\log_{10}$ decrease in HIV RNA. The 0.5 $\log_{10}$ criteria used was based on the rollover criteria for study 1182.17 where subjects were allowed to enroll if they did not achieve at least 0.5 $\log_{10}$ decline in HIV RNA)
- Other
  - Add new ARV: (also see chart below)
    - NRTI in class substitution regardless of time (see chart below)
  - TEXPL categories - No VR prior to: or Unconfirmed VR prior to:
    - Subjects with HIV RNA data only through week 8 and did not achieve at least a 0.5 log decrease in HIV RNA.
    - Subjects with HIV RNA data through week 16 and/or 24
- "Blank" - n=7 subjects from RESIST 2 with week 24 data - included the following subjects pt ID 1601 (responder), 5096, 6279, 7140 (responder), 9039, 9149, 9151

Censored:

- "BLANK" (no info in either TRESPDC and TEXPL - these subjects are from RESIST 2 who did not reach week 24 - only week 16 data available)
- Other –
  - Add new ARV: subjects were censored for the following reasons
    - Added new ARV
    - Change in PI, including change to TPV
    - Added therapeutic dose of RTV
  - TEXPL categories: No VR prior to: or Unconfirmed VR prior to
    - Subjects with no week 8-24 data (D/C between Week 0-4)
    - Subjects with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 $\log_{10}$ decrease
- D/C While Suppressed
- D/C Before Achieve Viral Suppression:
  - Subjects with no week 8-24 HIV RNA data (D/C between Week 0-4)
  - Subjects with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 $\log_{10}$ decrease

Overall number of subjects in Resistance dataset from BIPI	**1482**
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:	324

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FDA dataset and reasons for censoring/ Differences from BIPI dataset

Overall Number in BIBPI dataset	1482
Overall number of subjects in Resistance dataset from FDA	1015
FDA Censored	467
Reasons for Censoring	
D/C While Suppressed Category	61
D/C before achieve viral suppression category	
• Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 $\log_{10}$ decrease at week 8	5
• Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4)	45
Other Category	
• Added new ARV or changed PI	28
• Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 $\log_{10}$ decrease at week 8	11
"BLANK" Category (RESIST 2 subjects censored because did not have week 24 data)	317
FDA Included the following	
Responders	349
Failures	152
D/C While Suppressed	0
D/C Before achieve viral suppression	229
Other	278
"Blank" RESIST 2 subjects – included 7 in this category because they had HIV RNA data at week 24	7

PT ID	Change	Study Week	Week 8 Change	Censor
1401	IDV to FosAPV	11.4	-0.11	Y
1412	APV to SQV + ABC	8.9	-1.2	Y
3065	D/C coded wrong	.	+0.11	N
3068	Added therapeutic RTV dose	0	-1.99	Y
3110	ABC to DDI	2.3	+0.03	N
3174	TPV to APV	13.4	0.21	Y
3176	D/C coded wrong	.	+0.001	N
3186	+LPV/SQV	12.7	+0.04	Y
3306	APV to TPV	17.1	-0.81	Y
4013	APV to TPV	8	+0.01	Y
4021	TPV to LPV	13.7	-0.02	Y
4033	ABC to ZDV	7.9	-1.31	N
4055	TPV to LPV	23.6	-0.14	Y
4103	+ LPV	14	-0.72	Y
4178	APV to TPV	8.3	+0.21	Y
4221	+ TPV	8	-0.41	Y
5052	Added	0	+0.21	Y

	therapeutic RTV dose			
6131	+ IDV	18	+0.03	Y
6137	ddI to d4T	25.4	+0.10	N
6170	Added therapeutic RTV dose	1.1	-2.5	Y
6209		3	None	N
6224	+ T20	15.6	+0.07	Y
7014	+ ddI + 3TC	23	-1.3	Y
7016	+ ABC	8.9	-0.28	Y
7144	d4T to ABC	4	-2.5	N
8049	+ ddI, T20, TDF	11.6	-3.1	Y
9025	D/C coded wrong	.	-0.11	N
Study 12				
1176	+T20	5.1	0.0610701	Y
1644	D/C coded wrong	.	0.0984307	N
1738	+T20	23.3	-0.0746593	Y
1742	D/C coded wrong	.	-0.0447976	N
1775	D/C coded wrong	.	-0.2162952	N
1888	D/C coded wrong	.	-0.5782496	N
1896	D/C coded wrong	.	0.09717764	N
2014		16.3	.	Y
2067	D/C coded wrong	.	0.00075222	N
2163	IDV to LPV	3.7	-0.0345212	Y
2177	TPV to LPV x 1 month then DC LPV protocol violation	0.3	-0.6275287	Y
2238	+ ddI, TDF	8.1	0.0253965	Y
2266	D/C coded wrong	.	.	Y
2325	+EFV	20.9	-0.3885877	Y
2498	ddI to 3TC	6.4	0.26883131	N
3083	+3TC, ZDV, ABC	4.1	-2.0693666	Y

Appendix C. Disposition of Censored DAVG24 Endpoint Dataset

Censoring Rules for DAVG analyses

- The TRESPDC and TEXPL columns for identification

Included the following categories in the analyses (did NOT censor) -

- Responder
- Virologic Failure
- "BLANK" (note: no info no info in either TRESPDC and TEXPL - these subjects are from resist 2 who did not reach week 24 - only week 16 data available)
- D/C While Suppressed
- D/C Before Achieve Viral Suppression (censored subjects if week 8, 16 and 24 values were missing; otherwise these subjects were included in the analyses – 234/279 subjects in this category were included)
- Other - included the following categories
  - unconfirmed VR prior to: ...
  - No VR prior to:...
  - Add new ARV:
    - NRTI in class substitution regardless of time (see chart below)

Censored:

- D/C Before Achieve Viral Suppression (censored subjects if week 8, 16 and 24 values were missing; otherwise these subjects were included in the analyses – 45 subjects in this category were censored)
- Other – Add new ARV: subjects were censored for the following reasons
  - Added new ARV
  - Change in PI, including change to TPV
  - Added therapeutic dose of RTV

Overall number of subjects in Resistance dataset from BIPI	1482
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:	324

FDA dataset and reasons for censoring/ Differences from BIPI dataset

Overall number of subjects in BIPI dataset	1482
Overall number of subjects in FDA resistance dataset	1409
FDA censored	73
Reasons for Censoring D/C before achieve viral suppression category • Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4) Other Category • Added new ARV or changed PI	 45 28
FDA Included the following	
Overall number of subjects in Resistance dataset from FDA	1409
Responders	349

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Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression • **45** had no week 8-24 HIV RNA data • censored **28**/43 who added new ARV or changed PI; remaining 15 subjects had NRTI in class substitution	234
Other	289
"Blank:	324

PT ID	Change	Study Week	Week 8 Change	Censor
1401	IDV to FosAPV	11.4	-0.11	Y
1412	APV to SQV + ABC	8.9	-1.2	Y
3065	D/C coded wrong	.	+0.11	N
3068	Added therapeutic RTV dose	0	-1.99	Y
3110	ABC to ddI	2.3	+0.03	N
3174	TPV to APV	13.4	0.21	Y
3176	D/C coded wrong	.	+0.001	N
3186	+LPV/SQV	12.7	+0.04	Y
3306	APV to TPV	17.1	-0.81	Y
4013	APV to TPV	8	+0.01	Y
4021	TPV to LPV	13.7	-0.02	Y
4033	ABC to ZDV	7.9	-1.31	N
4055	TPV to LPV	23.6	-0.14	Y
4103	+ LPV	14	-0.72	Y
4178	APV to TPV	8.3	+0.21	Y
4221	+ TPV	8	-0.41	Y
5052	Added therapeutic RTV dose	0	+0.21	Y
6131	+ IDV	18	+0.03	Y
6137	ddI to d4T	25.4	+0.10	N
6170	Added therapeutic RTV dose	1.1	-2.5	Y
6209		3	None	N
6224	+ T20	15.6	+0.07	Y
7014	+ ddI + 3TC	23	-1.3	Y
7016	+ ABC	8.9	-0.28	Y
7144	D4t to ABC	4	-2.5	N
8049	+ ddI, T20, TDF	11.6	-3.1	Y
9025	D/C coded wrong	.	-0.11	N
Study 12				
1176	+T20	5.1	0.0610701	Y
1644	D/C coded wrong	.	0.0984307	N
1738	+T20	23.3	-0.0746593	Y
1742	D/C coded wrong	.	-0.0447976	N

1775	D/C coded wrong	.	-0.2162952	N
1888	D/C coded wrong	.	-0.5782496	N
1896	D/C coded wrong	.	0.09717764	N
2014		16.3	.	Y
2067	D/C coded wrong	.	0.00075222	N
2163	IDV to LPV	3.7	-0.0345212	Y
2177	TPV to LPV x 1 month then DC LPV protocol violation	0.3	-0.6275287	Y
2238	+ ddI, TDF	8.1	0.0253965	Y
2266	D/C coded wrong	.	.	Y
2325	+EFV	20.9	-0.3885877	Y
2498	ddI to 3TC	6.4	0.26883131	N
3083	+3TC, ZDV, ABC	4.1	-2.0693666	Y

Appendix D. Change from Baseline at Week 2, 4, 8, 16, and 24 Tables.

Mean and Median change in HIV RNA by Baseline Number of PI mutations – Week 2 – On Treatment Analyses

Number of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
< 4	-1.27 (382) -1.37	-1.22 (312) -1.27	-1.50 (70) -1.62	-0.90 (382) -0.93	-0.84 (315) -0.85	-1.28 (67 -1.42
4+	-1.27 (312) -1.42	-1.16 (224) -1.26	-1.53 (88) -1.71	-0.62 (299) -0.38	-0.54 (242) -0.34	-0.94 (57) -0.96
0-2	-1.24 (160) -1.24	-1.20 (13) -1.18	-1.43 (23) -1.64	-1.05 (155) -1.10	-0.95 (113) -0.92	-1.6 (22) -1.78
3-4	-1.29 (436) -1.44	-1.21 (334) -1.31	-1.56 (102) -1.73	-0.74 (436) -0.66	-0.66 (353) -0.56	-1.07 (83) -1.09
5+	-1.25 (89) -1.39	-1.14 (65) -1.20	-1.47 (33) -1.69	-0.52 (09) -0.21	-0.46 (71) -0.16	-0.77 (19) -0.75
0-1	-1.19 (53) -1.17	-1.10 (47) -1.09	-1.91 (6) -1.74	-1.06 (45) -1.17	-1.02 (43) -1.13	-1.78)
2-3	-1.29 (329) -1.41	-1.24 (265) -1.31	-1.48 (64) -1.67	-0.89 (337) -0.90	-0.81 (272) -0.83	-1.26 (65) -0.88
4+	-1.27 (312) -1.42	-1.16 (224) -1.26	-1.53 (88) -1.71	-0.62 (299) -0.38	-0.54 (242) -0.34	-0.94 (57) -0.96
1-2	-1.25 (155) -1.25	-1.22 (132) -1.20	-1.43 (23) -1.64	-1.06 (151) -1.12	-0.97 (130) -1.03	-1.60 (21) -1.81
3+	-1.28 (534) -1.43	-1.19 (399) -1.30	-1.54 (135) -1.72	-0.71 (526) -0.57	-0.63 (424) -0.48	-1.02 (102) -1.09

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Mean and Median change in HIV RNA by Baseline Number of PI mutations – Week 4 – On Treatment Analyses

Number of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
< 4	-1.40 (388) -1.59	-1.33 (316) -1.48	-1.68 (72) -2.06	-0.93 (382) -0.81	-0.89 (315) -0.80	-1.13 (67) -1.18
4+	-1.30 (312) -1.47	-1.19 (223) -1.34	-1.59 (89) -1.87	-0.59 (304) -0.26	-0.52 (245) -0.26	-0.88 (59) -0.26
0-2	-1.32 (161) -1.47	-1.29 (138) -1.44	-1.50 (23) -1.88	-1.11 (154) -1.20	-1.04 (131) -1.13	-1.54 (23) -1.73
3-4	-1.38 (444) -1.61	-1.29 (340) -1.51	-1.68 (102) -1.73	-0.74 (436) -0.43	-0.69 (352) -0.42	-0.95 (84) -0.50
5+	-1.27 (95) -1.33	-1.10 (61) -0.96	-1.58 (34) -1.60	-0.43 (96) -0.18	-0.38 (77) -0.14	-0.63 (19) -0.25
0-1	-1.21 (54) -1.39	-1.10 (48) -1.35	-2.08 (6) -1.99	-0.99 (44) -1.27	-0.97 (42) -0.93	-1.62 (2)
2-3	-1.43 (334) -1.66	-1.37 (268) -1.56	-1.65 (66) -2.07	-0.92 (338) -0.81	-0.88 (273) -0.80	-1.11 (65) -0.88
4+	-1.30 (312) -1.47	-1.19 (223) -1.34	-1.59 (89) -1.87	-0.59 (304) -0.26	-0.52 (245) -0.26	-0.88 (59) -0.26
1-2	-1.36 (155) -1.55	-1.34 (132) -1.50	-1.50 (23) -1.88	-1.13 (151) -1.21	-1.06 (129) -1.14	-1.53 (22) -1.65
3+	-1.36 (539) -1.56	-1.27 (401) -1.46	-1.65 (138) -1.91	-0.69 (532) -0.38	-0.64 (429) -0.37	-0.89 (103) -0.45

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Mean and Median change in HIV RNA by Baseline Number of PI mutations – Week 16 – On Treatment Analyses

Number of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
< 4	-1.42 (364) -1.43	-1.32 (292) -1.25	-1.80 (72) -2.11			
4+	-1.23 (302) -0.75	-1.03 (220) -0.57	-1.78 (82) -1.71			
0-2	-1.49 (145) -1.66	-1.43 (122) -1.42	-1.81 (23) -1.78			
3-4	-1.29 (427) -1.03	-1.13 (328) -0.71	-1.80 (99) -2.07			
5+	-1.29 (94) -0.80	-1.06 (62) -0.66	-1.74 (32) -1.54			
0-1	-1.40 (46) -1.66	-1.37 (41) -1.59	-1.66 (5) -1.76			
2-3	-1.42 (318) -1.42	-1.31 (251) -1.12	-1.82 (67) -2.16			
4+	-1.23 (302) -0.75	-1.03 (220) -0.57	-1.78 (82) -1.71			
1-2	-1.52 (141) -1.68	-1.47 (118) -1.66	-1.81 (23) -1.78			
3+	-1.29 (521) -0.96	-1.12 (390) -0.69	-1.79 (131) -1.91			

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Mean and Median change in HIV RNA by Baseline Number of PI mutations – Week 24 –On Treatment

Number of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
< 4	-1.46 (255) -1.38	-1.33 (188) -1.22	-1.84 (67) -2.13	-1.17 (178) -0.78	-1.04 (138) -0.72	-1.61 (40) -1.60
4+	-1.23 (231) -0.80	-0.97 (157) -0.40	-1.79 (74) -1.87	-0.77 (110) -0.45	-0.70 (79) -0.40	-0.97 (31) -0.65
0-2	-1.55 (102) -1.52	-1.43 (82) -1.41	-2.06 (20) -2.73	-1.27 (780) -1.10	-1.24 (63) -1.13	-1.40 (15) -0.67
3-4	-1.28 (310) -0.89	-1.10 (219) -0.59	-1.74 (91) -1.98	-0.96 (175) -0.60	-0.83 (128) -0.54	-1.32 (47) -1.09
5+	-1.35 (74) -1.03	-0.98 (44) -0.55	-1.89 (30) -2.47	-0.74 (35) -0.44	-0.60 (26) -0.32	-1.27 (9) -0.95
0-1	-1.55 (25) -1.49	-1.46 (21) -1.38	-2.04 (4) -2.15	-1.24 (20) -1.24	-1.27 (19) -1.42	-0.53 (1)
2-3	-1.45 (230) -1.32	-1.31 (167) -1.09	-1.83 (63) -2.13	-1.16 (158) -0.76	-1.00 (119) -0.67	-1.64 (39) -1.73
4+	-1.23 (231) -0.80	-0.97 (157) -0.40	-1.79 (74) -1.87	-0.77 (110) -0.45	-0.70 (79) -0.40	-0.97 (31) -0.65
1-2	-1.44 (123) -1.38	-1.46 (80) -1.45	-2.06 (20) -2.73	-1.28 (76) -1.10	-1.24 (62) -1.13	-1.46 (14) -0.67
3+	-1.29 (384) -0.92	-1.08 (263) -0.59	-1.77 (121) -2.06	-0.93 (210) -0.55	-0.78 (154) -0.50	-1.31 (56) -1.02

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

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Mean and Median change in HIV RNA by Baseline Number of PI mutations – Week 24 – LOCF

Number of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
< 4	-1.35 (310) -1.12	-1.20 (237) -0.82	-1.84 (73) -2.13	-0.74 (325) -0.36	-0.65 (259) -0.33	-1.12 (66) -0.52
4+	-1.16 (271) -0.64	-0.89 (185) -0.41	-1.73 (86) -1.87	-0.39 (252) -0.18	-0.34 (189) -0.15	-0.55 (63) -0.25
0-2	-1.39 (128) -1.29	-1.27 (104) -0.87	-1.89 (23) -2.14	-0.89 (133) -0.50	-0.85 (113) -0.48	-1.15 (20) -0.53
3-4	-1.22 (370) -0.74	-1.02 (268) -0.52	-1.76 (102) -2.06	-0.52 (365) -0.24	-0.43 (277) -0.18	-0.81 (88) -0.29
5+	-1.22 (83) -0.80	-0.88 (50) -0.49	-1.74 (33) -1.68	-0.40 (79) -0.18	-0.30 (58) -0.07	-0.66 (21) -0.55
0-1	-1.19 (39) -0.66	-1.09 (33) -0.65	-1.77 (6) -2.13	-0.74 (43) -0.48	-0.72 (41) -0.39	-1 (2)
2-3	-1.37 (271) -1.16	-1.22 (204) -0.94	-1.84 (61) -2.13	-0.74 (282) -0.34	-0.63 (218) -0.33	-1.12 (64) -0.48
4+	-1.16 (271) -0.64	-0.89 (185) -0.41	-1.73 (86) -1.87	-0.39 (252) -0.18	-0.34 (189) -0.15	-0.55 (63) -0.25
1-2	-1.44 (123) -1.38	-1.32 (99) -1.26	-1.89 (24) -2.14	-0.91 (128) -0.50	-0.87 (109) -0.49	-1.18 (19) -0.54
3+	-1.22 (453) -0.74	-0.99 (318) -0.51	-1.76 (135) -2.06	-0.50 (444) -0.22	-0.41 (335) -0.17	-0.76 (109) -0.30

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Mean and Median change in HIV RNA by Baseline Number of PI mutations–On Treatment Analyses

Number of Baseline PI mutations#	Wk	TPV/r			CPI/r		
		All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
0	2	-0.74 (5) -1.02	None		-0.63 (4) -0.38		
	4	-0.13 (6) -0.28			-0.34 (3) +0.12		
	16	-0.27 (4) -0.24					
	24	-0.0 (2) -0.09			-0.98 (2) -0.98	-1.42 (1)	-0.53 (1)
	24 - LOCF	-0.19 (5) -0.18			-0.33 (5) -0.08		
1	2	-1.24 (48) -1.21	-1.14 (42) -1.10	-1.9 (6) -1.74	-1.1 (41) -1.18		
	4	-1.35 (48) -1.42	-1.24 (42) -1.39	-2.08 (6) -1.99	-1.05 (41) -1.31		
	16	-1.51 (42) -1.72	-1.49 (37) -1.68	-1.66 (5) -1.76			
	24	-1.68 (23) -1.69	-1.60 (19) -1.49	-2.04 (4) -2.15	-1.26 (18) -1.33	-1.26 (18) -1.33	NONE
	24 - LOCF	-1.34 (34) -1.35	-1.25 (28) -1.29	-1.77 (6) -2.13	-0.79 (38) -0.52		
2	2	-1.26 (107) -1.27	-1.26 (90) -1.24	-1.25 (17) -1.64	-1.04 (110) -1.09		
	4	-1.37 (107) -1.58	-1.38 (90) -1.60	-1.29 (17) -0.72	-1.16 (110) -1.18		
	16	-1.53 (99) -1.67	-1.46 (81) -1.63	-1.85 (18) -2.16			
	24	-1.55 (77) -1.56	-1.42 (61) -1.41	-2.06 (16) -2,.99	-1.28 (58) -1.06	-1.22 (44) -1.13	-1.46 (14) -0.67
	24 – LOCF	-1.47 (88) -1.34	-1.35 (71) -1.09	-1.93 (18) -2.35	-0.97 (90) -0.50		
3	2	-1.30 (222) -1.45	-1.23 (175) -1.36	-1.56 (47) -1.74	-0.82 (227) -0.85		
	4	-1.45 (227) -1.67	-1.36 (178) -1.51	-1.77 (49) -2.11	-0.81 (228) -0.53		
	16	-1.37 (219) -1.23	-1.24 (170) -1.01	-1.80 (49) -2.16			
	24	-1.46 (153) -10.8	-1.25 (106) -0.82	-1.75 (47) -2.16	-1.09 (100) -0.68	-0.87 (75) -0.61	-1.74 (25) -1.82
	24 – LOCF	-1.32 (182) -1.08	-1.14 (133) -0.82	-1.81 (49) -2.13	-0.64 (192) -0.34		
4	2	-1.28 (214) -1.42	-1.18 (159) -1.28	-1.57 (55) -1.72	-0.65 (209) -0.50		

	4	-1.31 (217) -1.56	-1.22 (162) -1.51	-1.60 (55) -1.87	-0.66 (208) -0.35		
	16	-1.21 (208) -0.73	-1.02 (158) -0.51	-1.81 (50) -1.80			
	24	-1.18 (157) -0.65	-0.96 (113) -0.45	-1.73 (44) -1.81	-0.79 (75) -0.46	-0.77 (53) -0.46	-0.85 (22) -0.53
	24 – LOCF	-1.13 (188) -0.53	-0.90 (135) -0.41	-1.72 (53) -1.91	-0.39 (173) -0.18		
5	2	-1.23 (77) -1.38	-1.12 (52) -1.21	-1.46 (25) -1.78	-0.55 (80) -0.28		
	4	-1.28 (74) -1.33	-1.08 (49) -0.96	-1.67 (25) -1.90	-0.45 (84) -0.23		
	16	-1.34 (73) -0.84					
	24	-1.42 (58) -1.23	-1.10 (35) -0.70	-1.88 (23) -2.34	-0.71 (31) -0.44	-0.49 (23) -0.36	-1.34 (8) -1.17
	24 – LOCF	-1.28 (65) -0.90	-1.00 (40) -0.62	-1.75 (25) -1.68	-0.39 (88) -0.18		
6	2	-1.46 (16) -1.64	-1.46 /99) -1.65	-1.47 (7) -1.64	-0.34 (9) -0.06		
	4	-1.37 (16) -1.54	-1.41 (8) -1.70	-1.33 (8) -1.32	-0.37 (10) +0.11		
	16	-1.32 (16) -1.25	-1.08 (9) -0.77	-1.63 (7) -1.70			
	24	-1.30 (12) -1.04	-0.64 (7) -0.46	-2.08(6) -2.76	-1.11 (3) +0.06	-1.11 (3) +0.06	NONE
	24 – LOCF	-1.25 14) -0.82	-0.64 (7) -0.46	-1.85 (7) -2.67	-0.45 (9) +0.11		
7+	2	-0.94 (5) -0.83	-0.70 (4) -0.64	-1.89 (1)	-0.46		
	4	-0.83 (5) -0.77	-0.75 (4) -0.70	-1.17	-0.92		
	16	-0.38 (5) -0.42	-0.30 (4) -0.29	-0.72 (1)			
	24	-0.13 (3) +0.19	+0.21 (2) +0.21	 -0.8	-0.65 (1)	NONE	-0.65 (1)
	24 - LOCF	-0.14 (4) +0.01	+0.08 (3) +0.19	-0.8	-0.53		

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Appendix E. Outcome by Number of Baseline PI Mutations

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

# Baseline FDA PI Mutations#	TPV/r N=513			CPV/r N=502			LPV/r N=263		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/513)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
1	50% (7/14)	50% (7/14)	None	38% (8/21)	35% (7/20)	1/1	36% (5/14)	31% (4/13)	1/1
2	79% (23/29)	80% (20/25)	75% (3/4)	50% (11/22)	48% (10/21)	1/1	53% (9/17)	50% (8/16)	1/1
3	55% (40/73)	51% (30/59)	71% (10/14)	24% (19/79)	22% (13/60)	32% (6/19)	38% (14/37)	39% (11/28)	33% (3/9)
4	47% (77/163)	41% (48/117)	63% (29/46)	29% (41/142)	24% (26/109)	45% (15/33)	36% (24/67)	34% (16/47)	40% (8/20)
5	41% (56/136)	33% (32/97)	62% (24/39)	14% (20/144)	13% (15/114)	17% (5/30)	8% (6/78)	7% (4/58)	105 2/10)
6	39% (27/69)	21% (8/39)	63% (19/30)	14% (10/70)	10% (5/49)	24% (5/21)	10% (4/40)	7% (2/28)	17% (2/12)
7+	42% (11/26)	20% (3/15)	73% (8/11)	5% (1/22)	0% (0/15)	14% (1/7)	0% (0/9)	0% (0/6)	0% (0/3)

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

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814 **SN**: 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

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

# Baseline FDA PI Mutations#	TPV/r N=513			CPI/r N=502			LPV/r N=263		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/513)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0-3	59% (70/119)	56% (57/101)	72% (13/18)	31% (38/124)	29% (30/102)	36% (8/22)	41% (28/69)	40% (23/58)	45% (5/11)
4+	43% (171/394)	34% (91/268)	63% (80/126)	19% (72/378)	16% (46/287)	29% (26/91)	18% (34/194)	16^ (22/139)	22% (12/55)
0-4	52% (147/282)	48% (105/218)	66% (42/64)	30% (79/266)	27% (56/211)	42% (23/55)	38% (52/136)	37% (39/105)	42% (13/31)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)	8% (10/127)	7% (6/92)	11% (4/35)
0-2	65% (30/146)	64% (27/42)	75% (3/4)	42% (19/45)	40% (17/42)	67% (2/3)	44% (14/32)	40% (12/30)	100% (2/2)
3-4	50% (117/236)	44% (78/176)	65% (39/60)	27% (60/221)	23% (39/169)	40% (21/52)	37% (38/104)	36% (27/75)	38% (11/29)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)	8% (10/127)	7% (6/92)	11% (4/35)
0-3	59% (70/119)	56% (57/101)	72% (13/18)	31% (38/124)	29% (30/102)	36% (8/22)	41% (28/69)	40% (23/58)	45% (5/11)
4-5	44% (133/294)	37% (80/214)	62% (53/85)	21% (61/286)	18% (41/223)	32% (20/63)	21% (30/145)	19% (20/105)	25% (10/40)
6+	40% (38/95)	20% (11/54)	66% (27/41)	12% (11/92)	8% (5/64)	21% (6/28)	8% (4/49)	6% (2/34)	13% (2/15)

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

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DAVG 24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TPV/r N=704			CPI/r N=705			LPV/r N=344		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
1	-1.44 (30)	-1.44 (28)	-1.45 (2)	-1.08 (28)	-0.87 (27)	-1.30 (1)	-0.87 (19)	-0.86 (18)	-1.30 (1)
2	-1.43 (46)	-1.44 (41)	-1.42 (5)	-1.13 (37)	-1.07 (36)	-2.51 (1)	-1.44 (125)	-1.40 (24)	-2.51 (1)
3	-1.56 (107)	-1.48 (92)	-1.97 (15)	-0.72 (125)	-0.66 (100)	-0.86 (25)	-0.86 (51)	-0.86 (40)	-0.86 (11)
4	-1.29 (215)	-1.00 (167)	-1.93 (48)	-0.45 (191)	-0.39 (152)	-0.89 (39)	-0.45 (89)	-0.39 (67)	-0.76 (22)
5	-1.15 (181)	-0.91 (137)	-1.95 (44)	-0.24 (198)	-0.26 (164)	-0.17 (34)	-0.16 (96)	-0.20 (75)	-0.06 (21)
6	-1.07 (89)	-0.72 (57)	-1.53 (32)	-0.27 (97)	-0.24 (74)	-0.79 (23)	-0.24 (51)	-0.22 (39)	-0.57 (12)
7+	-0.94 (33)	-0.64 (21)	-2.25 (12)	-0.02 (27)	+0.00 (20)	-0.52 (7)	+0.07 (12)	+0.11 (9)	-0.60 (3)

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

DAVG24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TPV/r N=704			CPI/r N=705			LPV/r N=344		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
0-3	-1.47 (186)	-1.46 (164)	-1.75 (22)	-0.84 (192)	-0.75 (164)	-1.13 (28)	-1.07 (6)	-1.01 (83)	-1.30 (13)
4+	-1.15 (518)	-0.91 (382)	-1.90 (136)	-0.29 (513)	-0.27 (410)	-0.45 (103)	-0.24 (248)	-0.21 (190)	-0.35 (58)
0-4	-1.39 (401)	-1.33 (331)		-0.59 (383)	-0.47 (316)	-0.90 (67)	-0.77 (185)	-0.71 (150)	-0.89 (35)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)	-0.20 (159)	-0.20 (123)	-0.14 (36)
0-2	-1.42 (79)	-1.41 (72)	-1.42 (7)	-1.13 (67)	-1.00 (64)	-1.30 (3)	-1.33 (45)	-1.33 (43)	-1.90 (2)
3-4	-1.36	-1.29	-1.96	-0.53	-0.44	-0.89	-0.57	-0.45	-0.86

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	(322)	(259)	(63)	(316)	(252)	(64)	(140)	(107)	(33)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)	-0.20 (159)	-0.20 (123)	-0.14 (36)
0-3	-1.47 (186)	-1.46 (164)	-1.75 (22)	-0.84 (192)	-0.75 (164)	-1.13 (28)	-1.07 (96)	-1.01 (83)	-1.30 (13)
4-5	-1.23 (396)	-0.93 (304)	-1.93 (92)	-0.32 (389)	-0.30 (316)	-0.44 (73)	-0.27 (185)	-0.73 (150)	-0.33 (43)
6+	-0.98 (122)	-0.70 (78)	-1.79 (44)	-0.22 (124)	-0.20 (94)	-0.56 (30)	-0.21 (69)	-0.20 (48)	-0.60 (15)

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

Median change from baseline WEEK 8 in HIV RNA by Number of Baseline FDA PI Mutations

# Baseline FDA PI Mutations	TPV/r			CPI/r			LPV/r		
	All	+T20	No T20	All	+T20	No T20	All	+T20	No T20
0-1	-1.50 (36)	-2.46 (2)	-1.47 (34)	-1.17 (33)	-1.91 (2)	-1.07 (31)	-1.48 (21)	-1.48 (1)	-1.28 (20)
2	-1.86 (61)	-2.12 (1)	-1.78 (50)	-1.26 (58)	-1.83 (10)	-1.23 (48)	-1.78 (33)	-2.11 (7)	-1.68 (26)
3	-1.53 (155)	-1.53 (26)	-1.53 (129)	-0.65 (150)	-1.17 (29)	-0.5 (121)	-0.68 (68)	-1.17 (13)	-0.55 (55)
4	-1.44 (207)	-2.22 (49)	-1.20 (158)	-0.32 (200)	-0.26 (38)	-0.35 (162)	-0.28 (90)	-0.22 (21)	-0.33 (69)
5	-1.56 (173)	-2.08 (50)	-1.08 (123)	-0.21 (181)	-0.31 (36)	-0.17 (145)	-0.11 (96)	-0.27 (21)	-0.08 (75)
>5 (6-9)	-0.88 (72)	-1.73 (22)	-0.68 (50)	-0.18 (64)	-0.21 (14)	-0.18 (50)	-0.21 (28)	-0.24 (7)	-0.17 (21)
0-4	-1.57 (459)	-2.12 (87)	-1.51 (372)	-0.52 (441)	-1.05 (79)	-0.48 (362)	-0.65 (212)	-1.05 (42)	-0.61 (170)
5-9	-1.19 (245)	-1.99 (72)	-0.81 (173)	-0.20 (245)	-0.29 (50)	-0.17 (195)	-0.13 (124)	-0.26 (28)	-0.08 (96)

Median DAVG WEEK 24 in HIV RNA by Number of Baseline FDA PI Mutations

# Baseline FDA PI Mutations	TPV/r			CPI/r			LPV/r		
	All	+T20	No T20	All	+T20	No T20	All	+T20	No T20
0-1	-1.34 (41)	-1.54 (3)	-1.07 (38)	-0.81 (36)	-1.23 (2)	-0.75 (34)	-0.86 (22)	(1)	(21)
2	-1.54 (67)	-1.85 (10)	-1.53 (57)	-0.97 (66)	-1.34 (10)	-0.97 (56)	-1.35 (38)	-1.78 (7)	-1.33 (31)
3	-1.34 (159)	-1.49 (26)	-1.34 (133)	-0.52 (166)	-0.89 (29)	-0.43 (137)	-0.45 (74)	-0.87 (13)	-0.35 (61)
4	-1.23 (221)	-1.94 (50)	-0.96 (171)	-0.36 (208)	-0.41 (40)	-0.34 (168)	-0.31 (93)	-0.29 (22)	-0.31 (71)
5	-0.93 (182)	-1.68 (54)	-0.84 (128)	-0.22 (192)	-0.28 (38)	-0.20 (154)	-0.16 (99)	-0.22 (32)	-0.16 (77)
>5 (6-9)	-0.83 (75)	-1.52 (24)	-0.65 (51)	-0.23 (69)	-0.46 (15)	-0.22 (54)	-0.22 (32)	-0.61 (7)	-0.21 (25)
<=3	-1.42 (267)	-1.67 (39)	-1.39 (228)	-0.68 (268)	-1.13 (41)	-0.48 (227)	-0.84 (134)	-1.20 (21)	-0.72 (113)
>3	-1.03 (478)	-1.87 (128)	-0.87 (350)	-0.27 (469)	-0.35 (93)	-0.27 (376)	-0.22 (224)	-0.28 (51)	-0.21 (173)
0-4	-1.33 (488)	-1.87 (89)	-1.24 (399)	-0.47 (476)	-1.09 (81)	-0.44 (395)	-0.48 (227)	-0.78 (43)	-0.45 (184)
5-9	-0.92 (257)	-1.61 (78)	-0.72 (179)	-0.22 (261)	-0.28 (53)	-0.21 (208)	-0.20 (131)	-0.28 (29)	-0.18 (102)

FDA Mutations: changes at amino acid positions D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, L90

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Median DAVG WEEK 24 in HIV RNA by Number and Type of Baseline FDA PI Mutations

# Baseline FDA PI Mutations	TPV/r			CPI/r			LPV/r		
	All	+T20	No T20	All	+T20	No T20	All	+T20	No T20
0-4 + 33	-1.10 (130)	-1.95 (24)	-0.87 (106)						
≥5 + 33	-1.30 (41)	-1.87 (20)	-0.93 (21)						
0-4 with 82	-1.33 (280)	-1.91 (47)	-1.25 (233)	-0.42 (271)					
≥5 with 82	-0.95 (183)	-1.72 (55)	-0.83 (128)						
0-4 with 84	-1.13 (115)	-1.81 (36)	-0.98 (79)	-0.40 (137)	-0.73 (36)	-0.34 (101)	-0.39 (97)	-0.71 (24)	-0.35 (73)
≥5 with 84	-0.66 (79)	-1.63 (25)	-0.49 (54)	-0.14 (92)	-0.14 (21)	-0.13 (71)	-0.15 (61)	-0.15 (16)	-0.16 (45)
0-4 with 90	-1.35 (210)	-1.79 (40)	-1.32 (170)						
≥5 with 90	-0.89 (188)	-1.49 (55)	-0.61 (133)						
0-4 + 89	-1.01 (78)	-1.52 (20)	-0.98 (58)						
≥5 + 89	-0.99 (58)	-1.37 (22)	-0.92 (36)						

FDA Mutations: changes at amino acid postions D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, L90

Appendix F. Outcome by Type of Baseline PI Mutation

TPV/r arm (n = 745)

HIV RNA Change from Baseline at Week 2, 4, and 24

Overall mean = -1.35; median = -1.06 (n = 486)
+T20 mean = -1.81; median = -2.06 (n = 141)
-T20 mean = -1.16; median = -0.71 (n = 345)

Mutation	Total n	Wk24 Mean	Wk24 median	n@ wk24	Wk2 Mean	Wk2 median	n@ wk2	Wk4 Mean	Wk4 median	n@ wk4
L90L	347	-1.46	-1.25	213	-1.30	-1.44	323	-1.39	-1.57	326
L90M/I/F	398	-1.27	-0.93	273	-1.25	-1.36	371	-1.32	-1.52	374
+T20	95	-1.69	-1.91	81	-1.56	-1.69	91	-1.55	-1.82	92
-T20	303	-1.1	-0.62	192	-1.14	-1.20	280	-1.24	-1.47	282
V82V	282	-1.32	-1.0	193	-1.2	-1.36	259	-1.29	-1.55	268
V82A	341	-1.44	-1.28	215	-1.33	-1.43	319	-1.44	-1.58	321
V82T	37	-1.22	-0.90	21	-1.19	-1.22	36	-1.24	-1.32	34
V82C/I/F/M/ S/G	85	-1.17	-0.57	51	-1.27	-1.42	80	-1.28	-1.38	77
+T20	102	-1.85	-2.32	86	-1.58	-1.73	96	-1.74	-2.12	96
-T20	361	-1.17	-0.66	207	-1.24	-1.31	339	-1.29	-1.44	336
L33L	574	-1.34	-1.08	374	-1.26	-1.38	533	-1.34	-1.52	535
L33F/I/M/V/ E	171	-1.38	-1.01	112	-1.30	-1.49	161	-1.39	-1.58	165
+T20	44	-1.87	-2.06	41	-1.51	-1.69	41	-1.71	-2.05	42
-T20	127	-1.10	-0.49	71	-1.23	-1.33	120	-1.29	-1.47	123
I84I	551	-1.44	-1.32	337	-1.30	-1.38	512	-1.40	-1.58	513
I84V/A	194	-1.15	-0.7	149	-1.20	-1.42	182	-1.23	-1.39	187
+T20	61	-1.71	-1.91	52	-1.43	-1.69	59	-1.51	-1.87	61
-T20	133	-0.86	-0.49	97	-1.08	-1.22	123	-1.10	-1.24	126
L89L	609	-1.39	-1.19	395	-1.27	-1.39	567	-1.39	-1.57	571
L89A/F/M/V	136	-1.2	-0.63	91	-1.27	-1.39	127	-1.20	-1.39	129
+T20	42	-1.49	-0.69	35	-1.41	-1.71	39	-1.43	-1.83	40
-T20	94	-1.03	-0.60	56	-1.20	-1.29	88	-1.09	-1.22	89
I54I	179	-1.67	-1.79	111	-1.28	-1.28	162	-1.40	-1.58	165
I54V/M/A/L/ S	566	-1.26	-0.80	375	-1.27	-1.42	532	-1.34	-1.53	535
+T20	137	-1.78	-2.06	115	-1.54	-1.72	131	-1.65	-1.93	132
-T20	429	-1.03	-0.51	260	-1.18	-1.29	401	-1.24	-1.44	403
M36M	289	-1.52	-1.44	199	-1.28	-1.36	267	-1.40	-1.58	270
M36I/A/V/L/ N	456	-1.24	-0.65	287	-1.27	-1.43	427	-1.33	-1.54	430
+T20	115	-1.84	-2.22	99	-1.52	-1.73	108	-1.71	-2.10	112
-T20	341	-0.92	-0.44	188	-1.18	-1.28	319	-1.19	-1.38	318
E35E	409	-1.42	-1.28	278	-1.33	-1.44	382	-1.45	-1.66	382
E35D/G/N	336	-1.26	-0.80	208	-1.19	-1.28	312	-1.24	-1.39	318
+T20	73	-1.86	-2.09	60	-1.37	-1.58	68	-1.53	-1.83	71
-T20	263	-1.01	-0.57	148	-1.14	-1.21	244	-1.16	-1.32	247
E34E	674	-1.38	-1.23	440	-1.25	-1.36	626	-1.33	-1.51	629
E34D/A/V/R/ T/V/Q	71	-1.13	-0.71	46	-1.46	-1.63	68	-1.55	-1.85	71

+T20	16	-1.95	-2.00	14	-1.76	-1.88	16	-1.86	-2.28	16
-T20	55	-0.77	-0.52	32	-1.37	-1.50	52	-1.46	-1.79	55
I13I	496	-1.45	-1.31	322	-1.27	-1.40	466	-1.37	-1.55	473
I13V/A/L/M/S	249	-1.16	-0.60	164	-1.28	-1.38	228	-1.32	-1.56	227
+T20	61	-1.92	-2.41	52	-1.56	-1.76	59	-1.75	-2.15	58
-T20	188	-0.81	-0.36	112	-1.18	-1.21	169	-1.17	-1.33	169
L10L	83	-1.80	-1.96	45	-1.18	-1.19	77	-1.30	-1.41	75
L10I/F/V/Y/S	662	-1.31	-0.94	441	-1.28	-1.42	617	-1.36	-1.57	625
+T20	162	-1.77	-1.98	137	-1.52	-1.71	153	-1.62	-1.91	157
-T20	500	-1.10	-0.60	304	-1.20	-1.30	464	-1.27	-1.48	468
K45K	724	-1.36	-1.05	473						
K45R/I/A/Q/N/V	21	-1.18	-1.33	13						
+T20	2	-2.69	-2.69	2						
-T20	19	-0.90	-0.36	11						
V32V	648	-1.36	-1.16	417						
V32I/L	97	-1.31	-0.80	69						
+T20	30	-1.97	-2.67	27						
-T20	67	-0.89	-0.40	42						
D60D	598	-1.41	-1.20	383						
D60E/K/T/A	147	-1.13	-0.66	103						
+T20	34	-1.72	-1.80	29						
-T20	113	-0.89	-0.51	74						
G73G	527	-1.42	-1.25	349						
G73S/T/A/C/D/V	218	-1.19	-0.65	137						
+T20	57	-1.67	-1.91	46						
-T20	161	-0.94	-0.47	91						

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Type of PI Mutation at Baseline and Outcome

TPV/r arm (n = 745)
Week 24 HIV RNA Change from Baseline

Overall median = -1.06 (n = 486)
+T20 median = -2.06 (n = 141)
-T20 median = -0.71 (n = 345)

Comparative PI/r arm (n = 737) - APV/r = 194; IDV/r =23; LPV/r =358; SQV/r =162
Week 24 HIV RNA Change from Baseline

Overall median = -0.65
+T20 median = -0.93
-T20 median = -0.58

	TPV/r Arm			CPI/r Arm		
Mutation	**Total n**	**Wk24 median**	**n@ wk24**	**Total n**	**Wk24 median**	**n@ wk24**
L90L	347	-1.25	213	345	-0.55	141
L90M/I/F	398	-0.93	273	392	-0.71	147
+T20	95	-1.91	81	76	-1.02	38
-T20	303	-0.62	192	316	-0.67	109
V82V	282	-1.0	193	288	-1.04	114
V82A	341	-1.28	215	333	-0.51	128
V82T	37	-0.90	21	38	-0.69	17
V82C/I/F/M/S/G	85	-0.57	51	78	-0.61	29
V82 any change +T20	102	-2.32	86	78	-1.01	41
-T20	361	-0.66	207	371	-0.48	133
L33L	574	-1.08	374	580	-0.68	216
L33F/I/M/V/E	171	-1.01	112	157	-0.55	72
+T20	44	-2.06	41	34	-1.10	21
-T20	127	-0.49	71	123	-0.47	51
I84I	551	-1.32	337	508	-0.68	202
I84V/A	194	-0.70	149	229	-0.51	86
+T20	61	-1.91	52	57	-0.46	27
-T20	133	-0.49	97	172	-0.54	59
L89L	609	-1.19	395	599	-0.67	235
L89A/F/M/V	136	-0.63	91	138	-0.48	53
+T20	42	-0.69	35	31	-0.71	18
-T20	94	-0.60	56	107	-0.39	35
I54I	179	-1.79	111	164	-1.65	71
I54V/M/A/L/S	566	-0.80	375	573	-0.53	217
+T20	137	-2.06	115	111	-0.73	56
-T20	429	-0.51	260	462	-0.47	161
M36M	289	-1.44	199	281	-0.66	109
M36I/A/V/L/N	456	-0.65	287	456	-0.65	179
+T20	115	-2.22	99	87	-0.77	45
-T20	341	-0.44	188	369	-0.53	134
E35E	409	-1.28	278	420	-0.58	157
E35D/G/N	336	-0.80	208	317	-0.71	131
+T20	73	-2.09	60	61	-0.77	29
-T20	263	-0.57	148	256	-0.69	102

E34E	674	-1.23	440	660	-0.67	264
E34D/A/V/R/T/V/Q	71	-0.71	46	77	-0.25	24
+T20	16	-2.00	14	11	-0.99	6
-T20	55	-0.52	32	66	-0.193	18
I13I	496	-1.31	322	483	-0.73	184
I13V/A/L/M/S	249	-0.60	164	254	-0.49	104
+T20	61	-2.41	52	54	-1.09	29
-T20	188	-0.36	112	200	-0.39	75
L10L	83	-1.96	45	73	-1.28	38
L10I/F/V/Y/S	662	-0.94	441	664	-0.63	250
+T20	162	-1.98	137	125	-0.85	66
-T20	500	-0.60	304	539	-0.54	184
K45K	724	-1.05	473	716	-0.65	285
K45R/I/A/Q/N/V	21	-1.33	13	21	-0.92	3
+T20	2	-2.69	2	0		
-T20	19	-0.36	11	21	-0.92	3
V32V	648	-1.16	417	658	-0.66	259
V32I/L	97	-0.80	69	79	-0.65	29
+T20	30	-2.67	27	17	-0.67	10
-T20	67	-0.40	42	62	-0.55	19
D60D	598	-1.20	383	624	-0.68	254
D60E/K/T/A	147	-0.66	103	113	-0.51	34
+T20	34	-1.80	29	21	-0.65	9
-T20	113	-0.51	74	92	-0.40	25
G73G	527	-1.25	349	519	-0.69	212
G73S/T/A/C/D/V	218	-0.65	137	218	-0.44	76
+T20	57	-1.91	46	53	-0.67	23
-T20	161	-0.47	91	165	-0.40	53
K20K	282	-1.46	182	295	-0.73	124
K20I/M/R/T/S/V	463	-0.70	304	442	-0.56	164
+T20	111	-1.91	93	84	-0.67	43
-T20	352	-0.49	211	358	-0.52	121
K43K	626	-1.19	408	636	-0.67	252
K43T/R/Q/I	119	-0.64	78	101	-0.46	36
+T20	30	-2.06	23	24	-0.63	10
-T20	89	-0.49	55	77	-0.26	26
M46M	207	-1.25	127	220	-1.07	98
M46L/I/V	538	-1.04	359	517	-0.53	190
+T20	136	-1.98	115	94	-0.71	46
-T20	402	-0.66	244	423	-0.48	144
I47I	626	-1.32	401	623	-0.67	250
I47V/A	119	-0.49	85	114	-0.40	38
+T20	35	-1.95	30	29	-0.63	12
-T20	84	-0.29	55	94	-0.32	26
Q58Q	646	-1.21	417	607	-0.65	240
Q58E	99	-0.56	69	130	-0.63	48
+T20	24	-1.41	22	16	-0.50	9
-T20	75	-0.31	47	114	-0.71	39
H69H	640	-1.03	416	627	-0.68	251
H69K/Q/R/Y/V/N	105	-1.25	70	110	-0.29	37

+T20	24	-2.83	17	17	-1.19	8
-T20	81	-1.01	53	93	-0.18	29
T74	632	-1.00	410	612	-0.63	240
T74S/A/P/K/E	113	-1.52	76	125	-0.86	48
+T20	30	-2.32	25	23	-1.63	12
-T20	83	-1.19	51	102	-0.75	36
N83N	726	-1.05	475	718	-0.66	284
N83D/N/S	19	-1.08	11	19	-0.24	4
+T20	6	-2.06	5	6	-0.001	1
-T20	13	-0.55	6	13	-0.47	3

Comparative PI/r arm (n = 737) - APV/r = 194; IDV/r = 23; LPV/r = 358; SQV/r = 162

HIV RNA Change from Baseline at Week 2, 4, and 24

Overall mean = -1.02 ; median = -0.65
+T20 mean = -1.33 ; median = -0.93
-T20 mean = -0.92 ; median = -0.58

Mutation	Total n	Wk24 Mean	Wk24 median	n@ wk24	Wk2 Mean	Wk2 median	n@ wk2	Wk4 Mean	Wk4 median	n@ wk4
L90L	345	-0.96	-0.55	141	-0.81	-0.80	316	-0.80	-0.51	322
L90M/I/F	392	-1.07	-0.71	147	-0.76	-0.65	365	-0.76	-0.43	364
+T20	76	-1.50	-1.02	38	-1.08	-1.30	71	-0.94	-0.42	71
-T20	316	-0.94	-0.67	109	-0.68	-0.57	294	-0.72	-0.43	293
V82V	288	-1.25	-1.04	114	-0.83	-0.67	267	-0.87	-0.53	263
V82A	333	-0.82	-0.51	128	-0.73	-0.68	306	-0.72	-0.40	310
V82T	38	-1.08	-0.69	17	-0.94	-1.03	35	-0.86	-0.70	38
V82C/I/F/M/S/G	78	-0.91	-0.61	29	-0.78	-0.68	73	-0.70	-0.35	75
+T20	78	-1.33	-1.01	41	-1.11	-1.22	69	-1.06	-0.99	73
-T20	371	-0.72	-0.48	133	-0.69	-0.57	345	-0.66	-0.38	350
L33L	580	-1.05	-0.68	216	-0.78	-0.68	540	-0.79	-0.49	543
L33F/I/M/V/E	157	-0.91	-0.55	72	-0.80	-0.75	141	-0.75	-0.42	143
+T20	34	-1.24	-1.10	21	-1.14	-1.27	31	-0.99	-0.90	34
-T20	123	-0.77	-0.47	51	-0.71	-0.66	110	-0.67	-0.39	109
I84I	508	-1.02	-0.68	202	-0.83	-0.83	468	-0.84	-0.51	469
I84V/A/C	229	-1.02	-0.51	86	-0.68	-0.36	213	-0.66	-0.35	217
+T20	57	-1.09	-0.46	27	-1.01	-1.03	54	-0.80	-0.34	54
-T20	172	-0.99	-0.54	59	-0.56	-0.32	159	-0.61	-0.35	163
L89L	599	-1.07	-0.67	235	-0.78	-0.68	555	-0.80	-0.49	564
L89A/F/M/V	138	-0.78	-0.48	53	-0.79	-0.74	126	-0.70	-0.41	122
+T20	31	-0.99	-0.71	18	-1.00	-1.10	28	-0.77	-0.25	29
-T20	107	-0.68	-0.39	35	-0.73	-0.64	98	-0.68	-0.41	93
I54I	164	-1.53	-1.65	71	-1.10	-1.23	150	-1.20	-1.31	150
I54V/M/A/L/S/T/C	573	-0.85	-0.53	217	-0.69	-0.56	531	-0.67	-0.37	536
+T20	111	-1.18	-0.73	56	-1.04	-1.09	103	-0.90	-0.46	104
-T20	462	-0.73	-0.47	161	-0.61	-0.45	428	-0.61	-0.35	432
M36M	281	-1.10	-0.66	109	-0.79	-0.75	256	-0.86	-0.57	260
M36I/A/V/L/F/M	456	-0.97	-0.65	179	-0.78	-0.67	425	-0.73	-0.42	426
+T20	87	-1.31	-0.77	45	-1.05	-1.09	81	-0.91	-0.42	79
-T20	369	-0.86	-0.53	134	-0.72	-0.60	344	-0.69	-0.42	347
E35E	420	-0.96	-0.58	157	-0.78	-0.70	384	-0.79	-0.50	392
E35D/G/N/Q/K/S	317	-1.08	-0.71	131	-0.79	-0.68	297	-0.78	-0.42	294
+T20	61	-1.36	-0.77	29	-1.10	-1.09	57	-0.86	-0.31	54
-T20	256	-1.00	-0.69	102	-0.72	-0.57	240	-0.76	-0.42	240
E34E	660	-1.04	-0.67	264	-0.82	-0.76	606	-0.83	-0.50	614
E34D/A/V/T/K/Q	77	-0.80	-0.25	24	-0.50	-0.23	75	-0.41	-0.12	72
+T20	11	-1.21	-0.99	6	-0.83	-1.02	11	-0.60	-0.04	11

-T20	66	-0.66	-0.193	18	-0.45	-0.17	64	-0.38	-0.12	61
I13I	483	-1.10	-0.73	184	-0.78	-0.68	450	-0.81	-0.52	452
I13V/A/L/M/S/N	254	-0.87	-0.49	104	-0.80	-0.74	231	-0.72	-0.39	234
+T20	54	-1.25	-1.09	29	-1.09	-1.27	49	-0.88	-0.44	50
-T20	200	-0.72	-0.39	75	-0.72	-0.62	182	-0.68	-0.38	184
L10L	73	-1.20	-1.28	38	-1.16	-1.22	64	-1.21	-1.37	66
L10I/F/V/Y/S/R	664	-0.99	-0.63	250	-0.74	-0.64	617	-0.74	-0.42	620
+T20	125	-1.29	-0.85	66	-1.10	-1.26	115	-1.00	-0.53	118
-T20	539	-0.88	-0.54	184	-0.66	-0.52	502	-0.67	-0.41	502
K45K	716	-1.02	-0.65	285						
K45I/R/T/V	21	-1.11	-0.92	3						
+T20	0									
-T20	21	-1.11	-0.92	3						
V32V	658	-1.03	-0.66	259						
V32I/A/L/F	79	-0.91	-0.65	29						
+T20	17	-0.69	-0.67	10						
-T20	62	-1.03	-0.55	19						
D60D	624	-1.06	-0.68	254						
D60E/K/N/A	113	-0.72	-0.51	34						
+T20	21	-1.11	-0.65	9						
-T20	92	-0.59	-0.40	25						
G73G	519	-1.08	-0.69	212						
G73S/T/A/C/D/I/V	218	-0.84	-0.44	76						
+T20	53	-1.08	-0.67	23						
-T20	165	-0.74	-0.40	53						

DAVG24 by Type of PI mutations

Number and Type of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
	-1.31 (704)	-1.03 (546)	-1.89 (158)	-0.37 (705)	-0.34 (574)	-0.61 (131)
I13I	-1.39 (472)	-1.3 (373)	-1.87 (99)	-0.41 (463)	-0.36 (384)	-0.74 (79)
I13V/A	-1.01 (232)	-0.91 (173)	-2.13 (59)	-0.33 (242)	-0.30 (190)	-0.49 (52)
K20K	-1.46 (266)	-1.39 (213)	-1.98 (53)	-0.58 (283)	-0.47 (234)	-1.13 (49)
K20R/I/M/V/T/L	-1.07 (438)	-0.93 (333)	-1.79 (105)	-0.28 (422)	-0.27 (340)	-0.38 (82)
D30D	-1.3 (681)	-1.02 (527)	-1.89 (154)	-0.35 (681)	-0.32 (553)	-0.62 (128)
D30N	-1.48 (23)	-1.48 (19)	-1.82 (4)	-1.61 (24)	-1.73 (21)	-0.26 (3)
V32V	-1.34 (612)	-1.17 (482)	-1.87 (130)	-0.39 (630)	-0.34 (516)	-0.62 (114)
V32I/L/A	-0.88 (92)	-0.64 (64)	-2.11 (28)	-0.31 (75)	-0.28 (58)	-0.61 (17)
L33L	-1.32 (544)	-1.09 (429)	-1.83 (115)	-0.39 (556)	-0.36 (459)	-0.58 (97)
L33I/M/V/F	-1.28 (160)	-0.92 (117)	-1.98 (43)	-0.32 (149)	-0.27 (115)	-0.77 (34)
E34E	-1.30 (637)	-1.03 (494)	-1.87 (143)	-0.4 (632)	-0.36 (512)	-0.66 (120)
E34Q/R/T/V/N	-1.39 (67)	-1.14 (52)	-2.53 (15)	-0.15 (73)	-0.11 (62)	-0.28 (11)

E35E	-1.45 (385)	-1.37 (295)	-1.91 (90)	-0.39 (400)	-0.32 (329)	-0.86 (71)
E35D/N/G	-0.99 (319)	-0.85 (251)	-1.89 (68)	-0.36 (305)	-0.34 (245)	-0.38 (60)
M36M	-1.48 (273)	-1.46 (225)	-1.81 (48)	-0.47 (268)	-0.42 (221)	-0.87 (47)
M36I/V/L/A	-1.03 (431)	-0.91 (321)	-1.90 (110)	-0.33 (437)	-0.32 (353)	-0.45 (84)
M46M	-1.36 (199)	-1.30 (169)	-2.13 (30)	-0.75 (210)	-0.48 (171)	-1.15 (39)
M46I/L/V	-1.29 (505)	-0.99 (377)	-1.87 (128)	-0.32 (495)	-0.30 (403)	-0.46 (92)
I47I	-1.39 (590)	-1.25 (465)	-1.91 (125)	-0.45 (596)	-0.40 (485)	-0.64 (111)
I47V/A	-0.67 (114)	-0.51 (81)	-1.41 (33)	-0.21 (109)	-0.20 (89)	-0.57 (20)
G48G	-1.23 (600)	-0.99 (468)	-1.77 (132)	-0.39 (584)	-0.37 (481)	-0.53 (103)
G48V	-1.80 (104)	-1.58 (78)	-2.44 (26)	-0.29 (121)	-0.22 (93)	-1.24 (28)
I50I	-1.26 (661)	-1.0 (516)	-1.87 (145)	-0.38 (648)	-0.34 (529)	-0.58 (119)
I50V/L	-1.63 (43)	-1.61 (30)	-2.15 (13)	-0.29 (57)	-0.27 (45)	-1.16 (12)
F53F	-1.28 (590)	-1.00 (462)	-1.89 (128)	-0.40 (616)	-0.35 (505)	-0.64 (111)
F53V/L/I/W	-1.4 (114)	-1.22 (84)	-1.89 (30)	-0.29 (89)	-0.25 (69)	-0.57 (20)
I54I	-1.53 (169)	-1.45 (140)	-1.97 (29)	-1.0 (159)	-0.92 (136)	-1.41 (23)
I54V/M/L/A /S/T	-1.15 (535)	-0.93 (406)	-1.87 (129)	-0.3 (546)	-0.27 (438)	-0.46 (108)
Q58Q	-1.36 (606)	-1.17 (472)	-1.92 (134)	-0.43 (582)	-0.37 (466)	-0.7 (116)
Q58E	-0.93 (98)	-0.78 (74)	-1.54 (24)	-0.27 (123)	-0.28 (108)	-0.24 (15)
D60D	-1.34 (562)	-1.15 (437)	-1.91 (125)	-0.39 (599)	-0.35 (487)	-0.66 (112)
D60E	-0.90 (142)	-0.71 (109)	-1.87 (33)	-0.29 (106)	-0.27 (87)	-0.60 (19)
G73G	-1.36 (500)	-1.21 (396)	-1.97 (104)	-0.45 (501)	-0.37 (420)	-0.87 (81)
G73S/A/T/C /V	-1.03 (204)	-0.89 (150)	-1.58 (54)	-0.26 (204)	-0.25 (154)	-0.36 (50)
V82V	-1.26 (269)	-1.04 (206)	-1.75 (63)	-0.43 (271)	-0.4 (217)	-0.64 (54)
V82A	-1.37 (318)	-1.22 (255)	-1.98 (63)	-0.34 (327)	-0.32 (273)	-0.46 (54)
V82T	-1.08 (37)	-1.00 (22)	-1.4 (15)	-0.51 (37)	-0.38 (30)	-1.29 (7)
V82C/I/F/M/ S/G	-1.09 (82)	-0.80 (64)	-2.27 (18)	-0.20 (75)	-0.15 (58)	-0.56 (17)
N83N	-1.32 (686)	-1.03 (533)	-1.87 (153)	-0.38 (687)	-0.34 (561)	-0.66 (126)
N83D/S	-1.23 (18)	-0.25 (13)	-1.91 (5)	-0.15 (18)	-0.14 (13)	-0.15 (5)
I84I	-1.39 (517)	-1.28 (418)	-1.96 (99)	-0.45 (488)	-0.39 (412)	-0.85 (76)
I84V/A/C	-0.96 (187)	-0.75 (128)	-1.83 (59)	-0.29 (217)	-0.25 (162)	-0.39 (55)
N88N	-1.32 (683)	-1.03 (527)	-1.90 (156)	-0.35 (674)	-0.32 (547)	-0.61 (127)
N88D/S/T/G	-0.87 (21)	-0.87 (19)	-0.79 (2)	-1.25 (31)	-1.25 (27)	-1.0 (4)
L89L	-1.34 (572)	-1.10 (454)	-1.90 (118)	-0.41 (573)	-0.35 (473)	-0.80 (100)
L89V/M	-1.03 (132)	-0.96 (92)	-1.57 (40)	-0.30 (132)	-0.26 (101)	-0.38 (31)
L90L	-1.34 (327)	-1.13 (258)	-1.91 (69)	-0.41 (333)	-0.35 (275)	-0.76 (58)
L90M	-1.23 (377)	-1.00 (288)	-1.75 (89)	-0.35 (372)	-0.32 (299)	-0.48 (73)

Type of PI Mutation at Baseline and Primary Endpoint Outcome (n=1015)

Primary Endpoint - Proportion of Responders with confirmed 1 log_{10} decrease at Week 24

	TPV/r Arm (n=513)			CPI/r (n=502)		
Mutation	**All**	**+T20**	**-T20**	**All**	**+T20**	**-T20**
	47% (240/513)	65% (93/144)	40% (147/369)	22% (109/502)	30% (34/113)	19% (75/389)
L90L	49% (113/231)	68% 43/63	42% 70/168	22% (50/230)	30% (14/47)	20% (36/183)
L90M/I/F	45% 127/282	62% 50/81	38% 77/201	22% (59/272)	30% (20/66)	19% (39/206)
V82V	45% 91/202	62% (34/55)	39% (57/147)	28% (55/200)	28% (13/47)	27% (42/153)
V82 any change	48% (149/311)	66% (59/89)	41% (90/222)	18% (54/202)	32% (21/66)	14% (33/236)
V82A	50% (116/230)	67% (40/60)	45% (76/170)	17% (38/222)	33% (15/46)	13% (23/176)
V82T	44% (12/27)	42% (5/12)	47% (7/15)	19% (5/27)	43% (3/7)	10% (2/20)
V82C/I/F/M/S/G	39% (22/56)	82% (14/17)	21% (8/39)	20% (11/56)	21% (3/14)	19% (8/42)
L33L	47% (183/394)	64% (65/101)	40% (118/393)	22% (86/385)	28% (23/82)	21% (63/303)
L33F/I/M/V/E	48% (57/119)	65% (28/43)	38% (29/76)	20% (23/117)	35% (11/31)	14% (12/86)
I84I	49% (176/358)	66% (61/92)	43% (115/266)	23% (77/340)	38% (25/66)	19% (52/274)
I84V/A	41% (64/155)	62% (32/52)	31% (32/103)	20% (32/162)	19% (9/47)	20% (23/115)
L89L	48% (201/419)	69% (75/108)	41% (126/311)	23% (92/405)	31% (26/83)	20% (66/322)
L89A/F/M/V	41% (39/94)	50% (18/36)	36% (21/58)	18% (17/97)	27% (8/30)	13% (9/67)
I54I	58% (67/115)	68% (17/25)	56% (50/90)	40% (43/108)	48% (10/21)	38% (33/87)
I54V/M/A/L/S	43% (173/398)	64% (76/119)	35% (97/279)	17% (66/394)	26% (24/92)	14% (42/302)
M36M	57% (116/203)	69% (29/42)	54% (87/161)	24% (44/184)	35% (14/40)	21% (30/144)
M36I/A/V/L/N	40% (124/310)	63% (64/102)	29% (60/208)	20% (65/318)	27% (20/73)	18% (45/345)
E35E	51% (144/283)	68% (54/80)	44% (90/203)	20% (56/281)	33% (21/63)	16% (35/218)
E35D/G/N	42% (96/230)	61% (39/64)	34% (57/166)	24% (53/221)	26% (13/50)	23% (40/171)
E34E	48% (221/465)	65% (84/130)	41% (137/335)	23% (102/451)	30% (31/103)	20% (71/348)
E34D/V/R/T/Y/Q/K	40% (19/48)	64% (9/14)	29% (10/34)	14% (7/51)	30% (3/10)	10% (4/41)

I13I	50% (171/340)	62% (56/90)	46% (115/250)	23% (74/324)	28% (19/68)	21% (55/256)
I13V/A/L/S	40% (69/171)	69% (37/54)	27% (32/119)	20% (35/178)	33% (15/45)	15% (20/133)
L10L	53% (26/49)	100% (4/4)	49% (22/45)	36% (20/55)	44% (4/9)	35% (16/46)
L10I/F/V/Y/S/R/M	46% (214/464)	64% (89/140)	39% (125/324)	20% (89/447)	29% (30/104)	17% (59/343)
K45K	47% (234/500)	64% (91/142)	40% (143/358)	22% (108/493)	30% (34/113)	19% (74/380)
K45R/I/A/Q/N/V	46% (6/13)	100% (2/2)	36% (4/11)	11% (1/9)	0	11% (1/9)
V32V	48% (211/439)	66% (76/116)	42% (135/323)	23% (100/443)	32% (31/97)	20% (69/346)
V32I/L	39% (29/74)	61% (17/28)	26% (12/46)	15% (9/59)	19% (3/16)	14% (6/43)
D60D	49% (197/403)	65% (74/113)	42% (123/290)	23% (101/436)	32% (32/100)	21% (69/336)
D60E/K/A/N	39% (43/110)	61% (19/31)	30% (24/79)	12% (8/66)	15% (2/13)	11% (6/53)
G73G	49% (178/366)	68% (66/97)	42% (112/269)	25% (86/342)	37% (26/70)	22% (60/272)
G73S/T/A/C/D/E	42% (62/147)	57% (27/47)	35% (35/100)	14% (23/160)	19% (8/43)	13% (15/117)
K20K	55% (106/191)	73% (35/48)	50% (71/143)	27% (54/201)	42% (18/43)	23% (36/158)
K20I/M/R/T/S/V/L/A	42% (134/322)	60% (58/96)	34% (76/226)	18% (55/301)	23% (16/70)	17% (39/231)
K43K	48% (206/431)	66% (79/119)	41% (127/312)	23% (98/433)	34% (32/93)	19% (66/340)
K43T/R/Q/I	41% (34/82)	56% (14/25)	35% (20/57)	16% (11/69)	10% (2/20)	18% (9/49)
M46M	46% (63/136)	63% (17/27)	42% (46/109)	34% (49/144)	45% (14/31)	31% (35/113)
M46L/I/V	47% (177/377)	65% (76/117)	39% (101/260)	17% (60/358)	24% (20/82)	14% (40/276)
I47I	50% (211/420)	66% (75/113)	44% (136/307)	24% (100/420)	33% (31/94)	21% (69/326)
I47V/A	31% (29/93)	58% (18/31)	18% (11/62)	11% (9/82)	16% (3/19)	10% (6/63)
Q58Q	48% (212/439)	65% (79/122)	42% (133/317)	22% (92/409)	31% (31/99)	20% (61/310)
Q58E	38% (28/74)	64% (14/22)	27% (14/52)	18% (17/93)	21% (3/14)	18% (14/79)
H69H	46% (202/442)	63% (80/127)	39% (122/315)	23% (100/435)	30% (30/99)	21% (70/336)
H69K/Q/R/Y/V/N	54% (38/71)	76% (13/17)	46% (25/54)	13% (9/67)	29% (4/14)	9% (5/53)
T74T	46% (198/435)	64% (75/118)	39% (123/317)	21% (88/421)	29% (27/93)	19% (61/328)

T74S/A/P/K/E/R	54% (42/78)	69% (18/26)	46% (24/52)	26% (21/81)	35% (7/20)	23% (14/61)
N83N	47% (234/500)	64% (89/139)	40% (145/361)	22% (107/487)	31% (34/108)	19% (73/379)
N83D/N/S	46% (6/13)	80% (4/5)	25% (2/8)	13% (2/15)	0% (0/5)	20% (2/10)
K45K	47% (235/500)	64% (91/142)	40% (144/368			
K45R/A/I/V/N	46% (6/13)	100% (2/2)	36% (4/11)			
N88N	47% (238/503)	65% (93/142)	40% (145/361)	21% (102/487)	30% (33/110)	18% (69/377)
N88D/S/T/G	30% (3/10)	0% (0/2)	38% (3/8)	53% (8/15)	33% (1/3)	58% (7/12)
G48G	44% (191/433)	62% (74/120)	37% (117/313)			
G48V	63% (50/80)	79% (19/24)	55% (31/56)	22% (20/90)	42% (10/24)	15% (10/66)

Primary Endpoint - Proportion of Responders with confirmed 1 log_{10} decrease at Week 24

	TPV/r Arm (n=513)			LPV/r Arm (n=263)		
Mutation	**All**	**+T20**	**-T20**	**All**	**+T20**	**-T20**
	47% (240/513)	65% (93/144)	40% (147/369)	24% (62/263)	26% (17/66)	23% (45/197)
L90L	49% (113/231)	68% 43/63	42% 70/168	25% (26/105)	23% (5/22)	25% (21/83)
L90M/I/F	45% 127/282	62% 50/81	38% 77/201	23% (36/158)	27% (12/44)	21% (24/114)
V82V	45% 91/202	62% (34/55)	39% (57/147)	30% (43/141)	30% (11/37)	31% (32/104)
V82 any change	48% (149/311)	66% (59/89)	41% (90/222)	16% (19/122)	21% (6/29)	14% (13/93)
V82A	50% (116/230)	67% (40/60)	45% (76/170)	16% (15/95)	20% (4/20)	15% (11/75)
V82T	44% (12/27)	42% (5/12)	47% (7/15)	9% (1/11)	25% (1/4)	0% (0/7)
V82C/I/F/M/S/G	39% (22/56)	82% (14/17)	21% (8/39)	18% (3/17)	17% (1/6)	18% (2/11)
L33L	47% (183/394)	64% (65/101)	40% (118/393)	25% (54/215)	26% (14/53)	25% (40/162)
L33F/I/M/V/E	48% (57/119)	65% (28/43)	38% (29/76)	17% (8/48)	23% (3/13)	14% (5/35)
I84I	49% (176/358)	66% (61/92)	43% (115/266)	26% (37/145)	37% (11/30)	23% (26/115)
I84V/A	41% (64/155)	62% (32/52)	31% (32/103)	21% (25/118)	17% (6/36)	23% (19/82)
L89L	48%	69%	41%	25%	28%	24%

	(201/419)	(75/108)	(126/311)	(53/215)	(14/50)	(39/165)
L89A/F/M/V/I	41% (39/94)	50% (18/36)	36% (21/58)	19% (9/48)	19% (3/16)	19% (6/32)
I54I	58% (67/115)	68% (17/25)	56% (50/90)	44% (31/71)	50% (7/14)	42% (24/57)
I54V/M/A/L/S	43% (173/398)	64% (76/119)	35% (97/279)	16% (31/192)	19% (10/52)	15% (21/140)
M36M	57% (116/203)	69% (29/42)	54% (87/161)	28% (30/107)	38% (8/21)	26% (22/86)
M36I/A/V/L/N	40% (124/310)	63% (64/102)	29% (60/208)	21% (32/156)	20% (9/45)	21% (23/111)
E35E	51% (144/283)	68% (54/80)	44% (90/203)	23% (37/160)	31% (12/39)	21% (25/121)
E35D/G/N	42% (96/230)	61% (39/64)	34% (57/166)	24% (25/103)	19% (5/27)	26% (20/76)
E34E	48% (221/465)	65% (84/130)	41% (137/335)	25% (59/238)	25% (15/59)	25% (44/179)
E34D/V/R/T/Y/Q/K	40% (19/48)	64% (9/14)	29% (10/34)	12% (3/25)	29% (2/7)	6% (1/18)
I13I	50% (171/340)	62% (56/90)	46% (115/250)	25% (39/157)	24% (8/34)	25% (31/123)
I13V/A/L/M/S	40% (69/171)	69% (37/54)	27% (32/119)	22% (23/106)	28% (9/32)	19% (14/74)

	TPV Arm (n=513)			LPV/r Arm (n=263)		
Mutation	**All**	**+T20**	**-T20**	**All**	**+T20**	**-T20**
L10L	53% (26/49)	100% (4/4)	49% (22/45)	42% (14/33)	60% (3/5)	39% (11/28)
L10I/F/V/Y/S/R/M	46% (214/464)	64% (89/140)	39% (125/324)	21% (48/230)	23% (14/61)	20% (34/169)
K45K	47% (234/500)	64% (91/142)	40% (143/358)	24% (61/259)	26% (17/66)	23% (44/193)
K45I/R/A/Q/N/V	46% (6/13)	100% (2/2)	36% (4/11)	25% (1/4)	0% (0/0)	25% (1/4)
V32V	48% (211/439)	66% (76/116)	42% (135/323)	25% (58/234)	29% (17/58)	23% (41/176)
V32I/L	39% (29/74)	61% (17/28)	26% (12/46)	14% (4/29)	0% (0/8)	19% (4/21)
D60D	49% (197/403)	65% (74/113)	42% (123/290)	25% (58/235)	27% (16/59)	24% (42/176)
D60E/K/A	39% (43/110)	61% (19/31)	30% (24/79)	14% (4/28)	14% (1/7)	14% (3/21)
G73G	49% (178/366)	68% (66/97)	42% (112/269)	27% (47/172)	33% (13/40)	26% (34/132)
G73S/T/A/C/D/E	42% (62/147)	57% (27/47)	35% (35/100)	16% (15/91)	15% (4/26)	17% (11/65)
K20K	55% (106/191)	73% (35/48)	50% (71/143)	33% (34/104)	50% (10/20)	29% (24/84)
K20I/M/R/T/S/V/L	42% (134/322)	60% (58/96)	34% (76/226)	18% (28/159)	15% (7/46)	19% (21/113)
K43K	48%	66%	41%	24%	30%	23%

	(206/431)	(79/119)	(127/312)	(56/229)	(16/53)	(40/176)
K43T/R/Q/I	41% (34/82)	56% (14/25)	35% (20/57)	18% (6/34)	8% (1/13)	24% (5/21)
M46M	46% (63/136)	63% (17/27)	42% (46/109)	34% (26/76)	45% (9/20)	30% (17/56)
M46L/I/V	47% (177/377)	65% (76/117)	39% (101/260)	19% (36/187)	17% (8/46)	20% (28/141)
I47I	50% (211/420)	66% (75/113)	44% (136/307)	27% (61/222)	30% (17/57)	27% (44/165)
I47V/A	31% (29/93)	58% (18/31)	18% (11/62)	2% (1/41)	0% (0/9)	3% (1/32)
Q58Q	48% (212/439)	65% (79/122)	42% (133/317)	24% (51/213)	28% (16/58)	23% (35/155)
Q58E	38% (28/74)	64% (14/22)	27% (14/52)	22% (11/50)	13% (1/8)	24% (10/42)
H69H	46% (202/442)	63% (80/127)	39% (122/315)	24% (56/231)	25% (15/59)	24% (41/172)
H69K/Q/R/Y/V/N	54% (38/71)	76% (13/17)	46% (25/54)	19% (6/32)	29% (2/7)	16% (4/25)
T74T	46% (198/435)	64% (75/118)	39% (123/317)	24% (52/220)	26% (14/54)	23% (38/166)
T74S/A/P/K/E	54% (42/78)	69% (18/26)	46% (24/52)	23% (10/43)	25% (3/12)	23% (7/31)
N83N	47% (234/500)	64% (89/139)	40% (145/361)	24% (61/255)	27% (17/62)	23% (44/193)
N83D/N/S	46% (6/13)	80% (4/5)	25% (2/8)	13% (1/8)	0% (0/4)	25% (1/4)

	TPV/r Arm (n=513)				
Mutation	**All**	**P value**	**No T20**	**P value**	**+T20**
Overall	47% (240/513)		40% (147/369)		65% (93/144)
I13V/A/L/S	40% (69/171)	0.14	27% (32/119)	0.01	69% (37/54)
V32I/L	39% (29/74)	0.22	26% (12/46)	0.07	61% (17/28)
E34D/V/R/T/Y/Q/K	40% (19/48)	0.34	29% (10/34)	0.23	64% (9/14)
M36I/A/V/L/N	40% (124/310)	0.06	29% (60/208)	0.008	63% (64/102)
I47V/A	31% (29/93)	0.005	18% (11/62)	0.008	58% (18/31)
Q58E	38% (28/74)	0.15	27% (14/52)	0.07	64% (14/22)
D60E/K/A/N	39% (43/110)	0.14	30% (24/79)	0.11	61% (19/31)
V82 any change	48% (149/311)		41% (90/222)		66% (59/89)
V82A	50% (116/230)		45% (76/170)		67% (40/60)
V82T	44% (12/27)		47% (7/15)		42% (5/12)
V82C/I/F/M/S/G	39% (22/56)	0.29	21% (8/39)	0.018	82% (14/17)
I84V/A	41% (64/155)	0.23	31% (32/103)	0.10	62% (32/52)

Appendix G. Outcome by Key Mutation (Amino Acid Positions 33, 82, 94 and 90)

Proportion of Responders at Week 24 by Key mutations (33, 82, 94 and 90) and Number of PI mutations

Number of Key Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
0	8/16 (50)	6/14 (43)	2/2	7/17 (41)	7/16 (44)	0/1
1	74/144 (51)	57/116 (49)	17/28 (61)	40/133 (30)	29/112 (26)	11/21 (52)
2	153/336 (46)	83/231 (36)	70/105 (67)	59/335 (18)	40/251 (16)	19/84 (23)
3	6/17 (35)	2/9 (22)	4/9 (44)	4/17 (24)	0/10	4/7 (57)
0-1	82/160 (51)	63/130 (48)	19/30 (63)	47/150 (31)	36/128 (28)	11/22 (50)
2-3	159/353 (45)	85/239 (36)	74/144 (51)	63/352 (18)	40/261 (15)	23/91 (25)
33 + 82	40/78 (51)	21/51 (41)	19/27 (70)	14/90 (16)	5/64 (8)	9/26 (35)
33 + 84	9/22 (41)	3/11 (27)	6/11 (54)	3/13 (25)	2/9 (22)	1/3 (33)
33 + 90	11/30 (37)	5/17 (29)	6/13 (46)	7/25 (28)	4/19 (21)	3/6 (50)
82 + 84	12/33 (36)	6/24 (25)	6/9 (67)	6/34 (18)	4/22 (18)	2/12 (17)
82 + 90	59/128 (46)	34/89 (38)	25/39 (64)	20/115 (17)	11/89 (12)	9/26 (35)
84 + 90	40/96 (42)	20/63 (31)	20/33 (61)	21/109 (19)	14/77 (18)	7/32 (22)
33+82+84	1/2	1/2	NONE	0/2	0/1	0/1
33+82+90	2/6	1/4	1/2	2/8	0/4	2/3
33+84+90	3/7	NONE	3/7	1/3	0/2	1/1
82+84+90	0/2	0/2	NONE	1/4	0/2	1/1
< 4 including 33	6/10 (60)	3/7 (43)	3/3	2/10 (20)	2/9 (22)	0/1
4+ including 33	51/109 (47)	26/69 (38)	25/40 (63)	21/107 (20)	10/77 (13)	11/30 (37)
< 4 including 82	45/85 (49)	31/68 (46)	11/17 (65)	18/88 (20)	11/73 (15)	7/15 (54)
4+ including 82	107/226 (47)	59/154 (38)	48/72 (67)	37/214 (17)	23/163 (14)	14/51 (27)
<4 including 84	23/42 (55)	17/28 (61)	6/14 (43)	12/38 (32)	8/24 (33)	4/14 (29)
4+ including 84	41/113 (36)	15/75 (20)	26/38 (68)	20/124 (16)	15/91 (16)	5/33 (15)
< 4 including 90	45/79 (57)	39/67 (52)	6/12 (50)	23/62 (37)	18/50 (36)	5/12 (42)
4+ including 90	83/203 (41)	39/134 (29)	44/69 (64)	37/210 (18)	22/156 (14)	15/54 (28)

Key Mutation Score (33, 83, 84 and 90)	N	MEDIAN TPV/r FOLD CHANGE (Q25, Q75)	TPV/r ALL	TPV/r NO T20	TPV/r + T20
0	11	0.5 (0.3 – 2.3)	-1.55	-1.55 (9)	-2.20 (2)
1	97	1.2 (0.7, 2.05)	-1.42	-1.35 (78)	-2.26 (19)
2	217	2 (1, 4.45)	-1.22	-0.84 (143)	-2.05 (74)
3	10	7.75 (4.77, 13.92)	-0.32	-0.33 (5)	-0.31 (5)
4	1	4.7	-0.77	-0.77	None

Appendix H. Outcome by GSS Score

Genotypic Sensitivity Score for OBR and OUTCOME (Median Change from Baseline at Week 24)

GSS = minimum value of 0 and maximum value of total number of sensitive drugs determined to be part of OBR; T20 is considered sensitive

Proportion of Responders (confirmed 1 $\log_{10}$ decrease at Week 24) by Baseline Genotypic Sensitivity Score

# Baseline FDA PI Mutations#	TPV/r N=513			CPI/r N=502			LPV/r N=263		
	All	No T20	+ T20	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/513)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0	15% (8/53)	15% (8/53)	None	10% (7/71)	10% (7/71)	None	14% (5/37)	14% (5/37)	None
1	43% (71/164)	33% (37/111)	64% (34/61)	15% (25/162)	15% 19/125)	16% (6/23)	16% (15/92)	19% (13/70)	9% (2/22)
2	52% (110/211)	48% (72/150)	62% (38/61)	23% (41/178)	23% (31/137)	24% (10/41)	24% (21/87)	27% (17/63)	17% (4/24)
3	61% (45/74)	55% (28/51)	74% (17/23)	41% (32/79)	37% (19/51)	46% (13/28)	44% (18/41)	40% (10/25)	50% (8/16)
4+	64% (7/11)	75% (3/4)	57% (4/11)	42% (5/12)	0% (0/5)	71% (5/6)	50% (3/6)	0% (0/2)	75% (3/4)

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

Median Change from Baseline at Week 24 by Genotypic Sensitivity Score

Genotypic Sensitivity Score for OBR	TPV/r – No T20 Use	Control – No T20 Use	LPV/r – No T20 Use	TPV/r +T20	LPV/r + T20
0	-0.22 (50)	-0.33 (33)	-0.43 (20)	none	none
1	-0.48 (104)	-0.55 (60)	-0.61 (34)	-1.91 (52)	-0.29 (10)
2	-1.28 (141)	-0.68 (86)	-0.64 (44)	-1.80 (59)	-0.64 (12)
3	-1.62 (46)	-1.46 (33)	-2.19 (16)	-2.92 (24)	-1.20 (12)
4+	-1.76 94)	-0.32 (5)	+0.04 (2)	-2.32 (6)	-2.73 (4)

FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

Median Change from Baseline at Week 24 by Genotypic Sensitivity Score and Number of Baseline Mutations

Genotypic Sensitivity Score for OBR	Number of baseline PI mutations#	TPV/r – No T20 Use	Control – No T20 Use	LPV/r – No T20 Use
0	0-3	-0.32 (26)	-0.53 (17)	-0.60 (10)
	>3	-0.18 (24)	-0.19 (16)	-0.34 (10)
1	0-3	-0.87 (50)	-0.63 (35)	-1.10 (20)
	>3	-0.36 (54)	-0.47 (25)	-0.45 (14)
2	0-3	-1.39 (82)	-0.89 (62)	-1.36 (32)
	>3	-0.57 (59)	-0.34 (24)	-0.23 (12)
3	0-3	-1.56 (27)	-1.46 (21)	-2.63 (8)
	>3	-1.67 (19)	-1.34 (12)	-1.23 (8)
4+	0-3	-1.41 (3)	-0.32 (3)	+0.03 (2)
	>3	-1.92 (1)	-0.41 (2)	None

Genotypic Sensitivity Score for OBR and OUTCOME (Median DAVG Week 24)
GSS = minimum value of 0 and maximum value of total number of sensitive drugs determined to be part of OBR; T20 is considered sensitive

Median DAVG Week 24 by Genotypic Sensitivity Score

Genotypic Sensitivity Score for OBR	**TPV/r – No T20 Use**	**Control – No T20 Use**	**LPV/r – No T20 Use**	**TPV/r +T20**	**LPV/r + T20**
0	-0.53 (86)	-0.16 (100)	-0.16 (48)	none	none
1	-0.92 (176)	-0.25 (189)	-0.28 (98)	-1.79 (61)	-0.29 (25)
2	-1.30 (239)	-0.43 (224)	-0.32 (101)	-1.64 (72)	-0.63 (26)
3	-1.29 (72)	-0.89 (79)	-0.88 (35)	-2.15 (27)	-1.25 (16)
4+	-1.21 (5)	-0.78 (10)	-0.43 (4)	-1.90 (7)	-2.38 (5)

Appendix I. Outcome by Number and Type of Baseline PI Mutation

Proportion of Responders at Week 24 by PI mutation and Number of PI mutations

Number and Type of Baseline PI mutations#	TPV/r			CPI/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
0-3	59%	56%	72%	31%	29%	36%
4+	43%	34%	63%	19%	16%	29%
0-3 including 13	43% (16/37)	34% (10/29)	75% (6/8)	24% (9/37)	22% (7/32)	40% (2/5)
4+ including 13	40% (54/136)	26% (23/90)	67% (31/46)	18% (26/141)	13% (13/101)	33% (13/40)
0-3 including 20	59% (24/41)	57% (20/35)	67% (4/6)	28% (11/40)	23% (7/31)	44% (4/9)
4+ including 20	40% (111/281)	30% (57/191)	60% (54/90)	17% (45/261)	17% (33/200)	20% (12/61)
0-3 including 30	88% (7/8)	86% (6/7)	100% (1/1)	71% (5/7)	71% (5/7)	0
4+ including 30	33% (1/3)	0% (0/1)	50% (1/2)	67% (4/6)	75% (3/4)	50% (1/2)
0-3 including 32	67% (2/3)	67% (2/3)	0	100% (3/3)	100% (2/2)	100% (1/1)
4+ including 32	38% (27/71)	23% (10/43)	61% (17/28)	11% (6/56)	10% (4/41)	13% (2/15)
0-3 including 33	42% (8/19)	33% (5/15)	75% (3/4)	15% (4/27)	10% (2/21)	33% (2/6)
4+ including 33	49% (49/100)	39% (24/61)	64% (25/39)	21% (19/90)	15% (10/65)	36% (9/25)
0-3 including 34	57% (4/7)	40% (2/5)	100% (2/2)	20% (1/5)	0% (0/4)	100% (1/1)
4+ including 34	37% (15/41)	28% (8/29)	58% (7/12)	12% (11/91)	10% (7/68)	17% (4/23)
0-3 including 35	51% (19/37)	44% (14/32)	100% (5/5)	41% (17/41)	41% (14/34)	43% (3/7)
4+ including 35	40% (77/193)	32% (43/134)	58% (34/59)	21% (37/180)	20% (27/137)	23% (10/43)
0-3 including 36	37% (10/27)	35% (8/23)	50% (2/4)	31% (9/29)	31% (8/26)	33% (1/3)
4+ including 36	40% (114/283)	28% (52/185)	63% (62/98)	20% (57/289)	17% (38/219)	27% (19/70)
0-3 including 45						
4+ including 45						
0-3 including 46	68% (41/60)	65% (31/48)	83% (10/12)	26% (16/61)	27% (13/49)	25% (3/12)
4+ including 46	43% (137/317)	33% (71/212)	63% (66/105)	15% (45/297)	12% (28/227)	24% (17/70)
0-3 including 47	50% (1/2)	50% (1/2)	0	67% (2/3)	50% (1/2)	100% (1/1)

4+ including 47	31% (28/91)	17% (10/60)	58% (18/31)	9% (7/79)	8% (5/61)	11% (2/18)
0-3 including 48	50% (2/4)	33% (1/3)	100% (1/1)	38% (5/13)	33% (3/9)	50% (2/4)
4+ including 48	63% (48/76)	57% (30/53)	78% (18/23)	19% (15/77)	12% (7/57)	40% (8/20)
0-3 including 50	50% (2/4)	33% (1/3)	100% (1/1)	67% (2/3)	50% (1/2)	100% (1/1)
4+ including 50	57% (17/30)	53% (10/19)	64% (7/11)	17% (6/36)	4% (1/26)	50% (5/10)
0-3 including 53	67% (2/3)	67% (2/3)	0	0		
4+ including 53	51% (44/86)	39% (23/59)	78% (21/27)	22% (14/63)	20% (9/45)	28% (5/18)
0-3 including 54	50% (22/44)	44% (16/36)	75% (6/8)	15% (8/53)	10% (4/41)	33% (4/12)
4+ including 54	43% (151/354)	33% (81/243)	63% (70/111)	17% (59/341)	15% (39/261)	25% (20/80)
0-3 including 58	44% (7/16)	36% (5/14)	100% (2/2)	53% (9/17)	46% (6/13)	75% (3/4)
4+ including 58	36% (21/58)	24% (9/38)	60% (12/20)	11% (8/76)	12% (8/66)	0% (0/10)
0-3 including 60	62% (13/21)	56% (9/16)	80% (4/5)	33% (3/9)	33% (2/6)	33% (1/3)
4+ including 60	34% (30/89)	24% (15/63)	58% (15/26)	9% (5/57)	9% (4/47)	10% (1/10)
0-3 including 73	78% (18/23)	80% (16/20)	67% (2/3)	17% (4/24)	18% (3/17)	14% (1/7)
4+ including 73	35% (44/124)	24% (19/80)	57% (25/44)	14% (19/136)	12% (12/100)	19% (7/36)
0-3 including 82A/T	56% (19/34)	52% (16/31)	100% (3/3)	16% (7/44)	15% (6/39)	20% (1/5)
4+ including 82A/T	49% (109/222)	44% (67/153)	61% (42/69)	18% (37/202)	13% (20/155)	36% (17/47)
0-3 including 82C/I/F/M/S /G	58% (7/12)	38% (3/8)	100% (4/4)	44% (4/9)	33% (2/6)	67% (2/3)
4+ including 82C/I/F/M/S /G	35% (15/43)	16% (5/31)	77% (10/13)	15% (7/47)	17% (6/36)	9% (1/11)
0-3 including 83	0% (0/1)			50% (1/2)	100% (1/1)	0% (0/1)
4+ including 83	50% (6/12)	29% (2/7)	80% (4/5)	8% (1/13)	11% (1/9)	0% (0/4)
0-3 including 84	59% (17/29)	65% (13/20)	44% (4/9)	27% (7/26)	29% (5/17)	22% (2/9)
4+ including 84	37% (47/126)	23% (19/83)	65% (28/43)	18% (25/136)	18% (18/98)	18% (7/38)
0-3 including 88	100% (3/3)	100% (3/3)	0	67% (2/3)	67% (2/3)	0

4+ including 88	0% (0/7)	0% (0/5)	0% (0/2)	50% (6/12)	56% (5/9)	33% (1/3)
0-3 including 89	60% (9/15)	58% (7/12)	67% (2/3)	33% (4/12)	22% (2/9)	67% (2/3)
4+ including 89	38% (30/79)	30% (14/46)	48% (16/33)	15% (13/85)	12% (7/58)	22% (6/27)
0-3 including 90	66% (38/58)	67% (34/51)	57% (4/7)	35% (17/48)	36% (14/39)	33% (3/9)
4+ including 90	40% (90/224)	29% (44/150)	62% (46/74)	19% (43/224)	16% (26/167)	30% (17/57)

Number of protease mutations = any change at D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, or L90 at baseline

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814, **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

Proportion of Responders at Week 24 by PI mutation and Number of PI mutations

Number and Type of Baseline PI mutations#	TPV/r			LPV/r		
	All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
Overall	47% (241/513)	40% (148/369)	65% (93/144)	24% (62/263)	23% (45/197)	26% (17/66)
0-3	59%	56%	72%	31%	29%	36%
4+	43%	34%	63%	19%	16%	29%
0-3 including 13	43% (16/37)	34% (10/29)	75% (6/8)	31% (8/26)	29% (6/21)	40% (2/5)
4+ including 13	40% (54/136)	26% (23/90)	67% (31/46)	19% (15/80)	15% (8/53)	26% (7/27)
0-3 including 20	59% (24/41)	57% (20/35)	67% (4/6)	28% (7/25)	29% (6/21)	25% (1/4)
4+ including 20	40% (111/281)	30% (57/191)	60% (54/90)	16% (21/134)	16% (15/92)	14% (6/42)
0-3 including 30	88% (7/8)	86% (6/7)	100% (1/1)	75% (3/4)	75% (3/4)	None
4+ including 30	33% (1/3)	0% (0/1)	50% (1/2)	75% (3/4)	67% (2/3)	100% (1/1)
0-3 including 32	67% (2/3)	67% (2/3)	0	100% (1/1)	100% (1/1)	None
4+ including 32	38% (27/71)	23% (10/43)	61% (17/28)	11% (3/28)	15% (3/20)	0% (0/8)
0-3 including 33	42% (8/19)	33% (5/15)	75% (3/4)	13% (1/8)	14% (1/7)	0% (0/1)
4+ including 33	49% (49/100)	39% (24/61)	64% (25/39)	18% (7/40)	14% (4/28)	25% (3/12)
0-3 including 34	57% (4/7)	40% (2/5)	100% (2/2)	0% (0/1)	0% (0/1)	None
4+ including 34	37% (15/41)	28% (8/29)	58% (7/12)	13% (3/24)	6% (1/17)	29% (2/7)
0-3 including 35	51% (19/37)	44% (14/32)	100% (5/5)	48% (10/21)	53% (10/19)	50% (1/2)
4+ including 35	40% (77/193)	32% (43/134)	58% (34/59)	18% (15/82)	18% (10/57)	20% (5/25)
0-3 including 36	37% (10/27)	35% (8/23)	50% (2/4)	46% (6/13)	50% (6/12)	0% (0/1)
4+ including 36	40% (114/283)	28% (52/185)	63% (62/98)	18% (26/143)	17% (17/99)	205 (9/44)
0-3 including 46	68% (41/60)	65% (31/48)	83% (10/12)	41% (14/34)	43% (12/28)	33% (2/6)
4+ including 46	43% (137/317)	33% (71/212)	63% (66/105)	14% (22/153)	14% (16/113)	15% (6/40)
0-3 including 47	50% (1/2)	50% (1/2)	0	None	None	None
4+ including 47	31% (28/91)	17% (10/60)	58% (18/31)	2% (1/41)	3% (1/32)	0% (0/9)
0-3 including 48	50% (2/4)	33% (1/3)	100% (1/1)	63% (5/8)	60% (3/5)	67% (2/3)

4+ including 48	63% (48/76)	57% (30/53)	78% (18/23)	12% (5/42)	0% (0/30)	42% (5/12)
0-3 including 50	50% (2/4)	33% (1/3)	100% (1/1)	100% (2/2	100% (1/1)	100% (1/1)
4+ including 50	57% (17/30)	53% (10/19)	64% (7/11)	14% (3/21)	0% (0/15)	50% (3/6)
0-3 including 53	67% (2/3)	67% (2/3)	0	None	None	none
4+ including 53	51% (44/86)	9% (23/59)	78% (21/27)	17% (5/29)	16% (3/19)	20% (2/10)
0-3 including 54	50% (22/44)	44% (16/36)	75% (6/8)	29% (6/21)	25% (4/16)	40% (2/5)
4+ including 54	43% (151/354)	33% (81/243)	63% (70/111)	17% 25/171	14% (17/124)	17% (8/47)
0-3 including 58	44% (7/16)	36% (5/14)	100% (2/2)	56% (5/9)	57% (4/7)	50% (1/2)
4+ including 58	36% (21/58)	24% (9/38)	60% (12/20)	14% (6/41)	17% (6/35)	0% (0/6)
0-3 including 60	62% (13/21)	56% (9/16)	80% (4/5)	50% (2/4)	33% (1/3)	100% (1/1)
4+ including 60	34% (30/89)	24% (15/63)	58% (15/26)	8% (2/24)	11% (2/18)	50% (3/6)
0-3 including 73	78% (18/23)	80% (16/20)	67% (2/3)	25% (3/12)	22% (2/9)	33% (1/3)
4+ including 73	35% (44/124)	24% (19/80)	57% (25/44)	15% (12/79)	16% (9/56)	13% (3/23)
0-3 including 82 (any change)	56% (26/46)	49% (19/39)	100% (7/7)	40% (8/20)	39% (7/18)	50% (1/2)
4+ including 82 (any change)	46% (123/265)	39% (71/183)	63% (52/82)	11% (11/102)	8% (6/75)	19% (5/27)
0-3 including 82A/T	56% (19/34)	52% (16/31)	100% (3/3)	31% (5/16)	33% (5/15)	0% (0/1)
4+ including 82A/T	49% (109/222)	44% (67/153)	61% (42/69)	12% (11/89)	9% (6/67)	23% (5/22)
0-3 including 82C/I/F/M/S /G	58% (7/12)	38% (3/8)	100% (4/4)	75% (3/4)	67% (2/3)	100% (1/1)
4+ including 82C/I/F/M/S /G	35% (15/43)	16% (5/31)	77% (10/13)	0% (0/13)	0% (0/8)	0% (0/5)
0-3 including 83	0% (0/1)			50% (1/2)	100% (1/1)	0% (0/1)
4+ including 83	50% (6/12)	29% (2/7)	80% (4/5)	0% (0/6)	0% (0/3)	0% (0/3)
0-3 including 84	59% (17/29)	65% (13/20)	44% (4/9)	29% (6/21)	33% (2/15)	17% (1/6)
4+ including	37%	23%	65%	20%	21%	17%

84	(47/126)	(19/83)	(28/43)	(19/97)	(14/67)	(5/30)
0-3 including 88	100% (3/3)	100% (3/3)	0	67% (2/3)	67% (2/3)	None
4+ including 88	0% (0/7)	0% (0/5)	0% (0/2)	50% (3/6)	50% (2/4)	50% (1/2)
0-3 including 89	60% (9/15)	58% (7/12)	67% (2/3)	50% (3/6)	50% (2/4)	50% (1/2)
4+ including 89	38% (30/79)	30% (14/46)	48% (16/33)	14% (6/42)	14% (4/28)	14% (2/14)
0-3 including 90	66% (38/58)	67% (34/51)	57% (4/7)	38% (12/32)	37% (9/26)	50% (3/6)
4+ including 90	40% (90/224)	29% (44/150)	62% (46/74)	19% (24/126)	17% (15/88)	24% (9/38)

Number of protease mutations = any change at amino acid positions D30, V32, M36, M46, I47, G48, I50, F53, I54, V82, I84, N88, or L90 at baseline

Appendix J. Outcome by TPV Mutation Score

TPV/r arm (n = 745)

Overall mean = -1.35; median = -1.06 (n = 486)
+T20 mean = -1.81; median = -2.06 (n = 141)
-T20 mean = -1.16; median = -0.71 (n = 345)

TPV score	Total n	Wk24 Median change from BL	n@ wk24	<400	<50
0	44	-2.1	26	65%	50%
+T20	1				
-T20	43				
1	90	-2.13	63	67%	51%
+T20	16	-2.13	15	60%	47%
-T20	74	-2.13	48	69%	52%
2	105	-1.30	63	44%	38%
+T20	22	-1.68	19	53%	47%
-T20	83	-0.97	44	41%	34%
3	161	-0.64	103	37%	25%
+T20	29	-2.69	26	58%	42%
-T20	132	-0.49	77	30%	19%
4	183	-0.68	124	35%	18%
+T20	54	-1.91	48	48%	21%
-T20	129	-0.49	76	28%	16%
5	102	-0.43	67	24%	19%
+T20	25	-2.19	18	50%	44%
-T20	77	-0.34	49	14%	10%
6	43	-0.60	30	23%	13%
+T20	14	-1.42	10	30%	20%
-T20	29	-0.36	20	20%	10%
7	16	-1.44	10	40%	30%
+T20	5	-1.80	5	40%	20%
-T20	11	-1.08	5	40%	40%
8	1		0		
+T20					
-T20					

TPV score mutations:
10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY DRAFT REVIEW
NDA: 21814 **SN:** 000 **DATE REVIEWED:** 6/15/05
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

Median TPV Fold Change and DAVG24 by TPV Mutation Score

TPV MUTATION SCORE	N	MEDIAN TPV FOLD CHANGE (Q25, Q75)	TPV ALL	TPV NO T20	TPV +T20
0	18	0.6 (0.3-1.0)	-1.86	-1.07 (17)	-1.37 (1)
1	41	1.00 (0.65, 1.95)	-2.03	-2.10 (31)	-1.56 (10)
2	44	1.35 (0.6, 2.47)	-1.14	-1.09 (32)	-1.38 (12)
3	75	1.50 (0.70, 2.60)	-1.38	-0.93 (56)	-2.61 (19)
4	89	2 (0.95, 4.30)	-0.87	-0.61 (52)	-1.90 (37)
5	45	3.90 (2.0, 7.35)	-0.88	-0.44 (31)	-2.15 (14)
6	19	7.6 (1.10, 12.3)	-0.43	-0.40 (14)	-1.87 (5)
7	5	3.2 (2.3 , 5)	-0.64	-0.64 (3)	-1.43 (2)

TPV Mutation Score: Changes: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V

Appendix K. Listing of Patients with Protocol Violations

Treatment group/No. (%) of patients		
	TPV/r	CPI/r
No protease gene mutations at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M	6 9	3 4
More than two protease gene mutations at codons 33, 82, 84, 90	17 20	16 21

More than two protease gene mutations at codons 33, 82, 84, 90

STUDY	PTNO	ITRCDDC
1182_0012	1447	APV/r
1182_0012	4044	APV/r
1182_0048	1117	APV/r
1182_0048	4213	APV/r
1182_0012	2007	IDV/r
1182_0048	6118	IDV/r
1182_0012	1329	LPV/r
1182_0012	1418	LPV/r
1182_0012	1495	LPV/r
1182_0012	1660	LPV/r
1182_0012	2077	LPV/r
1182_0012	2161	LPV/r
1182_0012	3063	LPV/r
1182_0012	4072	LPV/r
1182_0012	4073	LPV/r
1182_0048	1137	LPV/r
1182_0048	6206	LPV/r
1182_0048	9067	LPV/r
1182_0012	1245	SQV/r
1182_0012	1786	SQV/r
1182_0012	3001	SQV/r
1182_0012	1013	TPV/r
1182_0012	1197	TPV/r
1182_0012	1269	TPV/r
1182_0012	1302	TPV/r
1182_0012	1390	TPV/r
1182_0012	1398	TPV/r
1182_0012	1633	TPV/r
1182_0012	1647	TPV/r
1182_0012	1724	TPV/r
1182_0012	1728	TPV/r
1182_0012	1827	TPV/r
1182_0012	2040	TPV/r
1182_0012	2376	TPV/r
1182_0012	3102	TPV/r
1182_0012	4079	TPV/r
1182_0012	4093	TPV/r
1182_0048	1109	TPV/r
1182_0048	4096	TPV/r
1182_0048	6097	TPV/r

1182_0048	6342	TPV/r

No protease gene mutations at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M

STUDY PTNO	ITRCDDC	
1182_0012	1711	LPV/r
1182_0012	1814	LPV/r
1182_0048	4006	LPV/r
1182_0012	2098	SQV/r
1182_0012	2243	TPV/r
1182_0012	2251	TPV/r
1182_0048	3079	TPV/r
1182_0048	3119	TPV/r
1182_0048	3295	TPV/r
1182_0048	3305	TPV/r
1182_0048	4048	TPV/r
1182_0048	7161	TPV/r
1182_0048	8056	TPV/r

Appendix L. Common Mutations Developing in Virologic Failures on TPV/r in RESIST Studies (n=59)

L10 11/59 (19%)

Patient No.	Change at L10
1094	F to S
1196	F to I
1259	F to I
1398	I to V
1571	I to V
1894	I to V
3129	F to L/V
3209	F to V
5011	F to I
6015	F to I/V
7102	L to V

I13 10/59 (17%) if remove mixtures 7/59 (12%)

Patient No.	Change at I13
1005	V
1094	V
1398	V
1607	I/V
1880	I/V
3128	V
3129	V
3275	V
4220	V
5011	I/V to V

E34 6/59 (10%) but if remove mixtures 2/59 (3%)

Patient No.	Change at E34
3041	E/D
3068	D
3275	D/E
6073	Q to H/Q
4046	Q to R
3296	E/Q to Q

E35 10/59 (17%) if remove mixtures 7/59 (12%)

Patient No.	Change at E35
1094	D
1571	D/N
1656	D
3024	E/G
3119	G
3203	D
3275	D
4009	D
4267	G
6073	D/E

M36 8/59 (14%)

Patient No.	Change at E36
1005	I/M
3024	I
3055	I
3068	I
3296	L/V to A
4046	L/V to A
6206	I
7102	I

I47 7/59 (12%) but if remove mixtures 6/59 (10%)

Patient No.	Change at I47
1894	V
3024	V
3108	V
3128	I/V
3189	V
5011	V
4241	V

I54 10/59 (17%)

Patient No.	Change at E34
1094	V to A
1196	M/V to A
1656	L to V
3071	V
3189	V to M
4085	V to A
6073	L to V
4267	M to T
4241	A
6015	V to A

K55 8/59 (14%)

Patient No.	Change at K55
1196	R/K
1398	R
2137	R/K
1880	R
2436	K/R to R
4009	R
3209	R
5011	R

D60 5/59 (8%)

Patient No.	Change at D60
1571	D/E to E
3128	D/E
3068	E
3296	E
6015	E/D

A71 7/59 (12%) but if remove mixtures 6/59 (10%)

Patient No.	Change at A71
1021	V
1259	I/V to V
1998	I to L
3209	V
3296	L to I
4220	V to F
4241	T to I

L89 7/59 (10%) but if remove mixtures 3/59 (5%)

Patient No.	Change at L89
1005	L/M
1250	L/W
3128	L/M
4009	M
3296	V
4090	L/V
6015	V

L33 15/59 (25%) but if remove mixtures 12/59 (20%)

Patient No.	Change at L33
1094	F
1159	F/L
1196	V
1607	F/L
1998	F
3055	V
3129	F
3083	F
3071	F
3119	I
4220	F
4205	L/V
6015	V
4267	I
4241	V

Appendix M. Proportion of Responders by C_{min}, Inhibitory Quotient (IQ) and Genotypic Inhibitory Quotient (GIQ)

Proportion of Responders (confirmed 1 log_{10} decrease at Week 24) by Median C_{min} and number of baseline PI mutations (FDA definition) – Overall Group

C_{min}	TPV/r - Overall N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	75% (15/20)	39% (51/131)	30% (27/91)
≥ 34	77% (14/18)	64% (61/95)	51% (66/130)
	1-4 PI Mutations		5+ PI Mutations
< 34	44% (66/151)		30% (27/91)
≥ 34	66% (75/113)		51% (66/130)

Proportion of Responders (confirmed 1 log decrease at Week 24) by Median C_{min} and number of baseline PI mutations (FDA definition) – No –T20

C_{min}	TPV/r - No T20 N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	74% (15/19)	37% (40/109)	28% (20/72)
≥ 34	80% (12/15)	59% (35/59)	32% (23/71)
	1-4 PI Mutations		5+ PI Mutations
< 34	42% (54/128)		28% (20/72)
≥ 34	64% (47/74)		32% (23/71)

Proportion of Responders (confirmed 1 log_{10} decrease at Week 24) by Median C_{min} and Number of Baseline PI mutations (FDA definition) – Plus T20

C_{min}	TPV/r - With T20 N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	100% (1/1)	50% (11/21)	37% (7/19)
≥ 34	67% (2/3)	72 (26/36)	73% (43/59)
	1-4 PI Mutations		5+ PI Mutations
< 34	52% (12/23)		37% (7/19)
≥ 34	72% (28/39)		73% (43/59)

Proportion of Responders (confirmed 1 log_{10} decrease at Week 24) by Inhibitory Quotient (IQ)

IQ	TPV/r N=301		
	All	No T20	+ T20
Median = 76.3			
< 76	29% (44/150	23% (24/104)	43% (20/46)
≥ 76	64% (97/151)	55% (56/102)	84% (41/49)
Quartiles			
0.4 – 29	24% (18/74)	15% (8/53)	48% (10/21)
>29-76	34% (26/76)	31% (16/51)	40% (10/25)
>76-189	55% (4276)	43% (23/53)	83% (19/23)
>189	73% (55/75)	67% (33/49)	85% (22/26)

Proportion of Responders (confirmed 1 log_{10} decrease at Week 24) by C_{min}

C_{min}	TPV/r N=513		
	All	No T20	+ T20
Median = 39.90			
< 34	38% (93/244)	37% (74/202)	45% (19/42)
≥ 34	58% (141/244)	48% (70/146)	72% (71/98)
Quartiles			
1.66-21	35% (41/118)	35% (35/101)	35% (6/17)
>21-34	41% (52/126)	39% (39/101)	52% (13/25)
>34-50	53% (62/117)	44% (35/80)	73% (27/37)
>50	62% (79/127)	53% (35/66)	72% (44/61)

Proportion of Responders by Genotype Inhibitory Quotient (GIQ) (C_{min}/# FDA Mutations)

GIQ	TPV/r N=301		
	All	No T20	+ T20
Median = 7.8			
< 7.8	34% (83/124)	32% (63/195)	43% (20/46)
≥ 7.8	62% (151/244)	54% (81/150)	74% (70/94)
Quartiles			
0.33 – 4.97	30% (36/11)	29% (30/103)	32% (6/19)
>4.97 - 7.8	40% (48/120)	36% (33/92)	54% (15/28)
>7.8 - 11.85	59% (73/123)	44% (34/76)	83% (39/47)
>111.85	64% (77/120)	64% (47/74)	65% (30/46)

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/s/

Lisa Naeger
6/22/05 10:13:31 AM
MICROBIOLOGIST
microbiology review

Julian O Rear
6/22/05 10:46:53 AM
MICROBIOLOGIST

James Farrelly
6/22/05 10:53:35 AM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 18, 2005

FROM: Kimberly A. Struble, PharmD
Division of Antiviral Drug Products, HFD-530

TO: NDA 21814

PATIENT: **Consult – Medical Review of Baseline Resistance Data and Outcome for Tipranavir/ritonavir versus Comparator Protease Inhibitors/ritonavir in Treatment-Experienced Patients.**

The purpose of this document is to present the FDA analyses of the clinical virology data from the two tipranavir/ritonavir (TPV/r) phase III pivotal studies 1182.12 (RESIST 1) and 1182.48 (RESIST 2). The clinical virology data was reviewed by microbiology (lead) and clinical (consult). Please refer to Dr. Lisa Naeger's review for a complete summary of the FDA analyses. This review focuses on analyses of virologic outcome by baseline genotype (number of protease inhibitor mutations) and baseline phenotype. The analysis plan used by FDA is consistent with the 2004 draft Guidance for Industry: Role of HIV Drug Resistance Testing in Antiretroviral Drug Development. Additional exploratory analyses were conducted and presented below.

Resistance Evaluation

Genotypic and phenotypic data on isolates from patients treated with TPV/r and comparator PIs/ritonavir (CPR/r) were assessed for studies RESIST 1 and RESIST 2. The relationship between number and type of baseline protease inhibitor mutations and virologic outcome and baseline phenotypic susceptibility and virologic outcome were assessed.

Study Population and Methods

Samples were obtained at baseline for all patients. On-treatment samples were obtained from patients who experienced virologic failure. Baseline genotype was preformed for all patients treated in RESIST 1 and 2. Randomly selected subsets of baseline samples were phenotyped; 400 samples from the TPV/r arms and 100 samples from the CPI/r arms. Genotyping was conducted by [redacted] using the TruGene HIV-1 test and VIRCO [redacted] and Virtual Phenotype assays. The VIRCO Antivirogram and Virologic PhenoSense assays were used for the phenotypic analyses.

Genotypes from 1482 isolates and 454 phenotypes from RESIST 1 and 2 were submitted for review. In the CPI/r arm most patients received LPV/r (n=358) followed by APV/r (n=194), SQV/r (n=162) and IDV/r (n=23).

Results

Baseline Genotype and Outcome

The FDA analysis of virologic outcome by baseline genotype is based on the as-treatment population.

Patients who discontinued study treatment while suppressed or who discontinued study treatment before confirmed suppression for adverse event, noncompliance, protocol violation, pregnancy, or withdrew consent were censored. Please refer to Appendix A for a summary of the censoring rules for the primary endpoint analyses (proportion of patients with 1 log decrease) and secondary analyses (time average change from baseline (DAVG24) and mean change from baseline at Weeks 2, 4, 8, 16 and 24. The FDA analyses conducted by Dr. Kimberly Struble are presented in the tables below. Because of the large number of potential comparisons, statistical testing was not conducted.

Differences between the FDA and Boehringer Ingelheim's (BI) approach to analyzing baseline resistance and virologic outcome includes the following:

- **Patient Population**
  - FDA pooled results from RESIST 1 and 2. FDA did not include the phase II studies in the main resistance analyses because the phase III primary endpoint (confirmed 1 log decrease from baseline) was used for the outcome parameter. Applying this endpoint to the phase II studies was not possible given the study designs.
  - BI pooled results from RESIST 1 and 2, and phase II studies (51 and 52)
- **Dataset**
  - FDA used an as-treated population (censored dataset, see Appendix A for details). FDA conducted analyses on a censored patient population in order to assess the impact of baseline resistance and outcome without confounding factors such as early discontinuation due to adverse events, etc. For example, classifying patients who discontinue at Week 2 for an adverse event as a treatment failure for resistance analyses may diminish the ability to determine true baseline genotype or phenotype predictors of virologic success or failure.
  - BI used an intent-to-treat population and included all patients with complete data available for the analyses
- **Baseline Protease Inhibitor Definition**
  - The FDA analyses focused on any amino acid change at the following positions: D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88 and L90. These mutations were included in the analysis based on their association with reduced susceptibility to currently approved PIs, as reported in various publications..
  - BI's analyses focused on TPV mutational score (10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V). The TPV score was generated from a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies. Mutations at the 16 positions described above were associated with reduced TPV susceptibility and/or reduced HIV RNA response. In addition, analyses were conducted by any change in the PR gene and by a pre-defined key mutation score (33, 82, 84, 90).
- **Endpoint**
  - The FDA conducted analyses based on the primary endpoint in RESIST 1 and 2, specifically the proportion of patients with confirmed 1 log decrease from baseline through Week 24. In addition, secondary endpoints including DAVG24 and median change from baseline at Weeks 2, 4, 8, 16 and 24 were assessed. In addition, because patients were stratified based on enfuvirtide (T20) use, we examined virologic outcomes in three separate groups - overall treatment groups (All), patients not receiving ENF (No T20), and patients receiving ENF (+T20) as part of the optimized background regimen. We focused on the 'No T20' group in order to assess baseline resistance predictors of virologic success and failure for TPV/r without the additive effect of T20 use on the overall response.
  - BI conducted analyses for mean change from baseline (last observation carried forward) for the overall treatment groups.

In addition, this review provides analyses for LPV/r-treated patients in the CPI/r group because LPV/r was the largest subgroup (approximately 49% of the CPI/r group).

Number of Baseline Mutations and Outcome:

Analyses were conducted to assess the impact of number of baseline PI mutations on virologic outcome. The following PI mutations were used in the analyses: D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88 and L90. These mutations were included in the analysis based on their association with reduced susceptibility to currently approved PIs, as reported in various publications. This mutation definition was used in FDA analyses for other approved PIs.

First, the data was analyzed by number of baseline PI mutations and outcome. The results of these analyses are shown in Tables 1 and 2. Secondly, the results were then reviewed to determine if the number of baseline mutations were associated with maximal, reduced or minimal responses. Analyses of various groupings by number of mutations and response were conducted as shown in Tables 3 and 4.

Regardless of the endpoint used for these analyses, the response rates were greater for the TPV/r treatment arm compared to the CPI/r arm. Our findings included the following:

- In both the TPV/r and CPI/r arms of RESIST 1 and 2, response rates were similar to or greater than the overall response rates for the respective treatment groups for patients with one to four baseline PI mutations.

- Response rates were reduced if five or more PI-associated mutations were present at baseline.

    - Patients with five or more PI mutations at baseline and not receiving T20:

        - 28% in the TPV/r arm and 11% in the CPI/r arm had a confirmed 1 $\log_{10}$ decrease at Week 24 (Table 3).

        - 0.86 $\log_{10}$ median decrease in viral load (as assessed by DAVG24) in the TPV/r arm compared to a 0.23 $\log_{10}$ median decrease in viral load (DAVG24) in the CPI/r arm (Table 4).

- In general, regardless of the number of baseline PI mutations or T20 use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 $\log_{10}$ decrease at Week 24) (Table 3) and greater declines in viral load by median DAVG24 (Table 4) compared to the CPI/r arm.

The median change from baseline by week for patients with one to four baseline mutations and five or more baseline mutations are summarized in Appendix B. Please refer to Dr. Lisa Naeger's review for further details. Regardless of the number of baseline PI mutations, the largest decline in HIV RNA was observed by Week 2 for all groups with the greatest decline observed in the TPV/r arms. A 1.5 $\log_{10}$ decrease in viral load at Week 2 was observed for patients receiving TPV/r regardless of the number of baseline PI mutations (1-4 or 5+). Patients who had five or more baseline PI mutations and who received TPV/r without T20 began to lose antiviral activity between Weeks 4 and 8 with their HIV RNA trending back toward baseline. However, sustained viral load decreases (1.5 – 2 $\log_{10}$) through Week 24 were observed in patients receiving TPV/r and T20.

Additional analyses were conducted to evaluate the number of baseline PI mutations and outcome as assessed by mean and median change from baseline by week. The results are

presented in Appendix C. Of note, these analyses were not conducted on the censored population as described above.

Table 1: Proportion of Responders (confirmed 1 log decrease at Week 24) by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TPV/r N=531			CPI/r N=502			LPV/r N=263		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
1	50% (7/14)	50% (7/14)	None	38% (8/21)	35% (7/20)	1/1	36% (5/14)	31% (4/13)	1/1
2	79% (23/29)	80% (20/25)	75% (3/4)	50% (11/22)	48% (10/21)	1/1	53% (9/17)	50% (8/16)	1/1
3	55% (40/73)	51% (30/59)	71% (10/14)	24% (19/79)	22% (13/60)	32% (6/19)	38% (14/37)	39% (11/28)	33% (3/9)
4	47% (77/163)	41% (48/117)	63% (29/46)	29% (41/142)	24% (26/109)	45% (15/33)	36% (24/67)	34% (16/47)	40% (8/20)
5	41% (56/136)	33% (32/97)	62% (24/39)	14% (20/144)	13% (15/114)	17% (5/30)	8% (6/78)	7% (4/58)	105 2/10)
6	39% (27/69)	21% (8/39)	63% (19/30)	14% (10/70)	10% (5/49)	24% (5/21)	10% (4/40)	7% (2/28)	17% (2/12)
7+	42% (11/26)	20% (3/15)	73% (8/11)	5% (1/22)	0% (0/15)	14% (1/7)	0% (0/9)	0% (0/6)	0% (0/3)

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

Table 2: DAVG 24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TP/r N=704			CPI/r N=705			LPV/r N=344		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
1	-1.44 (30)	-1.44 (28)	-1.45 (2)	-1.08 (28)	-0.87 (27)	-1.30 (1)	-0.87 (19)	-0.86 (18)	-1.30 (1)
2	-1.43 (46)	-1.44 (41)	-1.42 (5)	-1.13 (37)	-1.07 (36)	-2.51 (1)	-1.44 (125)	-1.40 (24)	-2.51 (1)
3	-1.56 (107)	-1.48 (92)	-1.97 (15)	-0.72 (125)	-0.66 (100)	-0.86 (25)	-0.86 (51)	-0.86 (40)	-0.86 (11)
4	-1.29 (215)	-1.00 (167)	-1.93 (48)	-0.45 (191)	-0.39 (152)	-0.89 (39)	-0.45 (89)	-0.39 (67)	-0.76 (22)
5	-1.15 (181)	-0.91 (137)	-1.95 (44)	-0.24 (198)	-0.26 (164)	-0.17 (34)	-0.16 (96)	-0.20 (75)	-0.06 (21)
6	-1.07 (89)	-0.72 (57)	-1.53 (32)	-0.27 (97)	-0.24 (74)	-0.79 (23)	-0.24 (51)	-0.22 (39)	-0.57 (12)
7+	-0.94 (33)	-0.64 (21)	-2.25 (12)	-0.02 (27)	+0.00 (20)	-0.52 (7)	+0.07 (12)	+0.11 (9)	-0.60 (3)

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

Table 3: Proportion of Responders (confirmed 1 log decrease at Week 24) by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TPV/r N=531			CPI/r N=502			LPV/r N=263		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0-3	59% (70/119)	56% (57/101)	72% (13/18)	31% (38/124)	29% (30/102)	36% (8/22)	41% (28/69)	40% (23/58)	45% (5/11)
4+	43% (171/394)	34% (91/268)	63% (80/126)	19% (72/378)	16% (46/287)	29% (26/91)	18% (34/194)	16^ (22/139)	22% (12/55)
0-4	52% (147/282)	48% (105/218)	66% (42/64)	30% (79/266)	27% (56/211)	42% (23/55)	38% (52/136)	37% (39/105)	42% (13/31)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)	8% (10/127)	7% (6/92)	11% (4/35)
1-2	70% (30/43)	69% (27/39)	75% (3/4)	44% (19/43)	41% (17/41)	100% (2/2)	45% (14/31)	41% (12/29)	100% (2/2)
3-4	50% (117/236)	44% (76/176)	65% (39/60)	27% (60/221)	23% (39/169)	40% (21/52)	37% (38/104)	36% (27/75)	38% (11/29)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)	8% (10/127)	7% (6/92)	11% (4/35)
0-1	59% (70/119)	56% (57/101)	72% (13/18)	31% (38/124)	29% (30/102)	36% (8/22)	41% (28/69)	40% (23/58)	45% (5/11)
4-5	44% (133/294	37% (80/214)	62% (53/85)	21% (61/286)	18% (41/223)	32% (20/63)	21% (30/145)	19% (20/105)	25% (10/40)
6+	40% (38/95)	20% (11/54)	66% (27/41)	12% (11/92)	8% (5/64)	21% (6/28)	8% (4/49)	6% (2/34)	13% (2/15)

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

Table 4: DAVG24 by Number of Baseline PI Mutations

# Baseline FDA PI Mutations#	TPV/r N=704			CPI/r N=705			LPV/r N=344		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
0-3	-1.47 (186)	-1.46 (164)	-1.75 (22)	-0.84 (192)	-0.75 (164)	-1.13 (28)	-1.07 (6)	-1.01 (83)	-1.30 (13)
4+	-1.15 (518)	-0.91 (382)	-1.90 (136)	-0.29 (513)	-0.27 (410)	-0.45 (103)	-0.24 (248)	-0.21 (190)	-0.35 (58)
0-4	-1.39 (401)	-1.33 (331)		-0.59 (383)	-0.47 (316)	-0.90 (67)	-0.77 (185)	-0.71 (150)	-0.89 (35)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)	-0.20 (159)	-0.20 (123)	-0.14 (36)
0-2	-1.42 (79)	-1.41 (72)	-1.42 (7)	-1.13 (67)	-1.00 (64)	-1.30 (3)	-1.33 (45)	-1.33 (43)	-1.90 (2)
1-2	-1.43 (76)	-1.44 (69)	-1.42 (7)	-1.13 (65)	-1.01 (63)	-1.90 (2)	-1.34 (44)	-1.34 (42)	-1.90 (2)
3-4	-1.36 (322)	-1.29 (259)	-1.96 (63)	-0.53 (316)	-0.44 (252)	-0.89 (64)	-0.57 (140)	-0.45 (107)	-0.86 (33)
5+	-1.07 (303)	-0.86 (215)	-1.81 (88)	-0.24 (322)	-0.23 (258)	-0.27 (64)	-0.20 (159)	-0.20 (123)	-0.14 (36)
0-3	-1.47 (186)	-1.46 (164)	-1.75 (22)	-0.84 (192)	-0.75 (164)	-1.13 (28)	-1.07 (96)	-1.01 (83)	-1.30 (13)
4-5	-1.23 (396)	-0.93 (304)	-1.93 (92)	-0.32 (389)	-0.30 (316)	-0.44 (73)	-0.27 (185)	-0.73 (150)	-0.33 (43)
6+	-0.98 (122)	-0.70 (78)	-1.79 (44)	-0.22 (124)	-0.20 (94)	-0.56 (30)	-0.21 (63)	-0.20 (48)	-0.60 (15)

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

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Key Mutations and Outcome:

We then analyzed response rates by number of key mutations in order to confirm BI's analyses (see Tables 5 and 6). BI's definition of key mutations included mutations at codons 33, 82, 84 or 90. These mutations were selected on the basis of in vitro studies of TPV resistance and mutations emerging in patients with virologic failure phase II studies. The L33F and I84V mutation are the first TPV-selected mutations in multiple passage experiments. Two mutational patterns were associated with reduced TPV susceptibility in a study of highly cross-resistant clinical HIV isolates: V82T with I84V and I84V with L90M, both with numerous secondary mutations. According to BI, the composite count of these four mutations was instrumental in the dose selection (TPV/r 500/200 mg twice daily) and although the L90M mutation was not detected or associated with reduced TPV susceptibility or reduced virologic response, the L90M mutation was included in the key mutation definition because this mutation appears to serve as a marker for multiple PI resistance.

BI included data from RESIST 1 and 2 and studies 51 and 52 in order to increase the numbers of patients with 3 or more key mutations, whereas the FDA analyses included data from RESIST 1 and 2. Of note, patients in RESIST 1 and 2 were required to have no more than two protease mutations at positions 33, 82, 84, or 90. Response rates are similar between TPV/r and CPI/r if no key mutations are present at baseline; however, this finding is based on a limited number of patients. Response rates appear to diminish as the number of baseline key mutations increase. Results from the FDA and BI's analyses were consistent.

Table 5: Proportion of Responders (confirmed 1 log decrease at Week 24) by Number of Key Mutations

# Key Mutations#	TPV/r N=531			CPI/r N=502			LPV/r N=263		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0	50% (8/16)	43% (6/14)	100% (2/2)	41% (7/17)	44% (7/16)	100% (1/1)	56% (5/9)	56% (5/9)	None
1	74% (51/144)	49% (57/116)	61% (17/28)	30% (40/134)	26% (29/113)	52% (11/21)	38% (27/71)	33% (19/57)	57% (8/14)
2	46% (153/336)	36% (83/231)	67% (70/105)	18% (59/334)	16% (40/250)	23% (19/84)	17% (29/174)	17% (21/126)	17% (8/48)
3	35% (6/17)	25% (2/8)	44% (4/9)	24% (4/17)	30% (3/10)	57% (4/7)	11% (1/9)	0%)/5)	255 (1/4)

Any change at positions 33 82, 84, and 90

Table 6: Median DAVG 24 by Number of Key Mutations

# Key Mutations#	TPV/r N=704			CPI/r N=705			LPV/r N=344		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
0	-1.40 (28)	-1.24 (24)	-1.54 (4)	-1.33 (25)	-1.33 (24)	-1.14 (1)	-1.44 (15)	-1.44 (15)	None
1	-1.43 (213)	-1.41 (181)	-1.87 (31)	-0.56 (207)	-0.46 (179)	-1.45 (28)	-0.70 (94)	-0.48 (80)	-1.69 (14)
2	-1.17 (444)	-0.92 (330)	-1.95 (114)	-0.29 (454)	-0.26 (359)	-1.05 (1)	-0.25 (225)	-0.24 (172)	-0.33 (53)
3	-0.36 (18)	-0.33 (9)	-0.47 (9)	-0.24 (19)	-0.10 (12)	-1.29 (7)	-0.20 (10)	-0.01 (6)	-0.99 (4)
4+	-0.77 (1)	-0.77 (1)	None	None	None	None	None	None	None

Any change at positions 33 82, 84, and 90

Genotypic Sensitivity Score and Outcome:

Analyses by baseline genotypic sensitivity score (GSS) for the optimized background regimens (OBR) were also conducted. The results of these analyses are shown in Tables 7 and 8. BI included a GSS for each patient in the resistance dataset. A number was assigned for each agent in the OBR. Agents in the OBR interpreted as not resistant or possibly resistant were given a score of one and agents interpreted as resistant were given a score of zero. A score of one was always assigned if T20 was part of the OBR regardless if T20 use was new or ongoing at the start of the study. The number assigned to each agent in the OBR were added to determine a patients individual GSS such that the higher the GSS, the more active drugs present in the regimen. The limitation of this analysis is how the GSS was determined. Agents interpreted as possibly resistant were given the same score (1) as agents not resistant. In previous trials susceptible agents are assigned a score of 1, possibly resistant agents are assigned a score of 0.5. A standard approach to calculating GSS is needed. Nevertheless, as expected, virologic response correlated with the number of active drugs in the regimen. Response rates (proportion of responders with confirmed 1 log decrease in HIV RNA at Week 24) were approximately 20-30 percent greater in the TPV/r group compared to the CPI/r group in patients with GSS of one to four. Response rates were similar between the treatment groups if the baseline GSS was zero. Of note, if the baseline GSS was zero, the decline in HIV RNA was approximately 0.4 $\log_{10}$ copies/mL greater in TPV/r group compared to the CPI/r group.

Table 7: Proportion of Responders (confirmed 1 log decrease at Week 24) by Baseline Genotypic Sensitivity Score

Baseline GSS	TPV/r N=531			CPI/r N=502			LPV/r N=263		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)	24% (62/263)	23% (45/197)	26% (17/66)
0	15% (8/53)	15% (8/53)	None	10% (7/71)	10% (7/71)	None	14% (5/37)	14% (5/37)	None
1	43% (71/164)	33% (37/111)	64% (34/61)	15% (25/162)	15% 19/125)	16% (6/23)	16% (15/92)	19% (13/70)	9% (2/22)
2	52% (110/211)	48% (72/150)	62% (38/61)	23% (41/178)	23% (31/137)	24% (10/41)	24% (21/87)	27% (17/63)	17% (4/24)
3	61% (45/74)	55% (28/51)	74% (17/23)	41% (32/79)	37% (19/51)	46% (13/28)	44% (18/41)	40% (10/25)	50% (8/16)
4+	64% (7/11)	75% (3/4)	57% (4/11)	42% (5/12)	0% (0/5)	71% (5/6)	50% (3/6)	0% (0/2)	75% (3/4)

Table 8: DAVG 24 by Baseline Genotypic Sensitivity Score

Baseline GSS	TPV/r N=704			CPI/r N=705			LPV/r N=344		
	All	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**	**All**	**No T20**	**+ T20**
Overall	-1.31 (704)	-1.02 (546)	-1.88 (158)	-0.36 (705)	-0.33 (574)	-0.60 (131)	-0.33 (344)	-0.32 (273)	-0.45 (71)
0	-0.56 (80)	-0.56 (80)	None	-0.17 (96)	-0.17 (96)	None	-0.15 (47)	-0.15 (47)	None
1	-1.29 (223)	-0.97 (166)	-1.87 (57)	-0.26 (226)	-0.25 (180)	-0.34 (46)	-0.29 (118)	-0.29 (93)	-0.28 (25)
2	-1.40 (297)	-1.31 (229)	-1.73 (68)	-0.45 (257)	-0.44 (213)	-0.86 (44)	-0.34 (120)	-0.33 (95)	-0.39 (25)
3	-1.60 (93)	-1.47 (67)	-2.24 (26)	-0.93 (105)	-0.93 (75)	-1/03 (30)	-1.05 (50)	-0.92 (34)	-1.25 (16)
4+	-1.49 (11)	-1.22 (4)	-1.90 (7)	-1.06 (20)	-0.71 (9)	-1.48 (11)	-0.85 (9)	-0.42 (4)	-2.37 (5)

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Baseline Phenotype and Outcome:

Baseline phenotype and outcome analyses were conducted. The as-treated population was also used in the following phenotype analyses. This analysis focused on the TPV/r treatment group. Limited data in the CPI/r group was available for comparison. Again, the analyses focused on the 'No T20' group in order to more accurately assess the effect of baseline phenotype on virologic response for TPV/r.

First, patients with virologic success and failure by baseline phenotype for the TPV/r group were plotted to aid in the determination of susceptibility breakpoints (see Appendix C for graphs). Next, the data were analyzed by narrow susceptibility ranges then by quartiles and median baseline phenotype. Results of some of the analyses are presented in Tables 9 and 10. Finally, we reviewed the results of these analyses and we determined the susceptibility ranges of 0-3, >3-10 and >10 best described the data. These susceptibility ranges show reduced response as the baseline phenotypic susceptibility range increases. In patients not receiving T20, the proportion of responders was 45% if the fold change in IC_{50} value from reference of TPV susceptibility was 3-fold or less at baseline (Table 10). The proportion of responders decreased to 21% when the TPV baseline phenotype values were >3- to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

These baseline phenotype groups are not meant to represent definitive clinical susceptibility breakpoints for TPV/r. These analyses are based on a select patient population. More data are needed in order to determine the susceptibility breakpoints for TPV/r. These data are provided to give clinicians information on the likelihood of virologic success based on pretreatment susceptibility to TPV/r in PI-experienced patients.

Table 9: Proportion of Responders by Baseline TPV phenotype

Baseline Phenotype	TPV		
	All	**No T20 Use**	**T20 Use**
0-1	64% (64/101)	60% (46/77)	75% (18/24)
>1-2	42% (33/78)	27% (14/51)	70% (19/27)
>2-3	52% (23/44)	40% (14/35)	100% (9/9)
>3-4	40% (8/20)	29% (4/14)	67% (4/6)
>4-5	23% (3/13)	17% (1/6)	29% (2/7)
>5-6	9% (1/11)	0% (0/7)	25% (1/4)
>6-7	43% (3/7)	50% (2/4)	67% (1/3)
>7-8	22% (2/9)	0% (0/5)	50% (2/4)
>8-9	56% (5/9)	43% (3/7)	100% (2/2)
>9-10	0% (0/4)	0%	0%
>10	27% (4/15)	0% (0/8)	57% (4/7)
	Quartiles (overall)		
0- 0.8	69% (55/80)	66% (38/58)	77% (17/22)
>0.8 – 1.8	40% (35/85)	31% (20/64)	67% (14/21)
>.8 – 3.7	52% (37/71)	37% (19/51)	90% (18/20)
>3.7	26% (20/77)	16% (7/45)	41% (13/32)

Table 7: Proportion of Responders and DAVG24 by Baseline TPV Phenotype

Baseline Phenotype	TPV		
	All	No T20 Use	T20 Use
Overall	47% (146/313)	39% (84/218)	65% (62/95)
0-3	54% (120/223)	45% (74/163)	77% (46/60)
>3-10	29% (22/75)	21% (10/47)	43% (12/28)
>10	27% (4/15)	0% (0/8)	57% (4/7)
0-3	-1.55 (237) (-2.32, -0.58)	-1.31 (176) (-2.09, -0.46)	-2.23 (61) (-2.76, -1.19)
>3-10	-0.53 (79) (-1.70, -0.04)	-0.41 (49) (-1.09, +0.02)	-1.30 (30) (-2.35, -0.08)
>10	-0.84 (20) (-1.84, -0.21)	-0.24 (11) (-0.95, +0.01)	-1.87 (9) (-2.49, -0.53)

RELATIONSHIP BETWEEN GENOTYPE AND PHENOTYPE AND OUTCOME

The relationship between PI mutations, TPV phenotypic susceptibility and outcome were evaluated. Again, this analysis was conducted on the as-treated population. Three categories of mutations were used and included the TPV mutation score (as determined by BI), the FDA mutation score and key PI mutations. The results of these analyses are shown in Table 11.

A strong correlation between genotype and phenotype was not apparent in the FDA mutation score analysis. In BI's analyses, data from studies 51 and 52 were included to provide a broader range of baseline susceptibility and number of baseline mutations. BI's analyses show three key protease gene mutations or > 4 TPV-associated mutations produce decreased susceptibility (> 3-fold WT) in vitro or reduced antiviral responses compared to the overall study population. High level TPV resistance (>10-fold WT) was seen if all 4 key mutations or >7 TPV-associated mutations were present. Three key mutations showed >3-fold resistance to TPV/r.

Table 11: Median fold change from wild type for TPV by number of mutations

TPV Mutation Score	N	Median TPV fold change (Q25, Q75)	TPV All	TPV No T20	TPV + T20
0	16	0.6 (0.3-0.97)	69% (11/16)	69% (11/16)	None
1	37	1 (0.55, 2.15)	78% (29/37)	81% (22/27)	70% (7/10)
2	42	1.35 (0.6, 2.42)	40% (17/42)	35% (11/31)	55% (6/11)
3	68	1.55 (0.72, 2.60)	46% (31/68)	33% (16/49)	79% (15/19)
4	88	2 (0.93, 4.17)	41% (36/88)	27% (14/51)	59% (22/37)
5	44	3.85 (1.9, 4.17)	31% (14/44)	19% (6/31)	61% (8/13)
6	18	7.7 (1.17, 13.75)	38% (7/18)	23% (3/13)	80% (4/5)
7	5	3.2 (2.3 , 5)	40% (2/5)	33% (1/3)	50% (1/2)
FDA Mutation Score					
0-2	95	1 (0.5, 2.1)	60% (57/95)	59% (44/74)	61% (13/21)
3-4	156	4 (3, 4)	43% (67/156)	30% (30/100)	66% (37/56)
5+	67	3.9 (2.2, 8.1)	34% (23/67)	21% (10/47)	65% (13/20)
Key Mutation Score (33, 83, 84 and 90)					
0	8	1.2 (0.3, 4.9)	63% (5/8)	57% (4/7)	100% (1/1)
1	93	1.2 (0.7, 2.05)	53% (49/93)	50% (37/74)	63% (12/19)
2	207	2 (1, 4.4)	44% (91/207)	31% (42/135)	68% (49/72)
3	10	7.75 (4.77, 13.92)	20% (2/10)	20% (1/5)	20% (1/5)

TPV Mutation Score: Changes: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V

ADDITIONAL EXPLORATORY ANALYSES :

Proportion of responders by inhibitory quotient (IQ), Cmin and genotypic inhibitory quotient (GIQ) were explored. In the resistance dataset provided by BI, IQs were calculated for subjects who had a Cmin value and individual IC50 (protein-binding corrected). The IQ is a ratio of Cmin/IC50. The GIQ is a ratio of Cmin/number of baseline PI mutations. For these analyses we used the FDA definition for number of baseline PI mutations. IQ ratios were explored in previous trials and were used as a tool to help predict virologic success. This concept is not widely used in clinical practice given the feasibility and cost concerns with obtaining Cmin and IC50 for individual patients. The concept of GIQ was introduced at an International workshop on HIV Clinical Pharmacology. In clinical practice more subjects receive genotypic resistance testing compared to phenotypic resistance testing; therefore, this method may serve as a useful tool in the management of HIV infection. Importantly, these analyses are exploratory and require additional validation. Nevertheless, consistent results were seen for the IQ and GIQ analyses.

IQ:

First we evaluated the proportion of responders (confirmed 1 log decrease at Week 24) by IQ. The median and quartiles ranges for the IQs were used to analyze the proportion of responders for the overall TPV-treated population and TPV with and without T20 use. The results of the analyses are shown in the Table 12. Subjects with IQs $\geq$ 76 had virologic response rates similar to or greater than the overall population. Virologic response rates were decreased for IQs < 76.

Table 12: Proportion of Responders (confirmed 1 log decrease at Week 24) by IQ

IQ	TPV N=301		
	All	**No T20**	**+ T20**
Median = 76.3			
< 76	29% (44/150	23% (24/104)	43% (20/46)
≥ 76	64% (97/151)	55% (56/102)	84% (41/49)
Quartiles			
0.4 – 29	24% (18/74)	15% (8/53)	48% (10/21)
>29-76	34% (26/76)	31% (16/51)	40% (10/25)
>76-189	55% (4276)	43% (23/53)	83% (19/23)
>189	73% (55/75)	67% (33/49)	85% (22/26)

Cmin:

Table 13 summarizes the proportion of responders by Cmin values. Cmin values alone were not a good predictor of virologic response. Response rates were similar (35-39%) for patients with Cmin values ranging from 1.66 – 21 ug/mL and > 21-34 ug/mL, respectively. Response rates were slightly greater (44%) in subjects with Cmin values > 34 ug/mL. Next, we evaluated the proportion of responders by Cmin and number of baseline PI mutation. The results of these analyses are shown in Tables 14-16. For these analyses the median Cmin value (34 ug/mL) was used. Cmin values did not appear to affect response for patients with 1-2 PI mutations. The response rates for these groups were 75% (Cmin < 34 ug/mL) and 77% (Cmin > 34 ug/mL). The

remaining analyses show response rates are affected by Cmin and the number of baseline PI mutations. For patients with Cmin values < 34 ug/mL, response rates were 44% when 1-4 baseline PI mutations were present compared to 30% in patients with five or more baseline PI mutations. In comparison, the proportion of responders was 66% in patients with Cmin values > 34 ug/mL and1-4 baseline PI mutations and 51% in patients with five or more baseline PI mutations.

Table 13: Proportion of Responders (confirmed 1 log decrease at Week 24) by Cmin

Cmin (ug/mL)	TPV N=513		
	All	**No T20**	**+ T20**
Median = 39.90			
< 34	38% (93/244)	37% (74/202)	45% (19/42)
≥ 34	58% (141/244)	48% (70/146)	72% (71/98)
Quartiles			
1.66-21	35% (41/118)	35% (35/101)	35% (6/17)
>21-34	41% (52/126)	39% (39/101)	52% (13/25)
>34-50	53% (62/117)	44% (35/80)	73% (27/37)
>50	62% (79/127)	53% (35/66)	72% (44/61)

Table 14: Proportion of Responders (confirmed 1 log decrease at Week 24) by Median Cmin and number of baseline PI mutations (FDA definition) – Overall Group

Cmin	TPV - Overall N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	75% (15/20)	39% (51/131)	30% (27/91)
≥ 34	77% (14/18)	64% (61/95)	51% (66/130)
	1-4 PI Mutations		5+ PI Mutations
< 34	44% (66/151)		30% (27/91)
≥ 34	66% (75/113)		51% (66/130)

Table 15: Proportion of Responders (confirmed 1 log decrease at Week 24) by Median Cmin and number of baseline PI mutations (FDA definition) – No –T20

Cmin	TPV - No T20 N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	74% (15/19)	37% (40/109)	28% (20/72)
≥ 34	80% (12/15)	59% (35/59)	32% (23/71)
	1-4 PI Mutations		5+ PI Mutations
< 34	42% (54/128)		28% (20/72)
≥ 34	64% (47/74)		32% (23/71)

Table 16: Proportion of Responders (confirmed 1 log decrease at Week 24) by Median Cmin and number of baseline PI mutations (FDA definition) – Plus T20

Cmin	TPV - With T20 N=513		
	1-2 PI Mutations	3-4 PI Mutations	5+ PI Mutations
< 34	100% (1/1)	50% (11/21)	37% (7/19)
≥ 34	67% (2/3)	72 (26/36)	73% (43/59)
	1-4 PI Mutations		5+ PI Mutations
< 34	52% (12/23)		37% (7/19)
≥ 34	72% (28/39)		73% (43/59)

GIQ:

The results of the GIQ analyses are shown in Table 17. Similar to the IQ and Cmin analyses response rates increased as the GIQ increased. Overall, the response rate was 34% for patients with a GIQ < 7.8 compared to 62% for patients with a GIQ ≥ 7.8. As stated previously the ranges used for the IQ, Cmin and GIQ analyses are not definitive "breakpoints." These data are exploratory and provide preliminary information the likelihood of virologic success based on pretreatment susceptibility and TPV Cmin values in PI-experienced patients.

Table 17: Proportion of Responders (confirmed 1 log decrease at Week 24) by GIQ (Cmin/# FDA Mutations)

GIQ	TPV N=301		
	All	**No T20**	**+ T20**
Median = 7.8			
< 7.8	34% (83/124)	32% (63/195)	43% (20/46)
≥ 7.8	62% (151/244)	54% (81/150)	74% (70/94)
Quartiles			
0.33 – 4.97	30% (36/11)	29% (30/103)	32% (6/19)
>4.97-7.8	40% (48/120)	36% (33/92)	54% (15/28)
>7.8- 11.85	59% (73/123)	44% (34/76)	83% (39/47)
>11.85	64% (77/120)	64% (47/74)	65% (30/46)

ASSESSMENT

In addition to the analyses conducted for baseline resistance and outcome, I reviewed the virology report and integrated summaries of efficacy and safety. With respect to clinical virology, BI is commended for the various resistance analyses presented in the NDA, particularly of their review of the phase II resistance data and novel methods to determine TPV specific mutational scores. The phase II studies showed reduced response rates to TPV/r when more than two baseline PI mutations were present at positions 33, 82, 84 and 90. Mutations at positions 82, 84 and 90 are also associated with high level resistance to currently approved PIs. As a result, this information was used to develop exclusion criteria in phase III trials. In RESIST 1 and 2, no more than two mutations at positions 33, 82, 84 or 90 were permitted. By limiting the number of these mutations, BI attempted to ensure all patients, regardless of randomized treatment, had a reasonable change of virologic response. Early determination of the effect of baseline genotype and phenotype for new investigational agents is important for patient selection into clinical trials thus stressing the need for comprehensive phase II development programs.

Another important clinical virology factor was a protocol amendment to allow for the inclusion of patients who were resistant to all available PIs. Of note, the available assays to determine resistance are largely based on unboosted PI data. The possibility exists patients may derive partial activity with treatment of a RTV-boosted PI even though a standard genotype resistance reports suggests resistance. As a result the decision to include these patients in trials is reasonable given these limitations and is consistent with clinical management of patients.

In addition, genotypic resistance testing was used to stratify patients according to pre-selected protease inhibitors (APV/r, IDV/r, LPV/r, SQV/r). For the purpose of stratification, protease inhibitor sensitivity was interpreted from genotypic reports as not resistant, possibly resistant or resistant. The statistical reviewer conducted subgroup analyses based on these stratification factors in order to determine the consistency of the treatment effect of TPV/r over CPI/r in different subgroups and between RESIST 1 and RESIST 2 trials. These analyses are important in the evaluation of clinical trials; however, the following information is also important when interpreting the results as presented by Dr. Rafia Bhore in advisory committee backgrounder.

Determinations of resistance differed between RESIST 1 and 2 and are based on two different methods. In RESIST 1, the TruGene assay was used whereas for RESIST 2 the Virtual Phenotype assay was used. Differences noted between the two studies in Dr. Bhore's review are likely attributed to the algorithms used to determine resistance. In addition, the Virtual Phenotype cut-offs used to determine the resistance strata are largely based on unboosted PI data and the interpretation of "possibly resistant" to individual RTV-boosted PIs is controversial. Of note, the analyses conducted by Dr. Bhore were for the purpose of evaluating stratification variables and virologic response. In the clinical virology reviews one algorithm was used to determine the impact of baseline genotype and outcome. The FDA mutation definition for baseline genotype and outcome analyses was used for both RESIST 1 and 2 and applied to both treatment groups.

In RESIST 1, only 8% were interpreted as not resistant to the pre-selected PI, 35% were interpreted as possibly resistant and 58% were interpreted as resistant to the pre-selected PIs. In comparison, 20% were interpreted as not resistant, 6% as possibly resistance and 74% as resistant to the pre-selected protease inhibitors in RESIST 2. The possible explanation for the differences between the two studies is the different assays used for the interpretation. I do not believe that this interpretation of resistance by genotype for this highly experienced patient population receiving RTV-boosted PI's is optimal and thus I did not use these stratification criteria for resistance analyses. As stated above, the primary reason for not using these stratification variables in the clinical virology analyses is that different algorithms for assessing resistance were used in RESIST 1 and 2.

In addition, we were unable to make definitive efficacy conclusions for this subgroup analysis because of the limited number of patients in the "not resistant" group. In the subgroup of patients for whom the pre-selected PI was not resistant to the HIV, the treatment difference between TPV/r and CPI/r was not consistent between RESIST 1 (-4.8%) versus RESIST 2 (15.4%). However, the result of the subgroup of patients with possible/definite resistance to PIs was consistent with the overall results for the primary efficacy endpoint (treatment effect of 19% to 20%).

CONCLUSIONS

The data shown in this consult review provide evidence of the antiviral efficacy of TPV/r compared to CPI/r. Overall, the analyses conducted by FDA and BI are consistent and complementary. Regardless of the endpoint used for these analyses, the response rates were greater for the TPV/r treatment arm compared to the CPI/r arm. Regardless of the number of baseline PI mutations or T20 use, the TPV/r arm had approximately 20% more responders by the primary endpoint (confirmed 1 $\log_{10}$ decrease at Week 24) and greater declines in viral load by median DAVG24 than the CPI/r arm. Response to TPV/r is reduced if five or more PI mutations are present at baseline or TPV baseline susceptibility is greater than three fold.

RECOMMENDATIONS :

Based on the results of the analyses conducted above, I recommend the following for the package insert. Please refer to Dr. Naeger's review for the final Microbiology section of the package insert.

1. Inclusion of a table displaying the proportion of responders by number of baseline PI mutations. Please refer to the Table below for an example.

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

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

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

2. A summary (in lieu of a graphic display) of median change from baseline in HIV RNA at weeks 2, 4, 8, 16, and 24 by the number of baseline PI mutaions (1-4 and $\geq$ 5) in subjects who received TPV/r with or without enfuvirtide.

3. Inclusion of table displaying the proportion of responders by number of baseline phenotype. Please refer to the Table below for an example. In addition, inclusion of relationships between baseline phenotypic susceptibility to tipranavir, mutations at protease amino acid codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response is recommended.

Proportion of Responders by Baseline TPV phenotype

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

_____
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APPENDIX A

Censoring Rules for primary endpoint

From the resistance datasets provided by BI, the column variables TRESPDC and TEXPL columns were used to identify patient outcome classifications.

Included the following in the analyses (did NOT censor) -

- Responders
- Virologic Failures
- Discontinuations Before Achieve Viral Suppression
    - Patients with HIV RNA data through week 16 and/or 24
    - Patients with HIV RNA data only through week 8 and did not achieve at least 0.5 log decrease in HIV RNA. The 0.5 log criteria used was based on the rollover criteria for study 1182.17 where patients were allowed to enroll if they did not achieve at least 0.5 log decline in HIV RNA)
- Other
    - Added new ARV: (also see chart below)
        - nRTI in class substitution regardless of time (see chart below)
    - TEXPL categories - No VR prior to: or Unconfirmed VR prior to:
        - Patients with HIV RNA data only through week 8 and did not achieve at least a 0.5 log decrease in HIV RNA.
        - Patients with HIV RNA data through week 16 and/or 24
- "Blank" - n=7 patients from RESIST 2 with week 24 data - included the following patients pt ID 1601 (responder), 5096, 6279, 7140 (responder), 9039, 9149, 9151

Censored:

- "BLANK" (no information in either TRESPDC and TEXPL - these patients are from RESIST 2 who did not reach week 24 - only week 16 data available)
- Other –
    - Add new ARV: patients were censored for the following reasons
        - Added new ARV
        - Change in PI, including change to TPV
        - Added therapeutic dose of RTV
    - TEXPL categories: No VR prior to: or Unconfirmed VR prior to
        - Patients with no week 8-24 data (D/C between Week 0-4)
        - Patients with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 log decrease
- D/C While Suppressed
- D/C Before Achieve Viral Suppression:
    - Patients with no week 8-24 HIV RNA data (D/C between Week 0-4)
    - Patients with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 log decrease

Overall number of patients in Resistance dataset from BIPI	**1482**
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:	324

FDA dataset and reasons for censoring/
Differences from BIPI dataset

Overall Number in BIBPI dataset	1482
Overall number of patients in Resistance dataset from FDA	1015
FDA Censored	467
Reasons for Censoring	
D/C While Suppressed Category	61
D/C before achieve viral suppression category	
• Patients with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8	5
• Patients with no week 8-24 HIV RNA data (D/C between weeks 0-4)	45
Other Category	
• Added new ARV or changed PI	28
• Patients with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8	11
"BLANK" Category (RESIST 2 patients censored because did not have week 24 data)	317
FDA Included the following	
Responders	349
Failures	152
D/C While Suppressed	0
D/C Before achieve viral suppression	229
Other	278
"Blank" RESIST 2 patients – included 7 in this category because they had HIV RNA data at week 24	7

Censoring Rules for DAVG and Mean Change analyses

From the resistance datasets provided by BI, the column variables TRESPDC and TEXPL columns for used to identify patient outcome classifications.

Included the following categories in the analyses (did NOT censor) -

- Responders
- Virologic Failures
- "BLANK" (note: no information in either TRESPDC and TEXPL column variables - these patients are from resist 2 who did not reach week 24 - only week 16 data available)
- D/C While Suppressed
- D/C Before Achieve Viral Suppression (censored patients if week 8, 16 and 24 values were missing; otherwise these patients were included in the analyses – 234/279 patients in this category were included)
- Other - included the following categories
    - unconfirmed VR prior to: ...
    - No VR prior to:...
    - Add new ARV:
        - nRTI in class substitution regardless of time (see chart below)

Censored:

- D/C Before Achieve Viral Suppression (censored patients if week 8, 16 and 24 values were missing; otherwise these patients were included in the analyses – 45 patients in this category were censored)
- Other – Add new ARV: patients were censored for the following reasons
    - Added new ARV
    - Change in PI, including change to TPV
    - Added therapeutic dose of RTV

Overall number of patients in Resistance dataset from BIPI	1482
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:	324

FDA dataset and reasons for censoring/
Differences from BIPI dataset

Overall number of patients in BIPI dataset	1482
Overall number of patients in FDA resistance dataset	1409
FDA censored	73
Reasons for Censoring D/C before achieve viral suppression category • Patients with no week 8-24 HIV RNA data (D/C between weeks 0-4) Other Category • Added new ARV or changed PI	 45 28
FDA Included the following	
Overall number of patients in Resistance dataset from FDA	1409
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression • **45** had no week 8-24 HIV RNA data • censored **28**/43 who added new ARV or changed PI; remaining 15 patients had nRTI in class substitution	234
Other	289
"Blank:	324

Appendix B

Median Change in HIV RNA From Baseline by Number of Baseline Mutations#

Median Change HIV RNA from baseline	TPV 1-4			TPV 5+		
	All N=398	No T20 N=328	+ T20 n=70	All N=303	No T20 N=215	+ T20 n=88
Week 2	-1.35 (378)	-1.24 (311)	-1.57 (67)	-1.51 (288)	-1.33 (204)	-1.78 (84)
Week 4	-1.58 (284)	-1.51 (315)	-1.88 (69)	-1.55 (289)	-1.28 (204)	-2.13 (85)
Week 8	-1.62 (387)	-1.54 (318)	-2.05 (69)	-1.19 (297)	-0.87 (211)	-2.08 (88)
Week 16	-1.59 (365)	-1.43 (297)	-2.06 (68)	-0.74 (289)	-0.54 (201)	-1.79 (83)
Week 24	-1.39 (262)	-1.25 (199)	-2.12 (63)	-0.70 (211)	-0.43 (136)	-2.21 (75)

Median Change HIV RNA from baseline	CPI 1-4			CPI 5+		
	All n=381	No T20 n=315	+ T20 N=66	All N=322	No T20 N=258	+ T20 n=64
Week 2	-0.97(352)	-0.87 (291)	-1.49 (61)	-0.38 (304)	-0.35 (244)	-0.95 (60)
Week 4	-0.93 (358)	-0.85 (294)	-1.45 (64)	-0.25 (312)	-0.24 (252)	-0.25 (60)
Week 8	-0.69 (363)	-0.55 (298)	-1.23 (65)	-0.22 (311)	-0.20 (249)	-0.24 (62)
Week 16	-0.64 (308)	-0.55 (254)	-1.39 (54)	-0.25 (242)	-0.22 (194)	-0.55 (48)
Week 24	-0.79 (173)	-0.73 (131)	-1.59 (42)	-0.45 (110)	-0.36 (62)	-0.66 (28)

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

APPENDIX C
Additional Exploratory Analyses

Mean and Median change in HIV RNA by Baseline Number of PI mutations–On Treatment Analyses

Number of Baseline PI mutations#	Wk	TPV			CPI		
		All	No T20 Use	T20 Use	All	No T20 Use	T20 Use
0	2	-0.74 (5) -1.02	None		-0.63 (4) -0.38		
	4	-0.13 (6) -0.28			-0.34 (3) +0.12		
	16	-0.27 (4) -0.24					
	24	-0.0 (2) -0.09			-0.98 (2) -0.98	-1.42 (1)	-0.53 (1)
	24 - LOCF	-0.19 (5) -0.18			-0.33 (5) -0.08		
1	2	-1.24 (48) -1.21	-1.14 (42) -1.10	-1.9 (6) -1.74	-1.1 (41) -1.18		
	4	-1.35 (48) -1.42	-1.24 (42) -1.39	-2.08 (6) -1.99	-1.05 (41) -1.31		
	16	-1.51 (42) -1.72	-1.49 (37) -1.68	-1.66 (5) -1.76			
	24	-1.68 (23) -1.69	-1.60 (19) -1.49	-2.04 (4) -2.15	-1.26 (18) -1.33	-1.26 (18) -1.33	NONE
	24 - LOCF	-1.34 (34) -1.35	-1.25 (28) -1.29	-1.77 (6) -2.13	-0.79 (38) -0.52		
2	2	-1.26 (107) -1.27	-1.26 (90) -1.24	-1.25 (17) -1.64	-1.04 (110) -1.09		
	4	-1.37 (107) -1.58	-1.38 (90) -1.60	-1.29 (17) -0.72	-1.16 (110) -1.18		
	16	-1.53 (99) -1.67	-1.46 (81) -1.63	-1.85 (18) -2.16			
	24	-1.55 (77) -1.56	-1.42 (61) -1.41	-2.06 (16) -2,.99	-1.28 (58) -1.06	-1.22 (44) -1.13	-1.46 (14) -0.67
	24 – LOCF	-1.47 (88) -1.34	-1.35 (71) -1.09	-1.93 (18) -2.35	-0.97 (90) -0.50		
3	2	-1.30 (222) -1.45	-1.23 (175) -1.36	-1.56 (47) -1.74	-0.82 (227) -0.85		
	4	-1.45 (227) -1.67	-1.36 (178) -1.51	-1.77 (49) -2.11	-0.81 (228) -0.53		

	16	-1.37 (219) -1.23	-1.24 (170) -1.01	-1.80 (49) -2.16			
	24	-1.46 (153) -10.8	-1.25 (106) -0.82	-1.75 (47) -2.16	-1.09 (100) -0.68	-0.87 (75) -0.61	-1.74 (25) -1.82
	24 – LOCF	-1.32 (182) -1.08	-1.14 (133) -0.82	-1.81 (49) -2.13	-0.64 (192) -0.34		
4	2	-1.28 (214) -1.42	-1.18 (159) -1.28	-1.57 (55) -1.72	-0.65 (209) -0.50		
	4	-1.31 (217) -1.56	-1.22 (162) -1.51	-1.60 (55) -1.87	-0.66 (208) -0.35		
	16	-1.21 (208) -0.73	-1.02 (158) -0.51	-1.81 (50) -1.80			
	24	-1.18 (157) -0.65	-0.96 (113) -0.45	-1.73 (44) -1.81	-0.79 (75) -0.46	-0.77 (53) -0.46	-0.85 (22) -0.53
	24 – LOCF	-1.13 (188) -0.53	-0.90 (135) -0.41	-1.72 (53) -1.91	-0.39 (173) -0.18		
5	2	-1.23 (77) -1.38	-1.12 (52) -1.21	-1.46 (25) -1.78	-0.55 (80) -0.28		
	4	-1.28 (74) -1.33	-1.08 (49) -0.96	-1.67 (25) -1.90	-0.45 (84) -0.23		
	16	-1.34 (73) -0.84					
	24	-1.42 (58) -1.23	-1.10 (35) -0.70	-1.88 (23) -2.34	-0.71 (31) -0.44	-0.49 (23) -0.36	-1.34 (8) -1.17
	24 – LOCF	-1.28 (65) -0.90	-1.00 (40) -0.62	-1.75 (25) -1.68	-0.39 (88) -0.18		
6	2	-1.46 (16) -1.64	-1.46 /99) -1.65	-1.47 (7) -1.64	-0.34 (9) -0.06		
	4	-1.37 (16) -1.54	-1.41 (8) -1.70	-1.33 (8) -1.32	-0.37 (10) +0.11		
	16	-1.32 (16) -1.25	-1.08 (9) -0.77	-1.63 (7) -1.70			
	24	-1.30 (12) -1.04	-0.64 (7) -0.46	-2.08(6) -2.76	-1.11 (3) +0.06	-1.11 (3) +0.06	NONE
	24 – LOCF	-1.25 14) -0.82	-0.64 (7) -0.46	-1.85 (7) -2.67	-0.45 (9) +0.11		

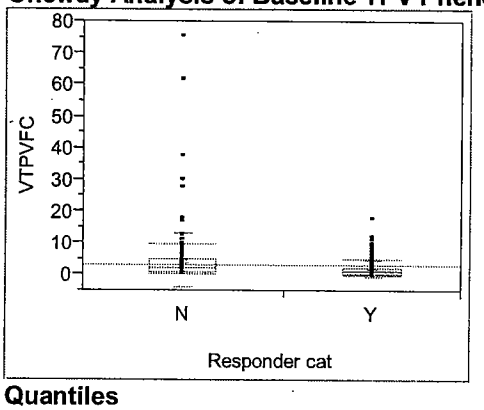
7+	2	-0.94 (5) -0.83	-0.70 (4) -0.64	-1.89 (1)	-0.46		
	4	-0.83 (5) -0.77	-0.75 (4) -0.70	-1.17	-0.92		
	16	-0.38 (5) -0.42	-0.30 (4) -0.29	-0.72 (1)			
	24	-0.13 (3) +0.19	+0.21 (2) +0.21	-0.8	-0.65 (1)	NONE	-0.65 (1)
	24 - LOCF	-0.14 (4) +0.01	+0.08 (3) +0.19	-0.8	-0.53		

#FDA definition: D30N, V32I, M46I/L, I47V, G48V, I50V, F53L, I54V, V82A/F/T/S, I84V, N88D/S, L90M

LOCF = last observation carried forward

APPENDIX D

Oneway Analysis of Baseline TPV Phenotype (VTPVFC) By Responder category



Quantiles

Level	Minimum	10%	25%	Median	75%	90%
N	0.2	0.6	1.1	2.1	5.1	8.44
Y	0.1	0.3	0.6	1.3	2.5	5.46

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
N	167	4.62934	8.67934	0.67163	3.3033	5.9554
Y	146	2.20548	2.69888	0.22336	1.7640	2.6469

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