Rash-
MO Comment: *On analysis of the datasets provided by the applicant, the types of rash varied; five were reported as rash with no other description, one was described as maculopapular and one was described as erythematous and macular. Of significance one subject in the low dose group reported angioneurotic edema and facial edema, one subject the high dose group reported facial edema, and two subjects in the high dose group had photosensitivity reactions. The remaining two skin AEs were pruritis and skin discoloration. These results suggest that a hypersensitivity reaction with facial swelling may be associated with TPV use. In addition, TPV is a sulfonamide, so it is not surprising that photosensitivity reactions have been reported with its use. However, the small number of subjects that needed to hold or stop TPV suggests that the skin AEs were not severe in most patients developing a rash.*

A high percentage of subjects in 1182.2 reported rash.

Other characteristics of the skin AEs are shown in the following Table 6.

Table 6: Rash AEs in Trial 1182.2

	Low Dose	High Dose
# of females/total # of subjects	4/19	5/22
# of subjects with any skin AE	8	6
Held or d/c TPV due to skin AE	0	1
# of females with skin AE	3	3
# of subjects with any rash	4	3
# of females with rash	0	0

[Source: Demographics, AE and exit datasets submitted by sponsor on 12/29/04]

Although females only represented 22% of the study population, 43% of the skin AEs were reported in women. The female predisposition was for all skin AEs but not for rash alone. The number of subjects with rash was small and results therefore must be viewed with caution.

SAEs
Five (5) subjects had 8 SAEs. One subject in the low dose group had two SAEs (both chest pain) and required hospitalization for each episode. A subject in the high dose group required hospitalization for myocardial infarction. No other subjects required hospitalization for an SAE. Subject 262 had three separate SAEs at two distinct time points: CMV infection with onset on day 59 and fever and diarrhea with onset on day 220. The other SAEs were avascular necrosis of the femoral head and sinusitis.

A) AEs leading to study discontinuation

Two subjects (1 in each treatment group) experienced AEs that led to study discontinuation. One subject in the low dose group experienced Grade 4 elevated GGT approximately 3.5 months after starting study treatment. A subject in the high-dose group was withdrawn from the study due to severe dizziness, diarrhea, nausea, tachycardia, and vivid dreams and vomiting.

B) Deaths

No deaths were observed during the course of this study.

C) Laboratory AEs

The most frequently observed clinically significant laboratory abnormality was increased GGT, which was reported in 39% of study subjects. Other frequently observed clinically significant laboratory abnormality were increased triglycerides (27%) and increased ALT in (23%) of the total subjects. The percentage of subjects with clinically significant TG elevations was higher in the low dose group. The median time to the development of elevations of TG, AST, and ALT levels were related to the dose of TPV administered, i.e subjects in the high dose group developed these abnormalities in a much shorter period of time.

MO Comment: *Since hepatotoxicity has been observed throughout the TPV development program, datasets were examined for evidence of liver toxicity in trial 1182.2.*

Table 7: Analysis of Hepatotoxicity in Trial 1182.2

	Low Dose n=19	**High Dose n=22**
# HBsAg +	3	0
#HCV Ab+	3	4
#HBV/HCV coinfected*	2	0
# of subjects w/ ALT ≥ Grade 1 at BL	6	5
# of subjects w/ Grade 3 ALT#	1	3
#of subjects w/Grade 4 ALT#	2	2
coinfected and Gr 3 or 4 ALT	1	0
% of subjects w/Gr 3 or 4 ALT	16%	23%
Median days to max ALT	138	57.5
Median maximum ALT and range	482 250-734	483 284-1128
Study drugs held 2° hepatotoxicity	1	4
Premature d/c 2° hepatotoxicity	1	0

[Source Data: AE, demographics, and exit datasets submitted 12/29/04.]

The frequency of hepatotoxicity as measured by increases in ALT was 16% in the low dose arm and 23% in the high dose arm. In addition,

hepatotoxicity appeared to occur earlier in the high dose group and at higher maximum values than in the low dose group. These findings imply that hepatotoxicity is dose related with hepatotoxicity observed more frequently, earlier, and more seriously in the high dose group. In addition, four subjects in the high dose group had to temporarily discontinue TPV/r due to hepatotoxicity compared to one in the low dose group.

- *Creatinine*

Only one subject with Grade 2 creatinine elevation was identified in trial 1182.2. This subject had a creatinine level of 2.4 at baseline, but increased to 3.7 on day 699.

F. CONCLUSIONS

Use of TPV/r in combination with EFV and a NRTI in a NNRTI-naïve but protease inhibitor experienced study population resulted in a more than two log decrease in viral load. However, the relative contribution of TPV over EFV cannot be determined. In addition, no dose related difference in efficacy was identified between TPV high dose vs low dose arms which also may have been related to the small number of subjects.

The numbers and types of adverse events reported in this study were similar to those observed in other studies of TPV, namely GI AEs, particularly diarrhea, nausea, rash, increases in ALT. The frequency of diarrhea and of hepatotoxicity appeared to be related to TPV dose. Photosensitivity reactions were reported in two subjects; angioneurotic edema with facial swelling was also reported. Patients receiving TPV should understand that it is a sulfonamide and therefore its use may be associated with photosensitivity reaction, with rash, and possibly with a hypersensitivity-type of reaction.

[3] Individual study report 1182.4

A. STUDY DESIGN

Trial 1182.4 was a Phase II, open-label, randomized, multicenter safety and antiviral activity study in HIV infected adults who had previously failed a single PI-containing regimen. A total of 75 subjects (25 per arm) were randomized in a 1:1:1 ratio to receive two NNRTIs plus low dose TPV/r (500/ 100 mg), high dose TPV/r (1250/ 100 mg), *or* SQV/r (400 mg / 400 mg). The study duration was initially 24 weeks, but was later modified for up to 96 weeks. The TPV SEDDS or the (**S**elf-**E**mulsifying **D**rug **D**elivery **S**ystem), the proposed marketed formulation was used.

> ***MO Comment:*** *SQV and RTV in combination have been approved by FDA for the treatment of HIV infection, but at a much lower RTV dose: SQV 1000 mg with RTV 100 mg twice daily. The approval was based on a study of 148 treatment-naïve and treatment experienced subjects. 61% subjects had a VL < 400 copies/mL at 48 weeks. (SQV package insert). However the comparator used in trial 1182.6 was SQV/r 400/400 mg bid, which resulted in lower saquinavir but higher ritonavir exposures than the approved dose. Therefore, it is possible that toxicity associated with the RTV dose used in the SQV/r arm in 1182.4 was increased compared to either the approved dose of SQV/r or the doses used to boost TPV in 1182.4.*

Study subjects were required to have failed one PI-containing regimen and have 2 new NRTI options available. There was no limit on the CD4 cell count at entry but plasma HIV-RNA had to be > 1,000copies/mL.

The primary objectives of the trial were 1) to compare the safety and antiviral activity of low and high dose boosted TPV with two NRTIs and 2) to compare the safety and activity of TPV/r with SQV/r when both were administered with two NRTIs for 24 weeks. Additionally, the PK profile of TPV was assessed at 2, 4, 8, 16 and 24 weeks of treatment.

B. STUDY RESULTS

1. Study Population

a. *Baseline characteristics*

This was a multinational, multicenter trial with 26 participating sites: 23 in the United States, 2 in France and 1 in Italy. The majority of subjects were male 78.5% (62/79). The median age was 39 years. The racial composition of the study population was fairly heterogenous, with 40.5% of subjects black, 49.4% white, 7.6% unknown, and 2.5% mixed. Treatment arms were similar in demographic characteristics. (See Table 8 below), with the exception of race, with TPV/r 1250/100 mg arm having 64% (16/25) white subjects compared with 44% (11/25) for TPV 500 mg/RTV 100 mg and 41.4% (12/29) for SQV 400 mg/RTV 400 mg.

Table 8: Baseline Demographic and Disease Characteristics in Trial 1182.4

	TPV/r 500mg/ 100 mg	TPV/r 1250 mg/ 100 mg	SQV/r 400 mg/ 400 mg	Total
Total treated	25	25	29	79
Age [years]				
Median	39.00	39.00	38.00	39.00
Range	30-50	29-56	20-56	20 - 56
Gender [N (%)]				
Male	19 (76.0)	21 (84.0)	22 (75.9)	62 (78.5)
Female	6 (24.0)	4 (16.0)	7 (24.1)	17 (21.5)
Race [N (%)]				
White	11 (44.0)	16 (64.0)	12 (41.4)	39 (49.4)
Black	12 (48.0)	7 (28.0)	13 (44.8)	32 (40.5)
Asian	0	0	0	0
Missing	2 (8.0)	2 (8.0)	4 (13.8)	8 (10.1)
Median CD4+ cell count [cells/mm3]	290	233	369	
Median Baseline HIV-1 RNA ($\log_{10}$ copies/mL)	4.45	4.35	4.18	

[Source Data: Clinical Trial Report for Trial 1182.4.]

As shown in the Table 8 above, there was also wide variation in the baseline CD4+ cell count, ranging from a 233cells/mm^3 in the high dose TPV/r arm to 369 cells/mm^3 in the SQV/r treatment arm. However, baseline HIV-1 RNA values were comparable between the arms.

MO Comments:

1) The number of study participants per study arm were small (range =25-29), but there was large proportion of females (21.5%) and non-white (40.5 %), study participants. This proportion of non-white and female subjects better approximates the distribution of HIV disease in the external population at large compared to many of the studies of TPV. Clinical trials are best designed to mirror or mimic to demographics of the population in which this drug will be eventually used.

2) The patient population was heterogeneous at baseline with respect to baseline CD4+ cell counts. The heterogeneity at baseline and the modest sample size of this trial lead to an underpowered comparison between treatment groups.

3) This is the only Phase II study with an active control arm, which allows for comparison of TPV/r with a previously studied boosted PI. Although the comparator PI was administered at a different dose than approved, there are other published studies, which used the SQV/r dose administered in this trial.

b. Treatment history

All 79 treated subjects in Trial 1182.4 had previously taken ARV medications. The most common were NFV (64.6%), 3TC (59.5%), d4T (53.2%), and ZDV (45.6%).

c. Resistance history

The 3 treatment groups differed significantly (P = 0.004) in the median number of protease gene mutations at baseline, with 10 mutations the TPV/r 500/100 mg group, 7 in the TPV/r 1250/100 mg group and 6.5 in the SQV/r 400 /400 mg group.

MO Comment: *It should be noted that among the treatment groups, there were significantly fewer PI mutations at baseline in the SQV/r group. This could have produced a bias in favor of SQV.*

2. Subject Disposition

Trial 1182.4 was prematurely terminated on July 12th 2001 after 79 subjects were randomized, because of difficulty in enrolling subjects in the study. All subjects receiving TPV/r and those experiencing virologic failure on SQV/r were eligible to enter the rollover trial, Trial 1182.17.

Of the 79 subjects who received treatment, 46 subjects completed the first 24 weeks of treatment. Of the 33 subjects withdrawing by 24 weeks: 12 subjects withdrew because of AEs; 9 subjects because of lack of efficacy (equally distributed among all study groups); 6 subjects were lost to follow up; 5 subjects withdrew consent and 3 were protocol violations.

A total of 7 subjects completed 96 weeks of treatment. 30 of the 79 subjects (38.0%) rolled over to Trial 1182.17 from Trial 1182.4 including 29 subjects from the TPV/r arms and 1 from the SQV/r arm. (See Table 9 below).

Table 9: Showing Disposition of Subjects in 1182.4

	TPV/r 500/100mg # (%)	TPV/r 1250/100mg # (%)	SQV/r 400/400mg # (%)	TOTAL # (%)
Subjects who completed week 24	16 (64)	16 (64)	14 (48)	46 (58.2)
Subjects who entered extended treatment after week 24	14 (56)	16 (64)	12 (41)	42 (53)
Subjects who completed week 48	10 (40)	15 (60)	5 (17)	30 (38)
Subjects who completed week 96	1 (4)	5 (20)	1 (3)	7 (8.9
Reason for Withdrawal				
Trial Terminated	11 (44)	11 (44)	7 (24)	29 (37)
AE	3 (12)	3 (12)	6 (21)	12 (15)
Lack of Efficacy	3 (12)	3 (12)	3 (10)	9 (11)
Lost to Follow-up	2 (8)	1 (4)	3 (10)	6 (8)
Consent Withdrawn	0	1 (4)	4 (14)	5 (6)
Protocol Violation	2 (8)	0	1 (3)	3 (4)

[Source Data: Appendix 16.1.9.2, Table 1.1: Appendix 16.2 LISTING 1.1]

C. PHARMACOKINETIC ANALYSIS

Please see Dr Derek Zhang's review.

Plasma TPV concentrations were collected from subjects at 2, 4, 8, 16, 20 and 24 weeks over the time period just after TPV/r drug administration to approximately 36 hours post-drug administration. A total of 94 samples were collected from 20 subjects, over the course of 24 weeks.

Concentrations of ritonavir for the higher dose group, TPV/r 1250/100 mg were substantially lower when compared to the TPV/r 500/100 mg group. This decrease may be attributed to CPV3A induction by the 1250 mg dose of TPV, which results in increased metabolism of RTV.

D. ANALYSIS OF EFFICACY

The primary efficacy endpoints were:

1. Change in HIV-1 RNA from baseline to weeks 16, 24, and 48.
2. Proportion of subjects with HIV RNA < 400 copies/mL and < 50 copies /mL
3. Proportion of subjects with ≥ 1 $\log_{10}$ decrease in HIV RNA from baseline

Secondary efficacy endpoints were:

1. Change in CD4+ cell counts from baseline to weeks 16, 24 and 48
2. Time to virological failure

The virologic and immunologic responses at week 24 are shown in the Table 10 below.

Table 10: Median Change in HIV RNA and CD4+ Cell Count from Baseline to 24 Weeks in Study 1182.4

	HIV RNA ($\log_{10}$ copies/ml)					CD4+ cell count (cells/mm^3)	
	Baseline	VL change from BL	% with ≥ 1 $\log_{10}$ ↓	% with <400 copies/ mL	% with <50 copies/ mL	Baseline	Change in CD4 cell count
TPV/r 500/100 n=25	4.45	-1.41	43.5	39.1	17.4	290	+79.5
TPV/r 1250/100 n=25	4.35	-1.36	58.3	29.2	20.8	233	+63.0
SQV/r 400/400 n=29	4.18	-1.75	25.0	25.0	14.3	369	+19.5

[Source Data: Appendix 16.1.9.2]

A treatment response was observed in all three cohorts. Although, the decrease in viral load at 24 weeks was slightly better in the SQV/r arm (1.75 $\log_{10}$ copies/mL) compared to the TPV/r arms (-1.41 and -1.36 $\log_{10}$ copies/mL), the proportion of subjects with undetectable viral loads and the increases in CD4+ cell counts were higher in the TPV/r arms than the SQV/r arm. At 48 weeks,

the reduction in VL was not sustained by the low dose TPV group (-0.50 $\log_{10}$ copies/mL), and decreased in the higher dose TPV/r group (-0.88 $\log_{10}$ copies/mL), but was maintained in the comparator SQV/r dose group (-1.41 $\log_{10}$ copies/mL).

> ***MO Comment:*** *TPV/r undoubtedly has short term efficacy activity, however the lack of durability of TPV/r over the long term (at 48 weeks) was also noted in the other Phase II dose trials; The absence of durability in some of these studies may be related to TPV's use as functional monotherapy in populations with multi-resistant HIV infection or to suboptimal TPV dosing in some study arms.*
> *The trial population was heterogenous with respect to baseline CD4 cell counts; it is possible that the smaller CD4+cell response in the SQV/r arm was related to the higher baseline CD4+ count.*

E. ANALYSIS OF SAFETY

Safety endpoints: The primary safety end points were: the number of treatment emergent and drug-related AEs and the number of Grade 3 and 4 laboratory abnormalities. The secondary safety end points were change from baseline in laboratory values of blood glucose, cholesterol, HDL and triglycerides (lipid profile).

1) Exposure to study drug
The median duration of exposure varied by treatment group and was longest for the TPV/r high dose (1250 mg/100 mg) group (450 days) compared to the TPV low dose group (253 days) and the SQV/r group (149 days).

> ***MO Comment:*** *The higher dose was not tolerated as well as in other studies. Therefore, this finding is surprising and may be because the study only lasted for 28 days.*

Adverse Events
Of the 79 subjects treated, 93.7% reported 1 or more AEs during the study. AEs were primarily observed in the gastrointestinal system (70.9%) of subjects; other organ systems commonly involved included infections and infestations (45.6%), general disorders and administrative site conditions (41.8%), nervous system disorders (32.9%), skin and subcutaneous tissue disorders (30.4%), metabolism and nutrition disorders (22.8%), and investigations (22.8%).
The most commonly reported AEs are shown in the Table 11 below.

Table 11: Adverse Events Reported in >10% of Subjects in Any Treatment Group in Study 1182.4

	High Dose TPV/r N=25	Low Dose TPV/r n=25	SQV/r n=29
Nausea	44%	16%	17%
Vomiting	40%	4%	10%
Diarrhea	36%	20%	24%
Fatigue	24%	4%	10%
Pyrexia	24%	8%	
Insomnia	16%	0	
Abdominal pain	12%	0	
Headache	0%	12%	0%

[Source Data: Appendix 16.1.9.2]

AEs were observed at a 10% or greater difference between the TPV/r arms with a higher percentage in the high dose group included vomiting, nausea, abdominal pain, hyperlipidemia, pyrexia, insomnia, and pruritis. Headache was more common in the low dose group as compared to the high dose TPV group.

> ***MO Comment:*** *The RTV exposure was actually lower in the high dose TPV group than in the low dose group. This finding was also noted in the '1182.52 study. The AEs listed above were more common in subjects receiving high dose TPV compared to low dose, suggesting that these AEs may be related to the TPV dose. Certainly, a dose response for GI AEs has been reported in other studies of TPV. Similarly, the hyperlipidemia associated with higher doses of TPV has also been reported in other studies.*

When comparing the combined data for the high and low dose TPV/r groups to the SQV/r group, a considerably higher percentage (>10% difference) experienced rash (16.0% vs 3.4%) and headache (18.0% vs 3.4%), as compared to the SQV/r group. Pharyngitis was observed more frequently in the SQV/r group compared to the combined TPV/r groups (17.2% vs 6.0%).

GI adverse events, particularly diarrhea, were the most common AEs observed in subjects receiving TPV. Further analysis showed that diarrhea was most common during the first four weeks in all three treatment groups. However, the frequency of diarrhea was highest in the TPV/r 1250/100 mg arm at all time points after day 7. Nausea also typically occurred early; nausea more commonly occurred early in the high dose TPV group compared to the low dose group or the SQV/r group. Vomiting occurred more frequently in the TPV/r 1250/100 mg group (10 subjects) compared with the TPV 500 mg/RTV 100 mg group (1 patient) and again the onset of vomiting was earlier in the 1250 mg / 100 mg with the TPV 500 mg/RTV 100 mg group.

MO Comment: *GI adverse events are common with the use of TPV. In this study, the frequency of GI AEs was higher in the high dose TPV arm compared to the low dose arm. In addition, the GI AEs occurred earlier in the high dose arm.*

MO Comment- RASH: *Due to an increased frequency of rash noted in Phase 1 studies, particularly in females, the frequency of rash was analyzed in study 1182.4. As seen in the Table 12 below, skin AEs and rash were slightly more common in the TPV/r high dose arm than in the low dose or SQV/r arms. However, the number of subjects in each arm was small, and, therefore, no definitive conclusions can be reached from the data.*

Table 12: Skin Adverse Events in Trial 1182.4

	TPV/r 500/100 n=25	**TPV/r 1250/100 n=25**	**SQV/r n=29**
# of subjects with any skin AE	5	8	6
Held or d/c TPV due to skin AE	0	1	0
# of subjects with any rash	3	5	1
hypersensitivity reaction	1	2	3
Pruritis	0	1	1
skin disorder	0	0	1
skin discoloration	1	0	0

[Source Data: AE and exit datasets. Submitted 12/29/04.]

Six of the episodes of rash were not described further. Two subjects had maculopapular rashes and one had urticaria. There were three hypersensitivity reactions in the SQV/r arm and three in the TPV/r arms. Only one subject had to temporarily hold or discontinue study drug due to a skin AE. There were ten females in the TPV/r arms and none experienced a rash during study participation.

Subjects discontinuing study drug due to AE:
Twelve subjects (15.2% of all subjects) permanently discontinued study drugs due to AEs. Three (3) subjects (12.0%) in each TPV/r group and 6 (20.7%) in the SQV/r group. Two of the AEs lead to permanent discontinuation of study drugs, and were considered to be serious AEs (gastrointestinal hemorrhage in Patient #135 in the TPV/r 500/100 mg group and pancreatitis in Patient #325 in the SQV/r 400 /400 mg group).

MO Comment: *There were more discontinuations due to AEs in the SQV/r arm than either of the TPV/r arms; however, there was no one predominant AE leading to discontinuation in any of the arms. Across treatments there were more subjects with AEs leading to discontinuation*

because of Gastrointestinal Disorders compared with the other organ systems.

Severe Adverse Events, Serious Adverse Events and Deaths:

1. *Severe AEs:* Overall, the most frequently observed AE of severe intensity was nausea in 4 subjects (5.1%), followed by increased GGT, increased ALT, increased AST, gastrointestinal hemorrhage, and vomiting, each observed in 3 subjects (3.8% each). Severe nausea was observed in the high dose TPV/r arm and the SQV/r arm but not the low dose TPV/r arm. No distinct pattern was observed in the frequency of severe increased ALT and AST among the three groups.

2. *Serious AEs*: Twelve subjects experienced 18 SAEs during the trial: 5 subjects in each TPV/r group and 2 subjects in the SQV/r group. In the low dose TPV/r group, there was one suicide attempt, one non-specific GI disorder, one GI hemorrhage (see death summary below), one Drug Abuser, and a subject with pancreatitis, anemia, adrenal insufficiency, renal impairment, and non specific renal impairment. In the high dose TPV/r group, there was one case of GI hemorrhage, one case of elevated BUN, a non specific case of hepatitis, one case of non-specific pain, and one accident at home. In the SQV/r group, one case of depression with suicide attempt was reported, and one case of pancreatitis.

3. *Deaths*: One death occurred in this study in the TPV/r 500/100mg group. A 35 year old black male with a history of alcohol abuse, thrombocytopenia, and hematemesis received TPV/r/ZDV/ABC during study participation. Four days after discontinuing study drugs, he was hospitalized with a GI bleed, Candida esophagitis, and pancytopenia. In spite of aggressive treatment, he became comatose and died. Death was attributed to an intracerebral hemorrhage.

Laboratory Adverse Events:

The most common Grade 3 or 4 elevations in laboratory parameters were increased triglycerides (n=10), increased GGT (n=7), increased ALT (n=7) and decreased white blood cell counts (n=6). Grade 3 or 4 elevations were uncommon for AST (5), total cholesterol (3), platelets (1), total bilirubin (0), hemoglobin (0), and creatinine (0). The percentage of subjects with clinically significant AST and ALT elevations were similar in both TPV/r groups.

Increases in GGT and total bilirubin at Weeks 2 and 4 were significantly different among the three arms. At Week 4, subjects in the TPV/r 1250/100 mg regimen had a median increase in GGT from baseline of 22.5 U/L; while the median increase in the TPV/r 500/100 mg arm was 21.5 U/L. These elevations were significantly greater than a median increase of 4 U/L for subjects in the SQV/r arm. ($p < 0.01$). The percentage of subjects with clinically significant GGT values was higher in the TPV/r 500/100 mg group. No significant differences in change from baseline in AST and ALT among treatment regimens were observed at Weeks 2 and 4.

MO Comment: *The elevations in GGT levels may be explained by previous observations that show that administration of drugs that induce the CYP-450 enzyme system may cause elevated GGT levels. In addition, as would be expected in this patient population of subjects who had advanced HIV-1 disease and had received a prior PI-based regimen, over one-third of all the subjects (31/76, 40.8%) entered the study (Day 1 values) with elevated triglyceride values.*

Additional analyses of hepatotoxicity were performed by the clinical reviewers. These analyses are shown in the Table 13 below.

Table 13: Analysis of Hepatotoxicity in Trial 1182.4

	TPV/r 500/100 n=25	**TPV/r 1250/100 n=25**	**SQV/r 400/400 n=29**
#HBV or HCV coinfected*	1	3	9
# of subjects w/ ALT ≥ Grade 1 at BL	1	4	2
# of subjects w/ Grade 3 ALT#	3	2	1
#of subjects w/Grade 4 ALT#	0	1	1
coinfected and Gr 3 or 4 ALT	0	0	2
% of subjects w/Gr3 or 4 ALT	12%	12%	7%
Median maximum ALT and range	412 295-511	472 406-939	496.5 342-651
Increased GGT	2	0	0
Study drugs held 2° hepatotoxicity	1	2	0
Premature d/c 2° hepatotoxicity	1	1	0

[Source Data: AE, exit, and demographics datasets. Submitted 12/29/04.]

As shown in Table 13, the proportion of subjects with Grade 3 or 4 increases in ALT was identical in the two TPV/r arms and slightly lower in the SQV/r arm. Co-infection with HBV or HCV did not appear to place subjects at increased risk of subsequent increases in ALT in this analysis. However, the numbers are again so small to make any definitive conclusions from this study alone. The maximum ALT was highest in the high dose TPV/r arm. In addition, five subjects receiving TPV/r had to hold or discontinue their study drugs due to hepatotoxicity compared to none in the SQV/r arm.

F. CONCLUSION

Pharmacokinetic analyses in this study showed that RTV concentrations in the higher dose groups (TPV/r 1250/100mg) were substantially lower when compared to the TPV/r 500/100 mg group. This decrease may be attributed to CYP3A induction by the higher dose of TPV, which results in increased metabolism of RTV.
All three treatment groups in this trial, TPV/r 500/100 mg, TPV 1250 /r 100 mg, and SQV/r 400/400 mg, were effective in producing a decline in plasma HIV-1 RNA concentrations. There was no substantial difference between the three treatment arms. The study was not powered to detect for efficacy differences.

The overall safety profile of TPV co-administered with RTV was similar to that observed in previous tipranavir trials in both HIV-1-negative healthy volunteers and HIV-1-positive adults. Low dose TPV/r was easier to tolerate than high dose due to the increased frequency of GI adverse events in the high dose TPV/r group. The tolerability and safety profile of TPV/r was similar to that of SQV/r, however, there was an increased frequency of GI adverse events, rash, and hepatotoxicity in subjects receiving TPV/r compared to those receiving SQV/r.

[4] Individual study report 1182.6

A. STUDY DESIGN

The study was designed as an open label study to determine the effects of three dose combinations of TPV/r on the steady state of zidovudine, lamivudine, stavudine, abacavir, didanosine, nevirapine and efavirenz. Three doses of TPV/r were administered to HIV+ adults on stable 3-drug regimens that did not include PI's.

The three TPV/r doses were: TPV/r 1250/ 100mg, TPV/r 750/100 mg and TPV/r 250/200 mg. At entry, all subjects were taking standard doses, and had viral loads < 20,000 copies/mL.

TPV/r doses were administered to subjects in seven different ARV background regimens: ZDV/3TC/EFV, ZDV/3TC/NVP, d4T/3TC/EFV, d4T/3TC/EFV, d4T/3TC/EFV, d4T/3TC/NVP, d4T/ddI/EFV, d4T/ddI/NVP, and ZDV/3TC/ABC.

The study objective was to test the effects of 3 doses of TPV/r on the steady state PK of ZDV, 3TC, d4T, ddI, ABC, NVP and EFV in a patient population.

The study was conducted in 2 phases:

1) *Pharmacokinetic Study Period*
   The first phase was designed to obtain PK measurements for all subjects during the first 28 days of TPV/r. Intensive PK blood sampling for NRTI's and NNRTI's was performed predosing, and at specific intervals post dosing, as described in the PK section later in this report.

2) *Optional Safety Extension*
   This optional second phase/safety extension lasted 20 weeks, and was open to all subjects achieving <499 copies/mL or > 0.5 copies/mL VL reduction at 28 days.

A total of 208 HIV positive subjects were randomized sequentially into one of three cohorts. The first group received (**high dose**) TPV/r 1250 /100 mg bid (n= 58). The second (**middle group**) received TPV/r 750/100 mg bid (n= 63), and the third (**low dose group**) received TPV/r 250/200 mg bid (n= 87).

B. STUDY RESULTS

1. Study Population

   a. Baseline characteristics

   The study population consisted of 173 males (84.1%), and 33 females (15.9%), and 164 (78.8%) white subjects, and 43 (20.7%) black subjects. The median baseline CD4 cell count was 502.5, with a mean of 532.8 cells/mm^3.

Table 14: Showing baseline characteristics and baseline disease characteristics

	TPV/r 1250mg/100mg	TPV/r 7500mg/ 100 mg	TPV/r 250 mg/ 200 mg	TOTAL
Number of Subjects	58 (100.0)	63 (100.0)	87 (100.0)	208 (100.0)
Sex				
Male	45 (77.6)	54 (85.7)	76 (87.4)	175 (84.1)
Female	13 (22.4)	9 (14.3)	11 (12.6)	33 (15.9)
Race				
White	40 (69.0)	47 (74.6)	77 (88.5)	164 (78.8)
Black	18 (31.0)	15 (23.8)	10 (11.5)	43 (20.7)
Asian	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.5)
Age				
Mean	44	40.9	41.0	41. 8
Median	43.0	39.0	39.0	40.0
HIV-1 RNA Copies/mL				
< 50	9 (15.5)	27 (42.9)	48 (55.2)	84 (40.4)
> 10,000	4 (6.9)	4 (6.3)	1 (1.1)	9 (4.3)
CD_4 cell count				
Mean	**444.5**	560.5	570.4	532.8
Median	**389.5**	535	566	502.5

[Source Data: Appendix 16.1.9.2, Tables 4.1.1 and 4.1.2]

MO Comment: *The treatment groups were not equally balanced at baseline, with the TPV/r 250/200 mg group having a higher baseline median CD4 count.*

b. Treatment history

All 164 subjects in Trial 1182.6 for whom the ARV history was available had previously taken 1 or more ARV therapies. The most frequently used therapies were ZDV (59.1%), 3TC (50.0%), IDV (39.0%), d4T (35.4%), ddI (26.2%), and ZDV with 3TC (26.2%). All other ARV's were each taken by less than 20% of subjects.

c. *Resistance*

Of the 208 treated subjects, 46 (22.1%) were tested for PI mutations at baseline. Of these 46 subjects, 26 had 5 or fewer mutations; 16 had 6 -10 mutations; and 4 had 11 - 15 mutations. The small numbers of subjects treated precluded any conclusion about similarities or differences among the treatment groups at baseline.

2. Subject Disposition
   Two hundred and eight (208) received study medication. Of the 208 treated subjects, 58 (27.9%) were allocated to receive TPV/r 1250/100 mg, 63 (30.2%) to receive TPV/r 750/100 mg and 87 (41.9%) to receive TPV/r 250/200 mg. All 208 allocated subjects received at least one dose of both study medications.

   Thirty three subjects or 15.9% were discontinued from study medication before the end of the extensive PK study. Similar proportions of treated subjects were prematurely discontinued across the three treatment groups. The most common reason for early discontinuation was one or more AEs (8.2%); The second most common reason for early discontinuation was administrative reasons (5.3%). This category included subjects lost to follow up (3.4%), patient non-compliance with protocol (1.4%) and patient withdrew consent (0.5%).

TABLE 15: SHOWING REASONS FOR EARLY DISCONTINUATIONS OF STUDY MEDICATIONS (By treatment group)

	TPV/r 1250/100 mg	**TPV/r 750/100 mg**	**TPV/r 250/200 mg**	**Total**
N randomized	58	63	87	208
Reasons treated subjects were discontinued:				
NOT prematurely discontinued	47 (81.0%)	53 (84.1%)	75 (86.2%)	175/208 (84.1%)
Adverse event	5 (8.6%)	5 (7.9%)	7 (8.0%)	17/208 (84.1)
Other AE	4 (6.9)	4 (6.3)	5 (5.7)	13/208 (6.3)
Worsening of preexisting disease	1 (1.7)	1 (1.6)	1 (1.1)	3/208 (1.4)
Worsening of disease under study	0	0	1 (1.1)	1/208 (0.5)
Administrative	4 (6.9)	3 (4.8)	4 (4.6)	11/208 (5.3)
Lost to follow up	4 (6.9)	2 (3.2)	1 (1.1)	7/208 (3.4)
Non-adherent with protocol	0	1 (1.6)	2 (2.3)	3/208 (1.4)
Consent withdrawn	0	0	1 (1.1)	1 /208 (1.4)
Other	2 (3.4)	2 (3.2)	1 (1.1)	5/208 (2.4)

[Source Data: Appendix 16.1.9.2 Table 1.1]

a) Exposure

One hundred and eighty two subjects received study drug for up to 28 days. Ten subjects received TPV/r for 29-56 days, and 16 subjects received TPV/r for greater than 56 days (part of the optional extension phase).

b) Protocol Deviations

Protocol deviations were experienced by 62.5% of treated subjects, and ranged from incorrectly timed visits, entrance criteria not met, incorrectly timed examination, and the taking of prohibited medications. The majority of deviations resulted from errors in visit or examination schedules. Protocol deviations were not concentrated in any specific study treatment or baseline ARV group.

MO Comment: *Such a high proportion of protocol violations can affect the inferences that can be obtained from the study.*

C. PHARMACOKINETIC ANALYSIS

Please refer to Dr Derek Zhang's report for further details of PK analysis.

The following PK endpoints were measured: Area under the concentration-time curve (AUC); Trough steady state concentration ($Cp_{12\,h}$, $Cp_{24\,h}$); Peak drug concentration ($C\,max_{SS}$) and Area under the concentration curve (AUC) for EFV

Drug concentrations of study drugs were measured at baseline, then at 30 minute intervals for the first 2 hours of dosing, and hourly thereafter up to 10 hours post-dosing, then 2 hourly thereafter for the first 24 hours of dosing. Drug concentrations were measured at steady state on day 14 and at hourly intervals on day 22 of the study.

Results PK analysis was as follows:

1. PK of the 3TC, d4T, EFV and NVP were unchanged by co-administration of TPV/r.
2. The AUC's of ABC, ddI, and ZDV were reduced.

A claim of no clinically relevant interaction was made if the 90% confidence interval of the ratio of outcome measures with and without TPV/r was shown to be within the range of 50-200%.

Abacavir AUC values were reduced by 35% to 44% in three TPV/RTV dose levels (TPV/RTV 250 mg/200 mg, 750 mg/100 mg and 1250 mg/100 mg). The extent of the interaction seemed not dose dependent. Appropriate doses for the combination of TPV/r with abacavir have not been established.

The interaction of TPV/r with ddI was initially studied in Study 1182.6 where enteric-coated didanosine AUC values were reduced by 33% in the TPV/r 250 mg/200 mg dose level but no changes in the TPV/r 1250 /100 mg and the 750 /100 mg dose levels.

The interaction of tipranavir with zidovudine was initially studied in Study 1182.6 where TPV was found to decrease ZDV AUC and C_{max} by 47% and 68%, respectively

There seemed to be no PK interactions between TPV/r and lamivudine, stavudine and tenofovir based on the 90% confidence intervals mostly residing within 80-120% boundaries.

D. ANALYSIS OF EFFICACY

Although efficacy was not a primary endpoint in 28 day duration trial, VL and CD4 counts were measured and 40.4% of subjects had a baseline viral load of <50 copies/mL prior to the addition of TPV/r. At day 28, 67% had a viral load of <50 copies /mL.

There were no clinically relevant changes in CD4 count when assessed at 28 days.

E. ANALYSIS OF SAFETY

1. Exposure to study drug

The protocol-specified duration of exposure was 28 days for all subjects, with extension to 20 weeks (for subjects with a viral load of <400 copies/mL or an absolute reduction from baseline of >0.5 log at Day 28).

Doses of study drugs administered consisted of the following: TPV/r 250/200 mg, TPV/r 750 /100 mg, and TPV/r 1250 /100 mg. The median exposure to study medication for all 208 treated subjects was 22 days, which was also the median exposure for each of the 3 treatment groups.

Most subjects, (87.5%) received study medication for 1 to 28 days, and few received study medication for 29 to 56 days (4.8%) or for more than 56 days (7.7%).

TABLE 16: Showing extent of exposure to study medication

	TPV/r 1250/100 mg	**TPV/r 750/100 mg**	**TPV/r 250/200 mg**	**Total**
N	58	63	87	208
Duration Class				
1-28 days	54 (93.1)	53 (84.1)	75 (86.2)	182 (87.5)
29-56 days	1 (1.7)	6 (9.5)	3 (3.4)	10 (4.8)
>56 days	3 (5.2)	4 (6.3)	9 (10.3)	16 (7.7)
Mean treatment duration (days)	27.6	31.6	37.4	32.9
Median treatment duration (days)	22.0	22.0	22.0	22.0

Source Data: Appendix 16.1.9.2 Table 7.1.1

MO Comment: *Most of the subjects who enrolled in this study (87.5%) appeared to enroll only for the first part or the PK portion of the study, with few subjects opting for the optional 20 week safety extension period.*

2. *Overall adverse events*

78.8% of the 208 subjects reported 1 or more AEs during the study. Most of these (66.8%) were gastrointestinal system AEs. This was followed by AEs in the nervous system in 21.6% of subjects. For other SOC's, the percentages of subjects reporting AEs were less than 20%.

For individual types of AEs, the most frequently reported AEs were observed in the following percentages of subjects: diarrhea (51.9%), nausea (33.6%), fatigue (14.4%), vomiting (13.9%), and headache (11.1%). All other individual types of AEs, regardless of causality, were each reported by less than 10% of subjects.

Among the 3 treatment groups, the highest proportion of subjects with AEs, regardless of causality, was observed in the TPV/r 250 /200 mg group (85.1%), followed by 77.8% in the TPV/r 750 /100 mg group, and 70.7% in the TPV/r 1250 mg/100 mg group.

Among the individual treatment groups, gastrointestinal AEs were more frequently reported in the TPV/r 750/100 mg group (76.2% of subjects) as compared with the TPV/r 250 /200 mg group (63.2%) or the TPV/r 1250 /100 group (62.1%).

Most subjects in Trial 1182.6 reported AEs that were mild (65.4%) or moderate (36.5%) in intensity. Severe AEs were reported by 7.7% of all subjects: 11.5% in the TPV/r 250 /200 mg group, 6.9% in the TPV/r 1250/100 mg group, and 3.2% in the TPV/r 750 mg/100 mg group. Severe AEs occurred in very small numbers across a variety of clinical and laboratory events. Diarrhea was the most frequently reported individual AE, but occurred in only 3 subjects (1.4%) in the 3 treatment groups combined.

3. *AEs leading to discontinuations*

Seventeen (8.2%) subjects reported 1 or more AEs that led to their discontinuation from study medication. The SOC with the highest percentages of subjects with AEs leading to discontinuation of study medication was the gastrointestinal system (3.4%). For the remaining SOCs, <2% of subjects in each SOC reported AEs leading to discontinuation. The only individual types of AEs leading to discontinuation that occurred in more than 2 subjects across all treatment groups were diarrhea (5 subjects, 2.4%) and nausea (3 subjects, 1.4%).

The 3 treatment groups were similar in the overall percentages of subjects with AEs leading to discontinuation from study medication, but did differ for gastrointestinal disorders: the TPV/r 250/200 mg group had 5 subjects (5.7%) who reported 10 AEs (including diarrhea, nausea, vomiting, abdominal pain and abdominal rigidity) that led to discontinuation, while the TPV/r 1250/100 mg group had 1 patient (1.7%) with 2 events (diarrhea and nausea) and the TPV/r 750/100 mg group had 1 (1.6%) patient with 1 event (diarrhea).

MO Comment- Rash

The data sets were examined to determine the features of the rash developing in the study subjects of 1182.6. The total number of subjects with any skin AEs was 3 (5.1%) for the high dose group, 6 (9.5 %) for the medium dose group and 7 (8%) for the low dose TPV group. No specific clinical information was reported regarding the nature of the rash, and only one subject was reported to have an urticarial type rash. The median time of onset of the rash was lowest (7 days) for the high and low dose TPV groups, and 21 days for the middle dose group.

Table 17: Rash in Study 1182.6

	TPV/r 1250/100 n=58	**TPV/r 750/100 n=63**	**TPV/r 250/200 n=87**
# of females/total # of subjects	13/58	9/63	11/87
# of subjects with any skin AE	3	6	7
Held or d/c TPV due to skin AE	0	0	1
# of females with skin AE	0	2	1
# of subjects with any rash	2	5	4
Median day of onset of rash	7.5	21	7
# of females with rash	0	2	1
pruritis	1	1	3
photosensitivity	1	0	0

Types of Rash:

	1250/100 n=2	**750/100 n=5**	**250/200 n=4**
"rash" no other information	2	5	3
urticaria	0	0	1

[Source Data: FDA analysis AE datasets 12/29/04 submission]

4. Severe adverse events (SAEs)

SAEs were experienced by 3.4% of study subjects. The summaries of SAEs noted in each of the 7 subjects are shown in tabular in the in the Table 18 below. These subjects were administered 4 different baseline therapies. Two subjects each received d4T/3TC/NVP, ZDV/3TC/ABC or ZDV/3TC/EFV, and one subject received d4T/ddI/NVP.

TABLE 18: Showing SAEs by individual subject

Treatment group	Patient #	Age	Gender	Baseline Rx	SAE	Day of SAE
TPV/r 1250/100 mg	215	52	M	d4T/ddI/NVP	Elevated LFT	21
	709	59	M	d4T/3TC/NVP	Myocardial infarction	17
					Intracranial hemorrhage	
TPV/r 750/100 mg	602	43	M	ZDV/3TC/ABC	Abdominal pain	97
					Diarrhea	97
					Nausea & vomiting	97
					Hypotension	97
TPV/r 250/200 mg	524	60	M	ZDV/3TC/EFV	Increased triglycerides	21
	601	52	M	ZDV/3TC/EFV	Hypertriglyceridemia	14
	644	34	F	d4T/3TC/NVP	Vomiting	2
	900	25	M	ZDV/3TC/ABC	Elevated liver function	16

[Source Data: Appendix 16.2. Listing 1.2 7.2.2]

5. Deaths

One death occurred, approximately 12 days after study treatment was discontinued. The patient was a 52 year old male taking TPV/r 1250/100 along with ddI/d4T/NVP medications and and Zoloft (for major depression). He was approved for entry into the study with normal baseline liver function tests and a uric acid levels. On day 14 of treatment, he developed an asymptomatic elevation (Grade 4 elevation of hepatic transaminases). On day 20, subject developed fatigue, with further transaminase elevations. At that point, TPV/r was discontinued, while DDI/d4T and NVP were continued.

Seven days later, he reportedly improved. Approximately 12 days after study treatment was stopped, on [ ], he presented to the ER, suffering from renal and respiratory failure, transaminase elevation and lactic acidosis. He was found to be acidotic, with bicarbonate of 7, a blood pH of 7.01, and WBC of 31.4 (without left shift). He became obtunded, with constricted pupils. He died after 5 days of hospitalization, with clinical diagnoses of hepatic transaminase elevation, Lactic Acidosis, Acute renal failure, Respiratory failure and Brain Stem Infarction.

An autopsy was performed, but the Applicant was unable to obtain the Autopsy results for the Agency to review.

6) Laboratory adverse events

Table 19 summarizes the clinically significant laboratory tests of special interest. Increases in serum triglyceride levels were experienced by 13.3% of study subjects. Most of these (17.6%) were noted in the TPV/r 250/200 mg treatment arm.

Of the remaining laboratory tests, only ALT elevations occurred in 5% or more subjects in any treatment group.

TABLE 19: SHOWING CLINICALLY SIGNIFICANT LABORATORY TESTS OF SPECIAL INTEREST (by treatment group): Study 1182.6

Test	TPV/r 1250/100 mg N=51%)	TPV/r 750/100 mg N=60(%)	TPV/r 250/200 mg N=85(%)	Total N= 196(%)
Triglyceride increase	59 (9.8)	6 (10.0)	15 (17.6)	26 (13.3)
ALT increase	3 (5.9)	1 (1.7)	4 (4.7)	8 (4.1)
AST increase	2 (3.9)	0	1 (1.2)	3 (1.5)
Platelet decrease	1 (1.9)	1 (1.7)	0	2 (1.0)
Prothrombin time increase	0	1 (1.7)	0	1 (0.5)
Cholesterol increase	0	0	1 (1.2)	1 (0.5)

Source Data: Appendix 16.1.9.2, Table 8.3

Hepatotoxicity AE: Study 1182.6

The data sets were analyzed in order to determine the features of the hepatotoxicity signal.

5% subjects in the TPV/r 1250/100 mg group, while 1.5% in the middle dose group, and 3% of subjects in the low dose group developed Grade 3 or 4 elevations of ALT. Increased GGT occurred in 1 subject in the high dose group and 3 subjects in the low dose group. None of the subjects demonstrated a concomitant rise of total bilirubin.
The median number of days to maximum ALT was 21 days for the high dose group, 27 days for the medium dose group and 17.5 days for the low dose group.

The 3 treatment groups however, were not equally randomized, with the TPV/r 250/200 mg group having the highest CD4 count at baseline. The relatively high percentage of subjects showing Grade 3 or 4 ALT elevations when compared to the TPV dose may have been a manifestation of a more robust immunological response in this treatment arm (566 cells/mm^3).

TABLE 20: SHOWING HBV/HCV AND ALT AND BILIRUBIN LEVELS OF STUDY SUBJECTS IN STUDY 1182.6

	TPV/r 1250/100 n=58	TPV/r 750/100 n=63	TPV/r 250/200 n=87
# HBsAg +	4	3	3
#HCV Ab+	14	5	13
#HBV/HCV coinfected*	2	0	0
# of subjects w/ ALT ≥ Grade 1 at BL	12	13	10
Median BL CD4 count	389.5	535	566
# of subjects w/ Grade 3 ALT	2	1	3
#coinfected and Gr 3 ALT	1	0	0
#of subjects w/Grade 4 ALT#	1	0	1
coinfected and Gr 4 ALT	0	0	1
% of subjects w/Gr3 or 4 ALT	5%	1.5%	3%
Median days to max ALT	21	27	17.5
Median maximum ALT and range	306 218-696	218	261 239-760
Median BL CD4 for subjects with Gr 3 or 4 ALT	301	246	557.5
# of subjects w/ Grade 3 total bili	0	0	0
# of subjects w/ Grade 4 total bili	0	0	0
increased GGT	1	0	3
increased ALT (gr 2) as AE	0	2	6
Study drugs held 2° hepatotoxicity	0	0	0
Premature d/c 2° hepatotoxicity	1	0	1

Source: AE dataset analysis – 12/29/04 submission

Safety Conclusions

The most frequently reported AEs involved the GI Tract.
These included: Diarrhea (51.9%); Nausea (33.6%); Vomiting (13.9%); Headache (11.1%) and Fatigue (14.4%)

Most AEs were of mild to moderate intensity. There was no clear evident dose relationship between the dose of study drug and the frequency of adverse event.

F. STUDY CONCLUSIONS

Study 1182.6 was primarily a PK study, designed to look at drug interaction between TPV/r and other commonly co prescribed antiretroviral agents. The results were as follows:

1) The addition of 3 doses of TPV/r did not change the PK of d4T, 3TC, EFV, or NVP. Therefore no dosage adjustments are required when these drugs are co-administered.
2) The AUC values of ABC, ddI, and ZDV were reduced when co-administered with TPV/r.

MO Overall Conclusion and Comments: *This study was designed primarily as a short PK study designed to determine the PK changes when TPV/r is co administered with NRTI's. The clinical relevance of these changes in the AUC's of ABC, ddI, ZDV are unclear as the NRTI's therapeutic windows were not well established, and plasma concentration of these NRTI's may not correlate with the active intra-cellular levels or levels of tri-phosphorylation. Intracellular levels or levels of triphosphorylation were not studied in this study.*

Conclusions regarding efficacy, and differences among treatment groups need to be tempered in view of the small numbers of subjects who continued in the study past 28 days, the absence of a control group, and the differences in viral loads and CD4 cell counts at baseline.

[5] Individual Study 1182.51

Study 1182.51 was an open-label, randomized, parallel-group, multicenter, 24 week, phase II trial in 315 treatment experienced subjects who failed to meet the entry criteria for one of the Phase III trials of TPV (RESIST 1 or RESIST 2). This study randomized subjects to two weeks of TPV/r + optimized background (OB), LPV/r + OB, APV/r + OB, or SQV/r + OB. TPV/r (500 mg/100 mg bid) was added to the other PI-containing regimens at week 2.

A. STUDY DESIGN

The objective of this trial was to determine the change in C_{12h} (average of Day 7 and Day 14) from weeks 2 to week 4 (average of Day 21 and 28); i.e., the change in PI trough from a boosted PI alone to the trough with TPV added.

The entry criteria included:

- Highly treatment experienced subjects, with antiretroviral (ARV) experience with 3 ARV classes (NRTI, NNRTI, PI).
- previous treatment with two different PI-based regimens for a minimum of 3 months each.
- Plasma HIV-1 RNA > 1000 copies/mL.
- At least 3 documented mutations at protease codons 33, 82, 84, or 90 at screening. (Genotypic testing was performed for these subjects at their screening visit for the RESIST 1 or RESIST 2 trials. Because study entry in the RESIST trials was limited to mutations of no less than 3 protease codons, these subjects were excluded from those trials and eligible for 1182.51).
- Any CD4 T cell count was acceptable

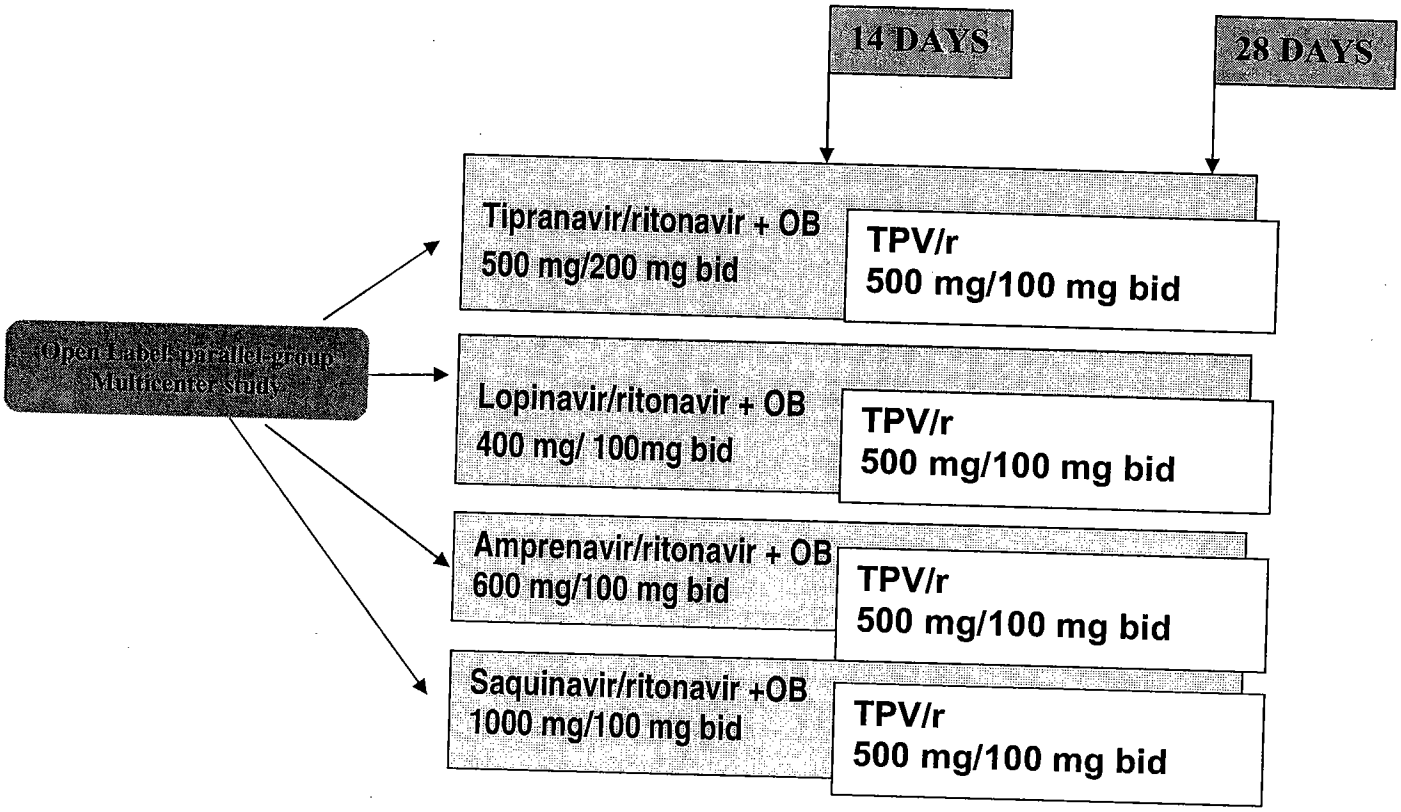
> ***MO Comment:*** *The study criteria included at least 3 mutations at codons 33, 82, 84, or 90. These mutations are associated with failure to most PIs, including TPV. See table 21 below.*

As a result of the entry criteria with multiple PI-resistant mutations, including mutations conferring TPV resistance, and the highly ARV experienced patient population, virologic response, particularly virologic suppression, was unlikely. In addition, because of the multiple mutations and treatment experience, it was possible that many subjects would be effectively receiving "monotherapy" or even "dual therapy" because of resistance to multiple ARVs in their OB regimens.

Treatment:

Subjects were randomized to receive one of four PIs boosted with TPV (TPV, LPV, APV, or SQV) plus on optimized, non-PI containing background. After the initial two weeks, TPV/r (500 mg/100 mg) was added to the LPV, APV, and SQV arms as shown in figure 1.

FIGURE 1: DESIGN SCHEMATIC FOR STUDY 1182.51



Pharmacokinetic measurements were obtained at the end of week 2 and of week 4. A pharmacokinetic substudy enrolled 91 subjects at selected sites, comprising 30 subjects in the TPV group, 20 in the LPV group, 21 in the SQV group, and 20 subjects in the APV group. Although the primary objective of this study was to compare PI troughs at two and four weeks, safety and efficacy were followed for a total of 24 weeks. Efficacy measurements were assessed at weeks 2, 4, and 24. At study completion, all subjects could continue their regimen in the long-term rollover study 1182.17.

MO Comment: *Although the study design allowed for conservative care of individual subjects and maximized treatment options in a very experienced study population, it confounded both the efficacy and safety analyses. However, by study design, all subjects in the three non-TPV containing study arms started TPV at week 2. Since this was a heavily pretreated, salvage population, investigators could change antiretrovirals anytime after week 4.*

The open label design and the absence of a comparator arm after two weeks, limits the usefulness of this study.

The primary end point of study 1182.51 was the comparison of mean trough levels ($C_{12\,h}$) of the non-tipranavir PI (that is, APV, LPV, SQV) at days 7 and 14 with the trough at days 21 and 28 after the addition of TPV/r on day 14.

For the pharmacokinetic analysis, comparisons were made using analysis of variance on log concentration values. The change from weeks 1-2 to weeks 3-4 were summarized by geometric means and confidence intervals derived from this analysis of variance.

The *primary efficacy endpoint* was change in viral load from baseline to weeks 2, 4 and 24. Results were compared using medians, and using non-parametric methods and as means using analysis of variance. The *secondary efficacy endpoints* included virological response (defined as proportion of subjects with viral load < 50 copies/mL and <400 copies/mL and proportion of subjects with ≥1 $\log_{10}$ decrease in HIV RNA; Time to virological failure, change in CD4+ cell counts from baseline; Reason for treatment failure; Proportion of subjects with a new CDC category progression event or death.

Additional analyses included analysis of PI mutations conferring decreased TPV phenotypic susceptibility and the comparison of genotypic and phenotypic resistance patterns with viral load response.

In a protocol amendment, the TPV/r alone arm was closed to accrual due to decreased efficacy. As a result, no further subjects were enrolled in the TPV/r arm during the last 6 weeks of the study. Investigators with subjects with TPV/r as the only PI were encouraged to add a second PI to their subjects' ARV regimen.

MO Comment: *The failure of the TPV/r arm to show durable efficacy is not surprising because of the entry criteria and the study population. These subjects were heavily pretreated and had protease mutations associated with TPV resistance at baseline.*

B. STUDY RESULTS

a. Baseline Demographics:

A total of 352 study subjects were randomized at 130 study centers: 75 in the USA and Canada and 55 in Western Europe and Australia. The majority of subjects were between 41 and 55 years of age. 93.3% of subjects were male and 6.7% were female. Some of the countries participating in this study would not allow recording of race, in the study population with racial and ethnic information, 76.2% were white, and 7.3% were black.

MO comments: *Overall, the treatment groups were generally similar in age, gender, and race demographics; see Table 21 below*

b. *Baseline HIV disease characteristics:*

Median HIV-1 RNA level was 4.97 $\log_{10}$ copies/mL, and median CD4+ cell count was 138 cells/mm3. The four treatment groups were similar except for HIV RNA with a range from 4.78 – 5.02 $\log_{10}$ copies/mL. (See Table 21 below). The

median CD4+ cell count varied between treatment arms and ranged from 115 cells/mm^3 in the SQV/r group to 181 cells/mm^3 in the TPV/r group.

TABLE 21: SHOWING BASELINE DEMOGRAPHIC DATA, HIV RNA-1 VALUE AND CD4+ CELL COUNT IN TRIAL 1182.51 (AS TREATED UP TO WEEK 4)

	TPV/r	A PV/r	SQV/r	APV/r	Total
Total treated	67	83	82	83	315
Age [years]					
N	67	83	82	83	315
Median	44.0	43.0	44.5	45.0	44.0
Range	31-67	26-66	29-69	30-64	26-69
Gender [N (%)]					
Male	62 (92.5)	78 (94.0)	77 (93.9)	77 (92.8)	294 (93.3)
Female	5 (7.5)	5 (6.0)	5 (6.1)	6 (7.2)	21 (6.7)
Race [N (%)]					
White	51 (6.1)	65 (78.3)	60 (73.2)	64 (77.1)	240 (76.2)
Black	4 (6.0)	6 (7.2)	8 (9.8)	5 (6.0)	23 (7.3)
Asian	0	0	0	0	0
Missing	12 (17.9)	12 (14.5)	14 (17.1)	14 (16.9)	52 (16.5)
Median baseline HIV-1 RNA [log10 copies/mL]	4.78	4.97	5.02	4.97	4.99
Median baseline CD4+ cell count [cells/mm3]	181	126	115	138	138

[Source Data: Table 15.1.4:4]

MO Comment: *As shown in the Table 21, the baseline CD4 count was higher in the TPV/r group than the other treatment arms. In addition, the baseline viral load was the lowest in the TPV/r arm. Although the differences between the arms were small, it is possible that this disparity affected the efficacy outcome.*

As further evidence of the advanced HIV disease observed in this study population, 91% of subjects were classified as having AIDS at baseline due to CD4 count or previous AIDS-defining event.

c. Treatment history

The median number of ARV's that patient's had received prior to enrollment in this study was 13 (range 7-19). At baseline, the history of previous ARV use was similar among the 4 treatment groups. The most frequently NRTI's used previously were ZDV (98.1%); 3TC (94.6%), d4T (93.7%). The most frequently used NNRTIs were EFV (79.8%) and NVP (67.1%). The most frequently used PIs were IDV (94.1%), SQV (85.4%), and nelfinavir (NFV) (73.7%). Overall, for all 315 subjects, 19.4% had prior enfuvirtide experience.

By design, subjects entering Trial 1182.51 had failed screening for one of the RESIST trials due to an HIV isolate containing >2 mutations at codons 33, 82, 84 or 90 and thus represented a more advanced and resistant population. Median numbers of protease gene mutations at baseline were approximately 18 in each treatment group. The median and maximum number of protease mutations at codons 33, 82, 84, and 90 at baseline were 3.0 and 4.0, respectively, in each of the 4 treatment groups.

2) Subjects Disposition:

Of the 352 subjects in study 1182.51, 315 received at least one dose of study medication:. 67 in the TPV/r arm, 83 in the LPV/r arm, 82 in the SQV/r arm, and 83 in the APV/r arm (See table 22 below). All 315 subjects were included in the pharmacokinetic analysis. Overall, 273 subjects completed the entire 24 weeks of the study, while 42 discontinued prematurely. The number of study subjects discontinuing prematurely in each arm are shown in the table below.

TABLE 22: STUDY DISCONTINUATIONS BY TREATMENT ARM IN STUDY 1182.51

	Week 0-2 (n=)	*Weeks 3-4 (n=)*	*Weeks 5-24 (n=)*	*After week 24 (n=)*
TPV/r	*0*	*0*	*4*	*1*
LPV/r	*1*	*0*	*5*	*0*
SQV/r	*1*	*1*	*12*	*0*
APV/r	*4*	*0*	*9*	*4*

Source: CSR 1182.51, Exit datasets.

MO Comment: *The applicant provided reasons for discontinuation after week 24. Presumably, these subjects were either still in the follow-up period for study 1182.51 or were enrolled in the rollover study 1182.17.*

Few subjects discontinued the study in the first 4 weeks. However, overall more subjects prematurely discontinued the study in the saquinavir and amprenavir arms than the other two arms. ARV tolerability did not appear to worsen after addition of TPV at week 2. The majority of discontinuations occurred during or after week 4. See below for a discussion of reasons for premature study discontinuations in each treatment arm.

The reasons for premature discontinuation by study arm are shown in the following Table 23.

Table 23: Reasons for Study Discontinuation by Treatment Arm in Study 1182.51

	TPV/r	LPV/r	SQV/r	APV/r	Total
Adverse events	2	3	10	10	25
Weeks 0-2	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*4 (4.8)*	*4 (1.3)*
Weeks 3-4	*0 (0.0)*	*0 (0.0)*	*1 (1.2)*	*0 (0.0)*	*1 (0.3)*
Weeks 5-24	*2 (3.0)*	*3 (3.6)*	*9 (11.0)*	*6 (7.2)*	*20 (6.3)*
Lack of efficacy	2 (3.0)	1 (1.2)	2 (2.4)	3 (3.6)	8 (2.5)
Administrative	*0 (0.0)*	*2 (2.4)*	*0 (0.0)*	3 (3.6)	5 (1.6)
Worsening of other preexistent disease	1 (1.5)	*0 (0.0)*	2 (2.4)	1 (1.2)	1 (1.3)
Worsening of HIV disease	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.3)

[Source Data: Table 15.1.1.1:1]

As shown above, the most common reasons for premature study discontinuation was adverse events. Unfortunately, the type of adverse event for the one TPV subject in Table 23 was not provided in text or in datasets. The AEs resulting in study discontinuation in the LPV/r arm were pancreatitis, renal failure, and URI. The reasons for early discontinuation in the APV/r arm were gastritis, diarrhea, Grade 4 increase in transaminases, weight loss, rash, bacterial meningitis, and malaise. Subjects in the APV/r arm discontinued prematurely due to increased liver enzymes (4), rash (3), peripheral neuropathy, diarrhea, and "feeling unwell".

> ***MO Comment:*** *There was no single adverse event associated with premature study discontinuation in any of the treatment arms. Many of the adverse events are known toxicities associated with marketed antiretroviral drugs or are associated with advanced HIV disease. There was no difference in the types of AEs after addition of TPV to the other PIs at week 2.*

Per Protocol ARV Changes after Week 4

As described earlier in this review, study subjects could change their protease inhibitors as needed.

TABLE 24: PI CHANGES BY TREATMENT ARM IN STUDY 1182.51

Treatment Arm	PI Switch	# subjects randomized	# (%) with PI switch
All subjects		N=315	42 (13.3%)
TPV/r	Total	N= 67	20 (29.9%)
	TPV/r to APV/ TPV/r		4 (6.0%)
	TPV/r to LPV/TPV/r		11 (16.4%)
	TPV/r to SQV/TPV/r		5 (7.5%)
LPV/TPV/r	None	N=83	0(0%)
SQV//TPV/r	Total	N=82	9 (11.0%)
	SQV//TPV/r to APV/TPV/r		2 (2.4%)
	SQV//TPV/r to LPV/TPV/r		7 (8.5%)
APV/TPV/r	Total	N=83	13 (15.7%)
	APV/TPV/r to LPV/TPV/r		10 (12.0%)
	APV/TPV/r to SQV/TPV/r		3 (3.6%)

[Source Data: Table 15.1.1:2]

MO Comment: *The degree of switching in the TPV/r arm was substantially higher than for the LPV/r arm and also higher than the SQV and APV arms. This was most likely due to the lack of efficacy reported in this arm. This degree of PI switching clearly hinders the safety and efficacy analysis of this study.As a result of these ARV study changes, the applicant provided efficacy results for the entire study population (FAS) and also provided limited efficacy analysis for those subjects who remained on their randomized treatment from weeks 2 to 24. The* ***efficacy analysis*** *for the FAS population is confounded by the PI switching, which makes it difficult to determine the antiviral activity associated with a TPV/PI/r containing regimen. The PP population is a more appropriate for determination of efficacy analysis.*

Protocol violations

According to the applicant, 188 subjects or 60% had at least one "important protocol violation." The violations are shown in the Table 25 below.

TABLE 25: IMPORTANT PROTOCOL VIOLATIONS IN STUDY 1182.51, FAS

	TPV/r		LPV/r		SQV/r		APV/r		Total	
	N	%	N	%	N	%	N	%	N	%
Total treated	67	100.0	83	100.0	82	100.0	83	100	315	100.0
Total with important protocol violation	34	50.7	58	69.9	50	61.0	46	55.4	188	59.7
Entrance criteria not Met	18	26.9	25	30.1	20	24.4	21	25.3	84	26.7
PK trough sample taken 8-16 hours after previous dose	10	14.9	23	27.7	14	17.1	15	18.1	62	19.7
TPV,SQV,APV,LPV added at wrong time or wrong visit	2	3.0	10	12.0	14.6	12	14.5	36	36	11.4
Non compliance	3	4.5	9	10.8	8	9.8	11	13.3	31	9.8
Incorrect dose of trial medication taken	1	1.5	10	12.0	1	1.2	6	7.2	18	5.7
Prohibited medication use	0	0.0	5	6.0	5	6.1	3	3.6	13	4.1
Incorrect timing of examination	1	1.5	3	3.6	3	3.7	4	4.8	11	3.5
Incorrect trial medication taken	0	0.0	4	4.8	2	2.4	2	2.4	8	2.5
Randomization order not followed	3	4.5	0	0.0	0	0.0	0	0.0	3	1.0
Missing data visit	0	0.0	1	1.2	1	1.2	1	1.2	3	1.0
Pt. intolerant to 2 or more study PI's	3	4.5	0	0.0	0	0.0	0	0.0	3	1.0
Incorrect timing visit	0	0.0	0	0.0	1	1.2	0	0.0	1	0.3
Missing data value	0	0.0	0	0.0	1	1.2	0	0.0	1	0.3
Trial medication	0	0.0	0	0.0	1	1.2	0	0.0	1	0.3
Pt. randomized to study PI that intolerant to	0	0.0	1	1.2	0	0.0	0	0.0	1	0.3

[Source Data: Table 15.1.2.1]

MO Comment: *The high numbers of protocol violations are partly due to the study population and study design. The study was open-label and the study population was of a salvage type, with subjects having few treatment options. The investigators undoubtedly tried to do the best for their individual subjects. However, this proportion of subjects with protocol violations that is so high (60%) may reflect issues with the conduct of the study.*

While it is difficult to determine the exact number or percentage of protocol violations that affected the efficacy and safety outcome of this study, it is clear that multiple violations may have influenced the study outcome. For example, 27% did not meet the entry criteria, 11% of subjects had their PI added at the wrong time during the study, and 10% were non-complaint. The number of protocol violations per treatment arm were similar, and therefore, the violations do not appear to be intentional or do not appear to bias the results in the favor of one treatment arm over another. However, this degree of protocol violations certainly influenced the overall study results and makes interpretation of the study results difficult.

C. PHARMACOKINETICS

The primary evaluation was the PK interaction between TPV/r and the RTV-boosted comparator PIs for mean trough levels (C12h) before (Days 7 and 14) and after (Days 21 and 28) addition of TPV/r to the current regimen. Subjects remained in the study until Week 24. The secondary endpoints were virologic response, VL, and proportion of virologic responders at Weeks 2, 4, 8, 16, and 24. Switch of background ARVs and PI was allowed after 4 weeks.

The population PK analysis of 1182.51 demonstrated that the addition of TPV/r to single-boosted LPV/r, SQV/r, or APV/r was associated with reductions in plasma trough concentrations for each of the single-boosted PIs (LPV ↓35%; SQV ↓69%; APV ↓50%.); RTV levels were also reduced.

An intensive PK subset analysis confirmed these data and demonstrated consistent reductions in C_{max} and AUC for each of the single-boosted PIs after the addition of TPV/r. There were essentially no changes in the TPV plasma concentration data when co-administered with any of the three PIs.

The drug exposure and minimal plasma concentrations required for antiviral effect varied depending on treatment-experience and other individual patient characteristics. In Study 1182.51, there did not appear to be significant antiviral benefit to the co-administration of TPV/r with any of the other RTV-boosted PIs as compared with TPV/r alone for this patient cohort. Some individual subjects may have benefited, however, because they either had higher CPI drug levels or because their individual IC50 requirements were lower.

MO Comment: *The addition of a second PI to the regimen of this salvage population, who already did not have complete viral suppression, and who continued to have circulating virus in the blood, decreased or suboptimal plasma levels of the co-administered PI. The addition of a second PI could result in the development of additional resistant mutations.*
Additionally, the efficacy of these dual PI's regimens was limited. (See analysis of Efficacy). It is possible that higher plasma concentrations of the 2nd PI could have resulted in a better Rx effect. However, participants were probably resistant to these PIs at baseline. Finally, some experts have theorized that high ARV plasma levels may overcome low level resistance; This however, would not be possible with the concomitant administration of TPV and a second PI.

MO OVERALL PK CONCLUSION: *PI C_{min} values were evaluated at the end of week 1, 2, 3 and 4 and a 12-hour intensive PK evaluation conducted both before and after addition of TPV to the other PI's. TPV's induction effect resulted in reductions in the C_{min} levels of amprenavir, lopinavir, and saquinavir by 56%, 55%, and 81% respectively, after TPV was added on day 14.*

Results were also seen during the PK interactions observed during the dual boosted phase. This suggests that in the overall management of HIV-experienced patient, the use of TPV/r in dual-boosted PI regimens will not be very helpful, and as stated in the proposed TPV label, it is not recommended that TPV be used in combination with any PI with the exception of RTV.

D. ANALYSIS OF EFFICACY

At Week 2, the TPV/r control arm had a median viral load reduction of 1.06 $\log_{10}$ while the other single-boosted PI arms had median viral load reductions of only 0.15-0.38 $\log_{10}$. From Weeks 4-24, the median viral load reductions were similar for all four treatment arms, though these data include those subjects who modified their regimen after Week 4. Despite the high level PI resistance, 17.1-26.5% of subjects had undetectable viral loads (<400 copies/mL) at Week 24.
The primary measure of efficacy was the change in plasma HIV RNA from baseline. This was measured at week 2, week 4 (after the addition of TPV to all treatment arms) and at week 24. Efficacy results for all subjects with last observation are shown in the Table 27 below.

Table 27: Median Change in HIV RNA (log_{10} copies/ml) at Week 2 and Week 4

Treatment Arm	Week 2	Week 4	Week 24
TPV/r + OB	- 1.06	- 1.27	- 0.28
LPV/r + OB	- 0.38	- 1.19	- 0.43
SQV/r + OB	- 0.19	- 0.96	- 0.24
APV/r + OB	- 0.15	- 1.12	- 0.47

[Source Data: CSR, Tables 11.4.1.2:4 and 11.4.1.2:5, page 84.]

As shown in Table 27, at week 2, there was a greater median decrease in HIV RNA level in subjects receiving TPV/r (-1.06 log_{10} copies/ml) than in subjects receiving the other booster PIs (-0.15 to -0.38 log_{10} copies/mL)
The proportion of subjects in the as treated population with HIV RNA levels less than 400 copies/ml at 2 weeks was 18% in the TPV/r arm compared to 5% in the LPV/r and APV/r arms and 4% in the APV/r arms. The proportion less than 400 at week 4 increased to 24% in the TPV and remained stable thereafter; 24% of subjects had viral loads less than 400 copies/ml at week 24. TPV was added to the other PI arms at week 2, by week four the proportion of subjects with viral loads less than 400 copies/ml in each arm ranged from 22% in the TPV/LPV/r arm to 12% in the TPV/SQV/r arm. The viral load continued to decrease slightly at 8 weeks before stabilizing. At 24 weeks the proportion of subjects with HIV RNA < 400 copies/ml was 26.5% in the TPV/LPV/r arm, 17% in the TPV/SQV/r arm, and 23% in the TPV/APV/r arm.

> ***MO Comment:*** *The use of TPV in all arms resulted in a decrease in viral load that was observed by two weeks of TPV use and appeared to stabilize at 4 weeks. By 24 weeks, the proportion of subjects on study with viral loads < 400 copies/ml was similar in all treatment arms except for the SQV arm. This may be due to the extremely low SQV levels reported after SQV co-administration with TPV. These results must be viewed with caution since this analysis includes all subjects on study regardless of any changes in ARVs during the study and more subjects in the TPV arm changed ARVs more than in any of the other PI arms.*

The per protocol analysis for one log decrease or more in subjects is shown in the Table 28 below. This analysis does not include subjects who changed ARV's during the study.

Table 28: Percentage of Subjects with One Log or More Decrease in HIV RNA (Per Protocol Population)

	TPV/r	LPV/r	SQV/r	APV/r
Week 2	62%	30%	22%	27%
Week 4	55%	54%	48%	60%
Week 8	51%	40%	37%	53%
Week 24	28%	30%	25%	40%
Rebound*	43%	25%	26%	24%

* Subjects with rebound had an initial virologic response and then ≥1 log increase in VL

***MO Comment*:**
1) *Study 1182.51 enrolled heavily pretreated, PI-experienced subjects; therefore, it is not surprising that these subjects derived little treatment benefit from the PI-containing regimens. However, given the protease codon mutations observed in this population at baseline, it is notable that subject in the TPV/r arm had a median viral load change of 1 log_{10} copies/ml at week 2 and that subjects in the other 3 treatment arms had a decrease in HIV RNA from week 2 to week 4.*

2) *Any further efficacy results after week 4 are difficult to determine since subjects could change their ARV regimen at any time after week 4. The highest proportion of subjects switching PIs was in the TPV arm. The PP analysis is an appropriate analysis in this case and is shown in Table 28 above.*

3) *The sponsor does not provide the reason for the premature discontinuation of the TPV/r arm by the DSMB. It is likely that the DSMB closed this arm due to the high numbers of subjects with virologic rebound (42.6%) in the TPV/r arm compared to the other treatment arms (24-26%).*

TABLE 29: SHOWING CONTRIBUTION OF ENFURVITIDE (ENF) TO THE EFFICACY OF TPV

	ENF in baseline regimen	ENF added during study	Total
TPV	19	1	20
LPV	31	1	32
SQV	21	2	23
APV	8	15	23

[Source Data: RM dataset, 12/29/04 submission]

MO Comment: *The contribution of ENF to the treatment effect was examined by this reviewer. Because the use of ENF may have provided a second active agent to the OB regimen, it is possible that its use affected the efficacy results. Overall, 98 subjects either started ENF as part of their ob regimen or added it during the study. The number of subjects on ENF was similar between treatment groups (20-23) except for the LPV/r arm in which 32 subjects received enf. However, there were no differences in treatment response that can be attributed to ENF, i.e. neither virologic response nor virologic relapse in the LPV/r arm were substantially different from the other three study arms. Therefore, it does not appear that the differential use of ENF influenced the efficacy results in this study.*

MO Comment and OVERALL EFFICACY CONCLUSION: *Although the applicant concludes that there was similar efficacy in all four treatment arms, there is clear evidence that there this is not true. First, the DSMB of this study closed the TPV/r arm for decreased efficacy. Second, the applicant based this conclusion on the full analysis population, which is not an appropriate population for analysis due to the inclusion of subjects who changed their PIs during the study. Third, a higher proportion of subjects had virologic rebound in the TPV/r arm compared to the other study arms when using the PP population. Finally, it is difficult to determine if the efficacy analysis is valid due to the high proportion of subjects with important protocol violations.*

E. ANALYSIS OF SAFETY

In the first two weeks, the safety of the TPV/r arm and the three comparator arms was similar. The addition of TPV to the three other RTV-boosted arms at Week 2 did not substantially change the AE profile. These safety data were confirmed at 24 weeks.

The applicant concluded that co-administration of TPV/r with LPV, SQV, or APV was safe and may provide clinical benefit in certain circumstances—especially where the PI trough concentrations were at or above target thresholds—and should be studied further.

Safety was assessed by the proportion of subjects with laboratory abnormalities and included hematology, chemistry, liver functions and lipid levels; the proportion of subjects who experienced adverse events and the proportion of subjects who reported serious adverse events (SAEs)

1. Exposure to study drug

The median exposure to study drugs was 182, 182, 176, and 181 days, for the TPV/r, LPV/TPV//r, SQV/TPV/r, and APV/ TPV/r groups, respectively. The majority of all subjects (83.5% of all treatments combined) received study drugs for ≥24 weeks: 94.0%, 88.0%, 73.2%, and 80.7%, for the TPV/r, LPV/TPV/r, SQV/TPV/r, and APV/TPV/r groups, respectively. At week 2, the three non-TPV groups added TPV 500 mg with an additional 100 mg of RTV. Approximately 4 months from trial initiation the TPV/r group was removed and the 3 remaining treatment groups continued.

MO Comment: *Subjects were allowed to switch PI after week 4- (See table 25. All FAS subjects that did not switch to another study arm until withdrawal or the end of the study. A total of 42 of 315 subjects switched study arms in study 1182.51.*

20 of 67 subjects (29.9%) switched from the TPV/r arm, of which 11 or 16.4% of these switched to the LPV/TPV/r arm. Nine of 82 subjects (11%) switched from the SQV/TPV/r arm, and 13 of 83 subjects (15.7%) switched from the APV/TPV/r arm. No subjects who were initially assigned

to the LPV/TPV/r switched study arms .Analysis was also complicated by closure of the TPV/r arm –This involved a total of 67 subjects in this arm, which closed 6 weeks before the other arms closed.

2. *Overall adverse events*

As discussed above, the first 2 weeks were the only time period in which TPV/r was administered separate from the PI's of the other treatment arms, and after week 4, subjects were allowed to switch PI's. Frequency of AEs for both time periods are shown in Table 30 below.

Table 30: Showing overview of subjects with AEs by treatment group, during the single boosted period (weeks 1-2) and dual-boosted period (weeks 3-24)

	Single – boosted PI period (week 0-2)			
	TPV/r %	**LPV/r %**	**SQV/r %**	**APV/r %**
Subjects with AEs	59.7	51.8	52.4	48.2
Subjects with drug-related AEs	31.3	14.5	19.5	15.7
Subjects with AE leading to discontinuation	0	0	0	4.8
Subjects with SAEs	4.5	0	1.2	0
Deaths	0	0	0	0
	Dual – boosted PI period (weeks 3-24)			
	TPV/r %	**LPV/TPV/r %**	**SQV/TPV/r %**	**APV/TPV/r %**
Subjects with AEs	80.6	78.0	80.9	83.5
Subjects with drug-related AEs	22.4	41.3	31.5	41.2
Subjects with AE leading to discontinuation	1.5	2.8	12.4	7.1
Subjects with SAEs	9.0	6.4	13.5	10.6
Deaths	0	0	2.2	1.2

[Source Data: Table 15.3.1: 8]

Single boosted PI period – (Weeks 0-2)

In general, proportions of subjects with AEs are very similar during the single-boosted PI period. The percentage of subjects with GI AEs, particularly diarrhea was highest in the

TPV group, accounting for 16.4% AEs, as compared to 13.3%, 4.9%, and 12% for the LPV/r, SQV/r and APV/r treatment group respectively.

Three SAEs that occurred in subjects receiving TPV were abdominal pain with ALT/AST elevations, Bacterial Meningitis and CMV infection; one subject receiving SQV developed Progressive Multifocal Encephalopathy. There were 4 subjects in the APV/r group that discontinued prematurely due to AEs. No deaths were reported during the first 2 weeks of the study.

> ***MO Comment:*** *No big difference in AEs was noted during the first 2 weeks of the study. However, some AEs may have emerged after the 2 week period.*

Dual boosted PI period – (Weeks 3-24)
It is impossible to determine the difference in AEs between arms and the contribution of TPV because all arms received TPV after week 2, and ARV agents were switched after week 4. The AEs observed were consistent with other TPV/r studies:

3. Deaths
A total of 3 subjects enrolled in study 1182.51 died while on study. The causes of death were varied and are shown in Table 31 below.

TABLE 31: SUMMARIZING THE 3 SUBJECTS WHO DIED IN 1182.51

Age/sex	Treatment at onset	Reason for Death	Baseline CD4/ VL	Other Medical Diagnoses
38/ M	LPV/r/TPV/ddI/3TC	Renal Failure	14/678,189	CMV Colitis and Retinitis Pancreatitis Candidiasis
40 /M	SQV/TPV/r	Bacterial Meningitis	19/286,000	SIADH Rhabdomyolysis Candiadiasis
41/ M	SQV/r/TPV/r	CMV Disease	6/308,000	Esophageal candiadiasis, Depression, Anemia

Individual deaths are described below:

1) Patient No: 1220 was a 38 year old black male, was randomized to LPV/r on 5/19/03 and added TPV/r two weeks later. His OB regimen included ddI and 3TC. He had a history of CMV colitis and retinitis, intermittent diarrhea, oral Candidiasis, wasting, peripheral neuropathy, and several hospitalizations for vomiting and diarrhea. His baseline CD4 count was 14 cells/mm^3 and his baseline viral load was 678,189 copies/ml. His treatment course was complicated by CMV colitis requiring total parenteral nutrition, renal failure, and pancreatitis. He died on [redacted] day due to renal failure.

2) Patient No: 1369 was a 40 year old white male, started his study drugs (SQV/r) on May 1, 2003. His baseline CD4 count and baseline viral load were 19 cells/ mm3 and 286,000copies/mL respectively. His treatment course was complicated by sinusitis, rhabdomyolysis, persistent oral candidiasis, peripheral neuropathy, weight loss, hypertension, and nocturia. On [ ] the patient was diagnosed with meningitis due to Streptococcus pneumoniae and treated with ceftriaxone. At that time, he had mental status changes, rhabdomyolysis, and hyponatremia. However, he became progressively less responsive, developed SIADH with hyponatremia, and finally aspiration pneumonia. He died on [ ] after his family's decision not to pursue aggressive treatment.

3) Patient No: 90, was a 41-year-old male, had a baseline CD4 counts of 6 cells/mm^3 and baseline viral load of 308,000 copies/ml. Significant relevant medical history included: CMV infection, esophageal candidiasis, depression, and anemia. On [ ] he was randomized to the APV/r arm. One month later, he was hospitalized for treatment of CMV retinitis and esophagitis. He was hospitalized for worsening of CMV disease on [ ] This hospitalization was complicated by hemorrhagic shock and the patient died on [ ] due to systemic CMV infection.

> ***MO Comments:*** *These subjects described above were typical of subjects with advanced HIV disease whose death was related to opportunistic infection or AIDS related concurrent infection, and were unrelated to study medication.*

4) Laboratory adverse events

The most frequently observed Grade 3/4 lab test abnormalities included triglycerides (range 16.4-21.1%), ALT (2.2-14.1%), and AST (0-7.1%); The TPV/APV/r arm had a higher rate of Grade 3/4 ALT elevation than the other arms. Most subjects with Grade 3/4 lab abnormalities were asymptomatic and continued treatment with spontaneous resolution of the abnormality. The lab test abnormality rate was low during Weeks 0-2, and then increased during Weeks 3-24. Most laboratory tests were unaffected by treatment with dual-boosted PI regimens.

Adverse laboratory events of specials interest

The AE and chemistry laboratory datasets were analyzed in order to evaluate for changes in serum creatinine, triglycerides, ALT's and bilirubin.

- Creatinine

  No subjects manifested Grade 3 or 4 elevations of creatinine during the study. Three (3) subjects developed Grade 2 serum creatinine elevations; one subject was assigned to each of the LPV/r, SQV/r, and TPV/r treatment arms. All three subjects were concomitantly receiving tenofovir (TDF). Elevated creatinine occurred on study day 15 for the subject on the TPV arm, and on

days 44 and 58 for the other two subjects. Treatment was temporarily held secondary to the elevations.
(See Tables 32 below)

TABLES 32: SHOWING LABORATORY CHANGES- CREATININE, ALT, TRIGLYCERIDES AND BILIRUBIN: 1182.51

	# of Subjects
Grade 3 or 4 Creatinine (Cr)	0
Temporarily held 2° to ↑Cr	3
Grade 3 ALT	15
Grade 4 ALT	7
Temporarily held 2° ↑ALT	8
Premature d/c 2° to ↑ALT	7
Grade 4 total bilirubin	1
Temporarily held 2° to ↑ bilirubin	1
Grade 3 TG	55
Grade 4 TG	22
Held or premature d/c 2° ↑TG	0

Source: AE, Chemistry laboratory datasets submitted 12/29/04

Pt #	Arm	*AE*	Baseline Cr/Gr	Max Cr/day	D/C	TDF
181	TPV/r	incr creat	1.85/1	2.64/57	held	Y
144	LPV/TPV/r	renal insuff	1.17/0	2.01/113	no	Y
232	LPV/TPV/r	incr creat	1.06/0	3.21/63	held	Y
1148	LPV/TPV/r	--	1.4/1	2.0/165	no	Y
1160	SQV/TPV/r	incr creat	2.1/2	2.8/70	held	Y
1425	SQV/TPV/r	renal insuff	2.4/2	3.7/16	held	Y
1138	SQV/TPV/r	--	2.4/2	3.4/110	no	N

Source: AE, Chemistry laboratory datasets submitted 12/29/04

MO Comment - Elevated serum creatinine: *The elevated creatinine described in the subjects concomitantly receiving TDF is probably a manifestation of the nephrotoxic effect of TDF.*

MO Comment - Hepatotoxicity: *The analysis of hepatotoxicity in study 1182.51 is complicated by the study design, i.e., all subjects received TPV after week 2. Only one liver AE or elevated ALT was noted in the first two weeks of the study, during the single-boosted period of the study.*

The following Table 33 shows hepatic AEs after week 2 based on analysis of AE, outcome, and baseline characteristics datasets provided by the applicant. Although it is impossible to distinguish the relative contribution of TPV compared to the other PIs in the ARV regimen, the table allows for comparison of

hepatotoxicity with the combination of TPV and individual PIs and gives an overview of hepatotoxicity in any PI-regimen containing TPV.

Table 33: Hepatotoxicity in Study 1182.51 during the dual-boosted period (weeks 3-24)

	TPV n=69	LPV n=86	SQV n=85	APV n=86	Total n=326
# HBsAg +	4	7	4	9	24
#HCV Ab+	4	9	7	7	27
#HBV/HCV coinfected*	1	1	1	1	4
# of subjects w/ ALT ≥ Grade 1 at BL	10	17	14	11	52
# of subjects w/ Grade 3 ALT#	5	3	1	5	14
coinfected and Gr 3 ALT	1	2	0	1	4
#of subjects w/Grade 4 ALT#	0	0	1	7	8
coinfected and Gr 4 ALT	0	0	1	2	3
% of subjects w/Gr3 or 4 ALT	1%	3%	2%	14%	7%
Median days to max ALT	113	88	131.5	59.5	86.5
Median maximum ALT and range	277 244-371	246 183-277	472 295-649	389 182-1096	
# of subjects w/ Grade 3 or 4 total bili	0	0	0	1	0
Study drug held 2° hepatotoxicity	1	1	0	7	9
Premature d/c 2° hepatotoxicity	1	1	1	2	5

[Source Data: Dataset analysis submitted 12/29/04.]

The analysis of this data is limited by the small numbers, which resulted in wide variation in some parameters such as median time to increases in ALT. However, some useful information can be garnered from this data. Seven percent of subjects had elevations in ALT during the study. The highest proportion of subjects with increased ALT values and the highest ALT elevations were observed in subjects receiving both TPV and LPV; this arm also had the highest number of subjects co infected with HBV or HCV at baseline and with elevated ALT at baseline. LPV is associated with hepatotoxicity (see Kaletra package insert) and the small number of subjects in this study cannot rule out an increase in hepatotoxicity with the co-administration of TPV, LPV, and RTV. However, TPV and LPV should not be co-administered because of the PK interactions, so a potential for increased hepatotoxicity with the two drugs does not need to be investigated further. Elevated ALT's occurred from day 15-168 in the TPV arm, day 94-140 in the SQV arm, day 44-50 in the LPV arm, and day 31-155 in the APV arm.

Approximately one-third of subjects with Grade 3 or 4 increases in ALT were co-infected with HBV or HCV at baseline. When analyzed a different way, 15% of subjects infected with HBV or HCV at baseline developed increases in ALT

during the study compared to only 5% of subjects who were not co-infected. In this study, co-infection with HBV or HCV was a risk factor for the subsequent development of hepatotoxicity.

Rash: ***MO Comment:*** *As seen in Table 34 below, during the first two weeks of the study, 12 subjects reported a rash including 3 in the TPV arm, 4 in the SQV arm and 5 in the APV arm. The number of females in the study was low, but none had skin rash. Hypersensitivity was reported in one subject receiving SQV/r.*

TABLE 34: SHOWING FEATURES OF SKIN RASH DEVELOPING IN STUDY 1182.51
Between week 0 and week 2, only the TPV arm was receiving TPV and below is the distribution of rash.

	TPV/r	LPV/r	SQV/r	APV/r
# of females/total # of subjects	5/69	6/86	5/85	6/86
# of subjects with any skin AE	4	1	6	5
Held or d/c TPV due to skin AE	2	0	0	2
# of females with skin AE	0	0	0	0
# of subjects with any rash	3	0	4	5
Median day of onset of rash	2	--	10	11
# of females with rash	0	0	0	0
hypersensitivity	0	0	1	0

MO Comment: *After week 2, when all subjects were receiving TPV, rash was observed in 27 subjects. The frequency was similar between arms. The frequency of rash was similar in females and males: 2/22 (9%) females compared to 26/304 males (8.5%). A description of the rash was not provided for the majority of subjects with a rash. However, one subject did develop urticaria. In addition, a rash associated with hypersensitivity was reported in two subjects.*

Between week 2 and week 4, TPV was added to all three treatment arms.

	TPV/r	LPV/TPV/r	SQV/TPV/r	APV/TPV/r	Total
# of females/total # of subjects	5/69	6/86	5/85	6/86	22/326
# of subjects with any skin AE	7	7	6	9	29
Held or d/c TPV due to skin AE	2	0	2	3	7
# of females with skin AE	0	1	0	1	2
# of subjects with any rash	6	7	5	9	27
# of females with rash	0	1	0	1	2
hypersensitivity	1	0	0	1	2

Source: Dataset analysis 12/29/04 submission

F. STUDY CONCLUSIONS

Data from Trial 1182.51 are used to demonstrate TPV/r robust short-term activity in the context of highly mutated virus.

1182.51 evaluated the safety of TPV/r co-administered with LPV/r, SQV/r and APV/r.

1) Co-administration of TPV/r with three other PI's were reasonably tolerated over the 4 weeks of treatment. However, large reductions in plasma AUC, C_{max}, and C_{min} of APV, LPV and particularly SQV were observed when co-administered with TPV/r.

A) Due to protocol-allowed treatment arm switches after Week 4, comparability of AE rates between arms was limited. However, the 24-week safety data suggest that use of TPV/r based dual-boosted PI regimens had no increased safety risk as compared with the single-boosted regimens.

B) Efficacy in TPV/r group- Over the 14 days of functional monotherapy, plasma HIV-1 RNA levels decreased by 1.2 $\log_{10}$ copies/mL in subjects taking TPV/r, compared with reductions of < 0.4 log10 copies/mL in each of the other boosted arms, clearly showing superiority of TPV/r in this short-term comparison in subjects with highly PI-resistant viruses. The addition of TPV/r to the other regimens at week 3 also resulted in reductions in median viral load. However, the antiretroviral effect appeared to be short lived in many subjects, as HIV-1 RNA levels were returned toward baseline by weeks 4 and 8 of the study.

MO COMMENTS AND OVERALL CONCLUSIONS IN STUDY 1182.51:
There are substantial issues associated with Study 1182.51, which complicate its interpretation and make reaching any definitive conclusions about the safety and efficacy of TPV difficult.

1) *First,* ***study design issues*** *made it difficult to determine the relative contribution of TPV to antiviral activity. During the first 2 weeks of the study, the ARV regimen consisted of optimized background plus a PI – TPV, LPV, SQV and APV. At 2 weeks, TPV was added to the respective treatment arms for 2 additional weeks. Then after 4 weeks subjects were allowed to switch and change treatment regimens. In fact, 30% subjects in the TPV arm did change ARV's compared to none in the LPV arm, 3.6% in the APV arm, and 8.5% in the SQV arm. Therefore, a clean determination of efficacy beyond two to four weeks is difficult.*

2) *Second,* ***baseline characteristics (BL)*** *between arms differed with the highest BL CD4 counts and lowest BL VL in the TPV/r Arm, which might have led to bias in favor of TPV.*

*3) Third, **study population**. This was an extremely difficult study to conduct because of the high level of baseline ARV resistance in these heavily pretreated study subjects. These subjects had little chance of virologic success and were often receiving TPV as functional monotherapy. Therefore, the high rebound rate in this study is not surprising.*

*4) Fourth, **study conduct**. A substantial number of subjects had protocol violations (60%). Some of these violations may have had a substantial impact on the study results such as 10% were non- compliant, 6 % took the wrong dose of PI, and 2.5% subjects took the wrong study drug. Although some of these violations may have been related to investigators' and subjects' attempts to maximize therapy, they severely impact the ability to interpret the study results.*

[6] INDIVIDUAL STUDY REPORT 1182.52

A. STUDY DESIGN

1182.52 was a randomized, double blind dose optimization study Phase IIb study, designed to demonstrate the most tolerable and effective TPV/r for use in the Phase III studies; To obtain information on TPV/r activity against HIV-1 with various patterns of PI resistance; To obtain longer- term safety data on TPV/r in the new and final formulation.

All subjects in the study were required to have had at least one primary PI mutation from among the following: 30N, 46I/L, 48V, 50V, 82A/F/T, 84V or 90M and not more than one from among 82L/T, 84V or 90M

The primary efficacy endpoint was VL change from baseline to week 2. The primary safety endpoints were the proportions of subjects with DAIDS Grade ≥2 for diarrhea, any grade of vomiting, and any SAE up to Week 4. Study subjects received treatment for 24-32 weeks.

A total of 216 HIV+ triple class experienced subjects who had failed at least 2 PI regimens and had at least 1 or more primary PI mutations. Subjects discontinued their current PI and added, in a blinded manner, TPV/r in 1 of 3 doses for 2 weeks. At the end of 2 weeks, the background regimen was optimized and blinded TPV/r dosing was continued.

The multiple PI-experienced subjects with primary PI resistance mutations on TRUGENE testing were randomized to three dose cohorts:

1) TPV 500 mg/RTV 100 mg (n=73)
2) TPV 500 mg/RTV 200 mg (n= 72)
3) TPV 750 mg/RTV 200 mg (n= 71)

Entry requirements included:

1) HIV-positive males or females of 18 years of age or older;
2) treatment with at least 3 months of NRTIs and NNRTIs;
3) treatment with at least two PIs;
4) a VL of at least 1000 copies/mL; and
5) a genotype screening of at least one per-protocol protease mutation with more than one of the 82 L/T, 84V, or 90M mutations.

After screening, qualifying subjects were randomized to one of the three blinded regimens, discontinued from their current PI, and administered TPV/r therapy for 2 weeks while remaining on their current background ARV therapy. After 2 weeks, background ARV medications were optimized and each patient remained on blinded TPV/r and optimized ARV medications for the remainder of the trial, which was a maximum of 32 weeks.

B. STUDY RESULTS

a. Study Population

a) Demographics and baseline characteristics

The median baseline VL was 4.53$\log_{10}$ copies/mL and median CD4+ cell count was 177 cells/mm^3.The median age in this trial 42 years (84.3%), with a mean of 43.6 years (+/- 7.8 years), and 182 subjects or 84.3% were males, and 165 subjects or 76.4% were white, while 50 subjects or 23.1% were black.

MO Comments: *The age and baseline characteristics were fairly evenly distributed across treatment arms (See Table 35 below).*
A significant achievement in this study however was the ability of the Investigators to enroll a 23% black population in this study; Such a significant enrollment, although not mimicking the distribution of HIV disease in the external environment, in which this drug will be eventually used, is significantly greater than the usual 5-10% proportion of Black enrollment that was seen in the other Phase II studies within this NDA specifically, and in other HIV study populations generally.

Table 35: Showing baseline demographic data, HIV-1 RNA value, and CD4+ cell count in Trial 1182.52 - FAS (as treated)

	TPV/r	TPV/r	TPV/r	Total
	500 mg/	500 mg/	750 mg/	
	100 mg	200 mg	200 mg	
Total treated	73	72	71	216
Age [years]				
N	*73*	*72*	*71*	*216*
Median	*43.00*	*42.50*	*42.00*	*42.00*
Range	*29-68*	*28-63*	*30-64*	*28-68*
Gender [N (%)]				
Male	*63 (86.3)*	*60 (83.3)*	*59 (83.1)*	*182 (84.3)*
Female	*10 (13.7)*	*12 (16.7)*	*12 (16.9)*	*34 (15.7)*
Race [N (%)]				
White	*56 (76.7)*	*56 (77.8)*	*53 (74.6)*	*165 (76.4)*
Black	*17 (23.3)*	*16 (22.2)*	*17 (23.9)*	*50 (23.1)*
Asian	*0*	*0*	*1(1.4)*	*1 (0.5)*
Missing	*0*	*0*	*0*	*0*
Median baseline HIV-1 RNA [log10	4.49	4.57	4.53	4.53
copies/mL]				
Median baseline CD4+ cell count	187	179	169	177
[cells/mm3]				

[Source Data: Clinical Trial Report for Trial 1182.52.]

b) Treatment history
Baseline ARV medication history was similar among the 3 treatment groups. The most frequently used NRTIs were 3TC (97.7%), d4T (95.4%), and ZDV (94.0%); NNRTIs were efavirenz (EFV) (65.3%) and nevirapine (NVP) (62.5%).

The most frequently used PIs were RTV (93.5%) and IDV (81.0%). The median number of ARVs that subjects had taken in previous regimens was 5 NRTIs (range 1-8), 1 NNRTI (range 0-3), and 5 PIs (range 1-6).

c) Resistance history
Median numbers of protease gene mutations at baseline were 17 in the TPV/r 500/100mg group, 18 in the TPV/r 500 /200 mg group, and 16 in the TPV/r 750 mg/200 mg group. Consistent with the higher median number of protease gene mutations in the TPV/r 500 /200 mg group, 72.3% of subjects in this group had 16 or more mutations compared with 61.7% in the TPV/r 500/100 mg group and 57.8% in the TPV/r 750/200 mg group.

Across treatment groups, proportions of subjects whose virus contained mutations at codons 33, 82, 84, and 90 at baseline were similar, although the TPV/r 500/200 mg group had the largest number of subjects with 3 mutations. High proportions of subjects in all 3 treatment groups showed genotypic mutations predicting resistance at baseline to PI, NRTI, and NNRTI medications, except LPV. Among treatment groups, the TPV/r 500/200 mg group had the largest proportion of subjects with genotypic resistance to all currently marketed PIs and NNRTIs.

Overall, subjects had baseline HIV isolates with an average drug susceptibility of 95.3-fold wild type for RTV, 77.0-fold wild type for LPV, 36.7-fold wild type for NVP, 12.1-fold wild type for IDV/r, 8.7-fold wild type for APV, 7.0-fold wild type for SQV, and 1.1-fold wild type for TPV. Among treatment groups, the TPV/r 500 /200 mg group showed the highest proportion of isolates with phenotypic evidence of resistance to all PIs, including TPV. However, the baseline phenotype results suggested that TPV would be effective in highly treatment-experienced populations.

Of the 216 subjects treated in BI 1182.52, more than 90% of the subjects had at least ten protease gene mutations at baseline; phenotypic resistance to individual PIs occurred for 67-91% of subjects.

2. Study Disposition
Two hundred and sixteen (216) subjects were randomized and received at least one dose of study medication. Of these 216 subjects, 166 (76.9% completed the study therapy in this trial).
The treatment groups differed in the proportion of subjects completing study therapy: 83.3% completed study dosing in the TPV/r 500/200 mg group, while 78.1% in the TPV/r 500/100 mg and only 69% in the TPV/r 750/200 mg group completed dosing.

Or expressed in another way, the proportion of subjects discontinuing prematurely for any reason was nearly twice in the TPV/r 750/200 mg group, as compared to the 500/100 mg group. The overall differences among treatment groups were attributable to cumulative differences for all the factors that led to premature discontinuations from study, including adverse events, lack of efficacy, non-adherence with the protocol, withdrawal of consent, lost to follow up, and "other' miscellaneous factors.

(See Table 36 below)

TABLE 36: SHOWING SUMMARY OF SUBJECT DISPOSITION BY TREATMENT ARM

Patient Disposition	TPV/r 500/100		TPV/r 500/200		TPV/r 750/200		Total	
	n	%	n	%	n	%	n	%
Randomized/ treated	73	100	72	100	71	100	216	100
Not prematurely d/c'ed	57	78.1	60	83.3	49	69	166	76.9
Prematurely d/c'ed	16	21.9	12	16.7	22	31	50	23.1
• **due to AE**	5	6.8	7	9.7	11	15.5	23	10.6
• **other AE**	1	1.4	4	5.6	6	8.5	11	5.1
worsening of pre-exist disease	1	1.4	3	4.2	4	5.6	8	3.7
unexpected worsening HIV	3	4.1	0	-	1	1.4	4	1.9
Lack of Efficacy	4	5.5	3	4.2	5	7.0	12	5.6
Non-adherent with protocol	3	4.1	1	1.4	2	2.8	6	2.8
Other	2	2.7	0	-	1	1.4	3	1.4
Consent withdrawn (non-AE related)	2	2.7	0	-	1	1.4	3	1.4
Lost to follow-up	0	-	0	-	2	2.8	2	0.9

Source Data: Appendix 16.1.9.2, Table 1.1

PROTOCOL VIOLATIONS

Among treated subjects, 16 (7.4%) had protocol violations that affected their evaluability for efficacy. Seven (9.9%) subjects in the TPV/r 750/200 mg group, five (6.9%) in the 500/200 mg group, and 4 (5.5%) in the 500/100 mg group. The most common protocol deviation was use of a non-study PI during the first 4 weeks of the study (2.8%), and a screening viral load of <1000 copies/m/L or baseline viral load of < 500 copies/mL (2.3%). The violations are listed in the Table 37 below.

TABLE 37: SHOWING PROTOCOL DEVIATIONS AFFECTING PATIENT EVALUABILITY FOR EFFICACY (by treatment arm): 1182.52 .

	TPV/r 500/100 (#/%)	TPV/r 500/200 (#/%)	TPV/r 750/200 (#/%)	Total
Total # of subjects randomized	73	72	71	**216**
Total #/% of subjects with violations	4(5.5)	5 (6.9)	7 (9.9)	16 (7.4%)
Violations:				
-Non-study PI used during the first 4 weeks of TPV/r Rx	2 (2.7)	3 (4.2)	1(1.4)	6 (2.8)
- Screening VL < 1000 copies/m/L or baseline VL < 500 copies/mL	1 (1.4)	1 (1.4)	3 (4.2)	5 (2.3)
- Background ARV medications changed during 2 weeks of functional monotherapy	1 (1.4)	1 (1.4)	1 (1.4)	3 (2.3)
- Genotypic resistance with one or more PI resistance mutations at baseline	1 (1.4)	0	0	1 (0.5)
- Current PI based ARV regimen taken for < 3 months before randomization	0	0	1 (1.4)	1 (0.5)
- Enfuvirtide taken within 30 days of study entry	0	0	1 (1.4)	1 (0.5)
- One dose of TPV/r medication taken; and no on-treatment efficacy results available	0	0	1 (1.4)	1 (0.5)

Source Data: Appendix 16.1.9.2, Table 2.1; Appendix 16.2 Listing 2.1

***MO Comments**: Among treated subjects only 16 (7.4%) had protocol violations that affected their evaluability for efficacy. These were fairly evenly distributed among treatment arms, and included seven or (9.9%) subjects in the TPV/r 750/200 mg group, five (6.9%) subjects in the 500/200 mg group, and 4 (5.5%) subjects in the 500/100 mg group.*

The most common protocol deviation was use of a non-study PI during the first 4 weeks of the study (2.8%), and a screening viral load of <1000 copies/m/L or baseline viral load of < 500 copies/mL (2.3%).

Overall, this Definitive Dose Optimizing study had much fewer protocol violations than study 1182.51. (60%)

C. PHARMACOKINETIC/ PHARMACODYNAMIC ANALYSIS

BI 1182.52 was the definitive dose-finding study for TPV/r. The primary study objective was therefore to determine the optimal TPV/r dose for use in PI-experienced subjects participating in the Phase III trial program.

The first two weeks of this trial represented a "functional monotherapy" phase in which subjects changed the failing PI they were taking at entry to one of three TPV/r doses but maintained their background regimen; these data provided a pure analysis of TPV/r effect. The antiviral effect observed in these first 2 weeks was likely due only to the TPV/r.

Pharmacokinetic data indicated that 50% of subjects in the TPV/r 500 /100 mg group had TPV trough levels above the 20 μM preliminary target while more than 75% of subjects in the higher dose groups attained this preliminary threshold. In addition, there was less inter-patient variability for subjects on the TPV/r 500 /200 mg dose compared to the other dose groups.

The TPV/r 500/100 mg dose was eliminated from consideration due to its inferior efficacy and PK profile in this advanced population. The two higher dose groups had similar efficacy profiles at 4-8 weeks and had similar proportions of subjects above the preliminary target of 20 μM; only safety could be used to distinguish the two doses.

The TPV/r 500/200 mg bid dose offered a better combination of safety, efficacy, and PK results for treatment-experienced subjects. All subjects were shifted to the TPV/r 500/200 mg dose once this data was analyzed and reviewed with regulatory authorities. While the dose finding decisions were initially based on short-term data, these data were confirmed at the 24-week analysis.

D. ANALYSIS OF EFFICACY

All three doses showed substantial short-term activity with 0.9-, 1.0- and 1.2 $\log_{10}$ reductions in viral load over 2 weeks with the 500/100 mg, 500/200 mg, and 750/200 mg bid doses respectively.

TABLE 38: Showing Median $\log_{10}$ change from baseline in VL in RNA copies/mL through 24 weeks of TPV/r by treatment arm (FAS-LOCF): Trial 1182.52

Weeks of treatment	TPV/r 500/100 (n=73)	TPV/r 500/200 (n=72)	TPV/r 750/200 (n=71)	Total (n=216)
Baseline	4.49	4.57	4.53	4.53
2 weeks	-0.85	- 0.93	-1.18	-1.02
4 weeks	-1.18	-1.29	-1.24	-1.22
8 weeks	-1.01	- 0.86	-0.93	-0.95
16 weeks	-0.57	-0.70	-1.08	-0.71
24 weeks	- 0.25	-0.55	-1.07	-0.60

Source Data: Table 14.2:1 and Appendix 16.1.9.2, Table 4.2.1

MO Comment: *All three treatment groups showed a short term response, but this response was not durable. The lack of durability was noted particularly in the TPV/r 500/100 mg group. For this highly treatment experienced population, the TPV/r 500/100 dose was inferior, and viral load reductions were not sustained to 24 weeks. The other two dose*

groups sustained at least a 0.5 log_{10} reduction to 24 weeks. Efficacy was most sustained in the TPV/r 750/200 mg group.

The Applicant also looked at treatment response as measured by median CD4 cell change from baseline, percentage of subjects achieving > 1 log_{10} drop, % achieving < 400 copies/mL, and % undetectable below 50 copies/mL after 2 weeks of functional monotherapy, and after 24 weeks. The results are shown in the table below.

TABLES 39: SUMMARIZING EFFICACY IN 1182.52 SHOWING EFFICACY (AS MEASURED BY MEDIAN CD4 CELL CHANGE)

At 2 weeks:

Treatment	Subjects entered/ completed @ 24 weeks	% achieving >/= 1 log10 drop	% achieving (<400 copies/mL)	% undetectable (<50 copies/ mL)	Baseline Median CD4 (cells/ mL)	Median CD4 cell Change (cells/ mm3)
TPV/r 500/100	73/72	43.1%	19.4%	2.8%	187	+16
TPV/r 500/200	72/69	46.4%	20.3%	n/a	179	+9
TPV/r 750/200	71/69	63.8%	18.8%	1.4%	169	+11

At 24 weeks:

Treatment	Subjects entered/ completed @ 24 weeks	% achieving >/=1 log10 drop	% achieving (<400 copies/mL)	% undetectable (<50 copies/ mL)	Baseline Median CD4 (cells/ mL)	Median CD4 cell Change (cells/ mm3)
TPV/r 500/100	73/72	31.5%	32.9%	24.7%	187	+11
TPV/r 500/200	72/69	40.3%	37.5%	20.8%	179	+19
TPV/r 750/200	71/69	45.1%	38.0%	21.1%	169	+47

Source Data: Appendix 16.1.9.2, Table 6.3.1

Efficacy Results

- A total of 216 subjects were evenly distributed among the treatments for demographics, previous treatment experience, baseline VL, and CD4+ cell count.

- All doses achieved a >0.5 log10 median reduction in VL at 2 weeks and efficacy was sustained through 24 weeks. The TPV/r 500/100 mg dose consistently showed less VL reduction than the TPV/r 500/200 mg or TPV/r 750/200 mg doses, which demonstrated comparable efficacy results throughout the trial.

- The TPV/r 500/200 mg dose was subsequently selected as the optimal treatment regimen. Subjects receiving 500/200 mg had the highest proportion of protease mutations at baseline and highest proportion of isolates resistant to all PIs.

- VL reduction was markedly less in subjects with at least three mutations at codons 33, 82, 84, and 90.

- All three dose combinations studied were effective in rapidly reducing plasma HIV-1 RNA counts: all three doses achieved a statistically significant ($p<0.0001$) VL reduction from baseline of >0.5 $\log_{10}$ after 2 weeks of TPV/r functional monotherapy, but this was not sustained at 24 weeks for the TPV/r 500/100 mg dose group. The TPV/r 500/200 mg and 750/200 mg doses sustained at least a 0.5 log10 reduction at 24 weeks.

Treatment Response as related to number of PRAMS

The Applicant not only sought to distinguish the treatment response between doses, but also the dose of TPV/r as it related to the number of PRAMS or (**P**rotease **R**esistant **A**ssociated **M**utations). Participation was therefore limited to those subjects who had no more than one mutation among 82A/F/T, 84V, or 90M, codon changes suggestive of reduced TPV susceptibility that had been identified by *in vitro* analyses.
The relationship between genotype and response was analyzed as shown in Table 40 below. The data demonstrated that subjects who had 3 or more resistance mutations at 4 specific protease gene codons had poorer virologic responses to TPV/r therapy. These loci (33, 82, 84 and 90) are known as PRAMS.

TABLE 40: SHOWING IMPACT OF PRAMS ON VIRAL LOAD RESPONSE OF TPV/r IN 1182.52 AT 2 WEEKS

# of PRAMs	TPV/r 500/100		TPV/r 500/200		TPV/r 750/200		Overall TPV/r	
	n	*Median change HIV-1 RNA* ($\log_{10}$ copies/ml	n	*Median change HIV-1 RNA* ($\log_{10}$ copies/ml	n	*Median change HIV-1 RNA* ($\log_{10}$ copies/ml	n	*Median change HIV-1 RNA* ($\log_{10}$ copies/ml
0	5	-1.32	0	-	4	-1.19	9	-1.32
1	19	-1.21	23	- 1.15	30	-1.25	72	-1.22
2	35	- 0.78	24	-1.40	19	-1.24	78	-0.97
3	13	-0.19	21	-0.33	16	-0.54	50	-0.32
Total N	72		68		69		209	

Source Data: Appendix 16.1.9.2, Table 6.2.1.1 and Statdoc 6.1.6.3.3

MO Comment: *IMPACT of Protease Resistant-Associated Mutations (**PRAMS**) on Viral Load (VL) Response to TPV/r.*

There was also an inverse relationship between the number of protease gene mutations and viral load reductions observed at 24 weeks, as well as the number of mutations at codons 33, 82, 84 and 90. The data demonstrated that subjects with three or more mutations at codons 33, 82, 84 and 90, had a poorer response, and none of the TPV/r dose combinations decreased viral load more than 0.5 log_{10} at 24 weeks.

TPV selected for protease gene mutations at codons 33, 34, 35, 36, 82 and 84. Viruses with V82A evolved to V82T. New mutations at V82L/T were correlated with significant phenotypic resistance.

The TPV and RTV concentrations over the 12 hour drug administration interval were within the range of concentrations observed in the other TPV/r studies conducted in both healthy HIV-1 negative volunteers and HIV-1 positive subjects.

E. ANALYSIS OF SAFETY

1. Exposure to study drugs
Subjects received 1 of the following 3 treatments: TPV/r 500/100 mg, TPV/r 500/200 mg and TPV/r 750/200 mg. In this trial, the 216 randomized and treated subjects were exposed to study medication for a median of 177 days. Two hundred and eleven of the 216 subjects randomized and treated. (97.7%) subjects completed the first 2 weeks of the study (TPV/r functional monotherapy) and 207 (95.8%) completed the first 4 weeks of the trial. In the 3 treatment groups combined, 71.3% of subjects completed >168 days (24 weeks).

The median exposure to study drugs was 185, 184, and 171 days, for the TPV/r 500 mg/100 mg BID, TPV/r 500 mg/200 mg BID, and TPV/r 750/200 mg groups, respectively. Differences in exposure among the 3 treatment groups were considered minor and not clinically significant.

MO COMMENT: *Exposure-response data analysis showed that participants receiving TPV/r 750/200 mg had lower RTV exposures and higher TPV exposures than TPV/r 500/200 mg group. This suggests that the increase in AEs seen with increased dose of study drug was related to TPV and not RTV.*

2. Overall adverse events:
Table 41 shown below shows the most frequent occurring AEs in this trial. AEs were mainly Gastrointestinal in nature, and evenly distributed across treatment groups.

TABLE 41: SHOWING MOST FREQUENT AES (>10%) THROUGH 24 WEEKS OF TRV/R TREATMENT: 1182.52

	TPV/r 500/100 mg (n= 73)		TPV/r 500/200 mg (n= 72)		TPV/r 750/200 mg (n= 71)		Total n= 216	
Total with any AE	65	(89)	65	(90.3)	65	(91.5)	195	(90.3)
diarrhea	28	(38.4)	29	(40.3)	26	(36.6)	83	(38.4)
nausea	23	(31.5)	21	(29.2)	21	(29.6)	65	(30.1)
headache	16	(21.9)	13	(18.1)	13	(18.3)	42	(19.4)
fatigue	9	(12.3)	13	(18.1)	13	(18.3)	35	(16.2)
vomiting	11	(15.1)	7	(9.7)	15	(21.1)	33	(15.3)
pyrexia	4	(5.5)	11	(15.3)	10	(14.1)	25	(11.6)
abdominal pain	8	(11.0)	7	(9.7)	6	(8.5)	21	(9.7)
insomnia	5	(6.8)	4	(5.6)	8	(11.3)	17	(7.9)

Source Data: Appendix 16.1.9.2, Table 7.2.1.6.1

3. Adverse event associated with study discontinuation

Discontinuations due to AEs were directly related to the dose of TPV/r- 5.5% in the TPV/r 500/100 mg group, 9.7% in the TPV/r 500 mg/200 mg group, and 15.5% in the TPV/r 750 /200 mg group.

MO Comment: *The increase in the percentage of discontinuations due to AEs is consistent with a dose response effect.*

4. Severe adverse events (SAEs)

33 of 216 subjects in 182.52 or 15.3% subjects experienced SAEs. Of these, 12.3% were in the TPV/r 500/100 mg group, 19.4% in the TPV/r 500/200 mg group, and 14.1% in the TPV/r 750/200 mg group.

5. Deaths

Three deaths occurred in this trial in subjects who were receiving study medication. Two deaths were in the TPV/r 500/100 mg group, and one in the 750/200 mg group. Neither death was considered to be treatment related; All deaths were considered to be AIDS-related. (Deaths are summarized in Table 42 below).

TABLE 42: SUMMARIZING DEATHS IN 1182.52

Age / Sex Patient #	Treatment group	Reason for Death	Baseline CD4+count/ VL
49/ M #1217	TPV/r 500/100	Progressive Multifocal Leukoencephalopathy	53/139,037
33/F #1121	TPV/r 750/100	Cryptococcal Meningitis	17/ 27,467
38/M #1372	TPV/r 500/100	Disseminated CMV Disease	2/ 952,365

Source: FDA Compilation based on information submitted by applicant.

The Deaths were as follows:

1) Patient # 1217 was a 49 y/o white male, who was started on TPV/r 500/100 mg bid on [redacted] Concomitant medications were Ziagen, Epivir, and Zerit. Approximately 7 weeks later he presented with a one week history of loss of balance, extreme fatigue, and difficulty speaking. Two days later a MRI Brain showed non-enhancing bilateral white matter lesions, consistent with Progressive Multifocal Leukoencephalopathy (PML). A spinal tap was performed. Results were not noted. A Brain biopsy was not performed. It is unclear whether an autopsy was performed.

2) Patient # 1121 was a 33 year old white female, who was randomized to TPV/r 750/200 mg. On day 14 she was admitted to hospital with a history of headache, nausea, and mental status changes. Spinal tap was positive for Cryptococcal Meningitis, and she was started on Amphotercin B. She died approximately 2 weeks after while receiving palliative hospice care.

3) Patient # 1372 was a 38 y/o white male on the TPV/r 500/100 mg arm of the study, died in hospice care with Disseminated CMV Disease, 3 days after discontinuing the study. Concomitant Diagnoses included probable Lymphoma of the lower extremity, Bilateral Pneumonia, Pyrexia of Unknown Etiology.

6. *Laboratory adverse event*

The most frequent AEs during the entire study were - diarrhea (38.4%), nausea (30.1%), headache (19.4%) and fatigue (16.2%).

Grades 3 or 4 elevations in ALT were: 5.5% in the TPV/r 500/100 mg group; 11.1% in the TPV/r 500/200 mg group and 21.2% in the TPV/r 750/200 mg group

All liver function test abnormalities resolved with drug discontinuation.

Adverse events of special interest

- **Hepatotoxicity**

This reviewer performed specific analyses of the datasets submitted by the Applicant.

The incidence of Grade 3 or Grade 4 elevation of ALT's increased across dose groups and was 5% of the subjects in the 500/100mg group, 10% in the 500/200mg group and 21% in the 750/200mg group. Hepatotoxicity was dose related as evidenced by the number of subjects holding or discontinuing study drug, (6 cases in the high dose group, 4 in the middle group, and 1 in the low dose group, the higher maximum ALT values with increasing TPV exposure), and the concomitant elevation of serum bilirubin (2 cases in the high dose group vs 0 cases in the other dose groups). Additionally, one subject in the 750/200mg group exhibited clinical jaundice, which is associated with severe hepatocellular injury. The number of study subjects co-infected with HBV or HCV was slightly higher in the 750/200 mg arm. The number of co-infected subjects with increased ALT values during the study was extremely small (three), therefore, in this trial, it is difficult to determine if hepatitis B or C was a risk factor for the development of hepatotoxicity.

Table 43: Analyzing HBV/HCV status and ALT and bilirubin datasets of subjects in Study 1182.52 by treatment arm

	500/100 n=73	**500/200 n=72**	**750/200 n=71**
# HBsAg +	2	4	6
#HCV Ab+	9	6	7
#HBV/HCV coinfected*	0	0	2
# of subjects w/ Grade 3 ALT#	3	4	9
coinfected and Gr 3 ALT	1	0	2
#of subjects w/Grade 4 ALT#	1	3	6
coinfected and Gr 4 ALT	0	0	0
% of subjects w/Gr3 or 4 ALT	5%	10%	21%
Median maximum ALT and range	277 216-348	652 202-972	338 205-1065
# of subjects w/ Grade 3 total bili	0	0	2
# of subjects w/ Grade 4 total bili	0	0	0
Drug held 2° hepatotoxicity	1	1	1
Premature d/c 2° hepatotoxicity	0	3	5

*includes subjects included in individual HBV and HCV categories.
subjects with both Grade 3 and Grade 4 ALT values are only included in Grade 3
Source: AE and laboratory dataset analysis, 12/29/04 submission

- ***Creatinine***

MO Comment: There were no Grade 3 or 4 increases in creatinine. Grade 2 increases in creatinine using the DAIDS Clinical Grading System were observed in 11 subjects. An additional subject was diagnosed with acute renal failure during this study. There were more increases in creatinine in the 750/200 arm (6 subjects) compared to the 500/100 (4 subjects) and the 500/200 (1 subject), suggesting that there might be a dose related decrease in renal function. Of the 12 subjects with elevations of creatinine or renal

failure, at least 8 (67%) subjects were also on tenofovir (TDF), which is associated with nephrotoxicity (see package insert for TDF).

However, these results must be viewed with caution. The applicant used the DAIDS Clinical Grading system, which by definition states that Grade 3 creatinine elevation is >1.9-3.5X the upper limit of normal (ULN). Therefore, many patients would have renal failure at Grade 2 creatinine levels and the DAIDS criteria underestimate the degree of nephrotoxicity with a study drug.

- ***Rash - Study 1182.52***

A dose relationship was also observed for the appearance of rash. Of the 18 subjects who developed rash (8.3%) during the study, the majority (10) were in the TPV/r 750/200 mg group. The rash also appeared to be more severe in the TPV/r 750/200 mg group, with 4 subjects study medication being held in 4 subjects in the treatment arm with the highest dose of TPV/r.

No inferences regarding gender predilection can be made based on this study, because of the small numbers of females with rash or any skin AE. Of interest, one subject had a rash associated with hypersensitivity and another had a photosensitivity rash. It is clear that TPV use is associated with a mild form of hypersensitivity in a small number of subjects. In addition, TPV is a sulfonamide and a small number of subjects will have photosensitivity reactions. This information will be communicated in the TPV package insert.

TABLE 44: SHOWING FEATURES OF SKIN RASH DEVELOPING IN STUDY 1182.52

	TPV/r 500/100	**TPV/r 500/200**	**TPV/r 750/200**
# of females/total # of subjects	10/73	12/72	12/71
# of subjects with any skin AE	8	8	13
Held or d/c TPV due to skin AE	0	0	4
# of females with skin AE	0	2	1
# of subjects with any rash	7	3	11
# of females with rash	0	1	1
hypersensitivity	1	0	0
photosensitivity	0	0	1

Source: Data Set Analysis- 12/29/04 Submission.

7. Safety Conclusions

a) The **TPV/r 500 /200 mg** dose was identified as the optimal combination in terms of efficacy, safety, and PK characteristics for use in highly treatment-experienced subjects, and was chosen for further study in Phase III clinical trials.

Safety analyses of Trial 1182.52 demonstrated a dose relationship with higher frequency of severe adverse events, discontinuations due to adverse events and DAIDS Grade 3 or 4 ALT elevations observed with increasing dose.

(The TPV/r 500 mg/100 mg group had fewer AEs than the two higher dose groups but showed suboptimal efficacy in highly treatment-experienced subjects, while the TPV/r 750 mg/200 mg group had the higher frequencies of AEs.

b) Overall, the predominant adverse events at 4 weeks in all dose groups were diarrhea (33.3%), nausea (23.1%), headache (15.3%) and vomiting (11.1%).

c) The most frequent Grade 3 and 4 laboratory abnormalities were noted for triglycerides (12.1%) and elevations of ALT 8.8%. There did not appear to be a strong dose response trend in adverse events or laboratory, except for Grade 3 or 4 ALT elevations in the respective treatment arms.

F. OVERALL STUDY CONCLUSIONS AND MO COMMENTS: 1182.52

1) *Subjects who had 3 or more resistance mutations at the protease resistance-associated mutations (PRAMS) specific protease gene codons (i.e loci 33, 82, 84 and 90) had poorer virologic responses to TPV/r therapy.*

2) *All 3 doses of TPV/r (500/100, 500/200, and 750/200) showed substantial short-term activity with 0.9, 1.0 and 1.2-log_{10} reductions over 2 weeks. However this response lacked durability. The lack of durability was noted particularly in the TPV/r 500/100 group. The TPV/r 500/100 dose was inferior, and viral load reductions were not sustained to 24 weeks. The other two dose groups sustained at least a 0.5 log10 reduction to 24 weeks. Efficacy was most sustained in the TPV/r 750/200 mg group.*

3) *Rationale of dose selection in study 1182.52:*
A composite of efficacy, tolerability and safety, coupled with PK led to the selection of TPV/r 500mg/200mg bid as the dose for Phase III studies. Three doses were studied in Study 1182.52: TPV/r 500/100, TPV/RTV 500/200, and TPV/RTV 750/200 mg. The median log_{10} changes from baseline viral load were -0.85, -0.93, and -1.18, respectively, following 2 weeks of treatment with the above doses, indicating that anti-viral activity was dose-dependent. The safety analysis also demonstrated a dose related relationship, between treatment dose arm and discontinuations due to AEs and Grade 3 ALT elevations demonstrably showing a direct relationship. (See Table 45 below)

TABLE 45: SHOWING THE PERCENT OF SUBJECTS WITH SAFETY/TOLERABILITY EVENTS (BY DOSE/TREATMENT ARM):

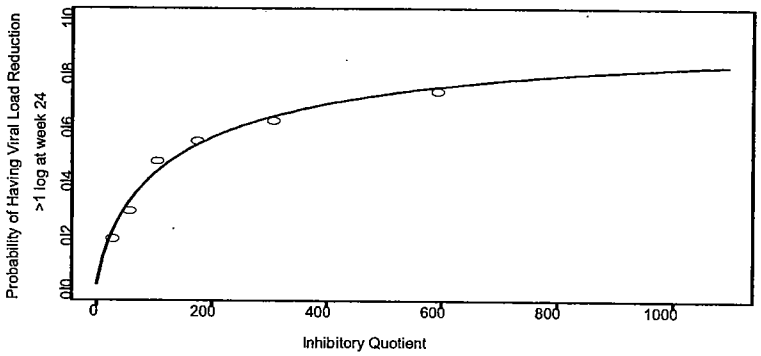
	500/100 TPV/RTV	500/200 TPV/RTV	750/200 TPV/RTV
Severe AE	17.8%	23.6%	39.4%
Discontinuation due to AE	5.5%	9.7%	15.5%
Grade 3 ALT	5.5%	11.1%	21.2%

Source: FDA Compilation based on information submitted by applicant.

4) *In the final analysis, dose selection for Phase III was based primarily on tolerability, as the two upper dose treatment arms showed comparable efficacy at 24 weeks. Hence, it is important to determine the proportion of subjects who may not benefit from treatment at this dose. An exposure-response analysis of Study 1182.52 data helped to determine the proportion of subjects who may have less than optimal exposures at the intended marketed dose level (TPV/r 500/200 mg). Also, large inter subject variability in trough concentrations of TPV (range: [redacted] ng/mL) observed from phase 3 studies, may cause subjects who receive TPV/r 500/200 mg (the intended marketed dose) to achieve low TPV plasma concentrations levels, that are not likely to be efficacious if their virus has a high IC_{50}. Logistic regression analysis of data from Study 1182.52, showed that an inhibitory quotient (C_{min}/IC_{50}) of 100 would result in 1 log_{10} reduction at week 24 in 43% of the subjects. When C_{min} and IC_{50} data on TPV in the pivotal phase 3 studies is analyzed, only 293 subjects or 53% subjects on the TPV/r 500/200 mg dose have an inhibitory quotient of 100 or greater. (See Figure noted below)*

Please see Pharmacometrics Review analysis performed by Dr Jenny J Zheng for further details.

Figure : Plot showing probability of subjects achieving at least 1 $_{log}$ VL reduction ↑ with higher IC



Source: FDA Pharmacometrics review by Dr Jenny J Zheng

APPENDIX

Table 1 : Drugs that Should Not be Co-administered with TPV/r	
Drug Class/Drug Name	**Clinical Comment**
Antiarrhythmics: Amiodarone, bepridil, flecainide, propafenone, quinidine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antimycobacterials: rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
HMG CoA reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptics: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedatives/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 2: Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions		
Concomitant Drug Class: Drug name	**Effect on Concentration of Tipranavir or Concomitant Drug**	**Comment**
HIV-Antiviral Agents		
Nucleoside reverse transcriptase inhibitors: Abacavir	↓Abacavir concentrations by approx. 40%	Appropriate doses for the combination of TPV/r and abacavir have not been established.
Didanosine	↓Didanosine approx 10-20%	Dosing of EC-didanosine and TPV/r should be separated by at least 2 hours. Preferably didanosine should be given just before lunch.
Emtricitabine	Interaction is not expected.	No interaction expected
Lamivudine	↔Lamivudine ↔Tipranavir	No interaction
Stavudine	↔ Stavudine ↔Tipranavir	No interaction
Tenofovir	↔ Tenofovir ↔Tipranavir	No interaction
Zidovudine	↓Zidovudine concentrations by approx. 50%	Appropriate doses for the combination of TPV/r zidovudine have not been established. Similar interaction observed between nelfinavir and zidovudine, ritonavir and zidovudine, with no dose adjustment.
Non-Nucleoside Reverse Transcriptase Inhibitors: Efavirenz	↔ Efavirenz ↔Tipranavir	No interaction (based on cross-study comparison)
Nevirapine	As with efavirenz, no interaction is expected.	The interaction between nevirapine and TPV SEDDS formulation in combination with low dose ritonavir was not evaluated.
Protease inhibitors (co-administered with low-dose ritonavir): Amprenavir Lopinavir Saquinavir	↓Amprenavir approx. 50%, ↓Lopinavir 50-70%, ↓Saquinavir 70-80%,	Appropriate doses for the combination of TPV/r with amprenavir, lopinavir or saquinavir have not been established.
Other PIs	Similar degree of interaction might be expected as that of amprenavir, lopinavir or saquinavir	No information available for indinavir, nelfinavir and atazanavir
Fusion inhibitor: Enfuvirtide	Interaction is not expected.	The interaction was not evaluated.

Table 2: Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions		
Concomitant Drug Class: Drug name	**Effect on Concentration of Tipranavir or Concomitant Drug**	**Comment**
Other Agents		
Antacids	↓ Tipranavir approx 30%	Reduced plasma concentrations of tipranavir are expected if antacids, including buffered medications, are administered with tipranavir. Tipranavir should be administered 2 h before or 1 h after these medications.
Antidepressants: SSRIs Atypical antidepressants	Expected ↑ SSRIs Expected ↑ Atypical antidepressants	Coadministration with TPV/r has the potential to produce serious adverse events and has not been studied. Patients should be monitored carefully for adverse events.
Antifungals: Fluconazole Itraconazole Ketoconazole Voriconazole	↑Tipranavir, ↔Fluconazole Expected ↑Itraconazole, Expected ↑Ketoconazole Expected ↑Voriconazole	Dose adjustments are not needed, for TPV/r administered with fluconazole. Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (>200 mg/day) are not recommended. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction.
Anticoagulant: Warfarin	Cannot predict the effect of TPV/r on warfarin due to conflicting effect of TPV and RTV on CYP2C9	Interaction was not evaluated. Warfarin concentrations may be affected. It is recommended that INR be monitored frequently when TPV/r is initiated.
Anti-diabetic agents	The effect of TPV/r on CYP2C8, which metabolizes most glitazones, is not known. Sulfonylureas are metabolized by CYP2C9, interaction is possible.	The interactions were not evaluated.
Antimycobacterials: Rifabutin	↓Tipranavir possible, but effect of multiple dose rifabutin was not evaluated. ↑Rifabutin 3-fold ↑ Desacetyl-rifabutin 20-fold	Dosage reduction of rifabutin by 75% is recommended (e.g. 150 mg every other day or three times a week).
Clarithromycin	↑Tipranavir (based on cross-study comparison) ↔Clarithromycin, ↓14-hydroxy metabolite	No dosage adjustments are needed.
Azithromycin	Interaction is not expected.	The interaction was not evaluated.

Table 2: Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions		
Concomitant Drug Class: Drug name	**Effect on Concentration of Tipranavir or Concomitant Drug**	**Comment**
Calcium Channel Blockers: e.g., felodipine, nifedipine, nicardipine	Cannot predict effect of TPV/r on calcium channel blockers due to conflicting effect of TPV/r on CYP3A and P-gp	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	Possible ↓ Tipranavir	Use with caution. TPV may be less effective due to decreased TPV plasma concentrations in patients taking these agents concomitantly.
HMG-CoA reductase inhibitors: Atorvastatin	↔Tipranavir ↑ Atorvastatin approx 5-9-fold ↓ Hydroxy-metabolites	Start with the lowest possible dose of atorvastatin with careful monitoring, or consider HMG-CoA reductase inhibitors not metabolized by CYP3A such as pravastatin, fluvastatin or rosuvastatin.
Narcotic analgesics: Methadone Meperidine	Expect ↓Methadone Expect ↓Meperidine, ↑Normeperidine	Dosage of methadone may need to be increased when co-administered with TPV/r. Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures)
Oral contraceptives/Estrogens: Ethinyl-estradiol	↓Ethinyl-estradiol concentrations by 50%	Alternative or additional contraceptive measures are to be used when estrogen based oral contraceptives are co-administered with TPV/r. Women using estrogens may have an increased risk of non-serious rash.
Despiramine	Expect ↑Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.
Theophylline	Cannot predict the effect of TPV/r on theophylline due to potential conflicting effect of TPV and RTV on CYP1A2	Concentrations of theophylline may be affected. Increased therapeutic monitoring is recommended, after TPV/r is initiated.
Disulfiram/Metronidazole		Tipranavir capsules contain alcohol which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).

Source: FDA Clinical Pharmacology Analysis

References

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

Table 3

SUMMARY TABLE SHOWING FEATURES OF TPV/r HEPATOTOXICITY IN PHASE II STUDIES

Study	TPV/r dose	HBsAg+	HCVAb+	HBV/HCV co-infected	# subjects ≥ gr 1 ALT @ bl	median bl CD4 count for Tx arm	median bl CD4 for subj w Gr3/4 ALT elev	Subj w Gr 3 or 4 ALT	Subj w gr 3 or 4 bili	% Subj w Gr3/4 ALT	Subj w clin jaundice	Med. Days to max ALT (+- range)	Drug held temp. 2'ry to toxicity	Drug prematurely d/ced 2'ry hepatoxicity
1182.2	500/100	3	3	2	6	258	375	3	1	16%		482	1	1
	1000/100	0	4	0	5	274	228	5	0	23%		483	4	0
1182.4	500/100	0	1	0	1	290	328	3	0	12%	0	85	1	1
	1250/100	0	3	0	4	233	208	3	0	12%	1	338	2	1
	SQV	3	6	2	2	369	257	3	0	7%	0	97	0	0
1182.6	1250/100	4	14	2	12	390	301	4	0	5%		306	0	1
	750/100	3	5	0	13	535	246	1	0	1.5%		218	0	0
	250/100	3	13	0	10	566	558	4	0	3%		261	0	1
1182.52	500/100	2	9	0	12	187	172	4	0	5%	0	38	1	0
	500/200	4	6	0	15	179	110	7	0	10%	0	48	1	3
	750/200	6	7	2	14	169	295	15	2	21%	1	57	1	5

Source: FDA compilation of December 29th 2004 database submitted by Applicant

Table 4: SUMMARY TABLE OF RASH IN PHASE II SUPPORTIVE STUDIES OF TIPRANAVIR, BY TREARMENT ARM AND GENDER

Study	TPV Dose and Formulation	TPV Duration	Gender	Rash (by Tx ARM)
1182.2	TPV/r 500/100 (n=19) TPV/r 1000/100 (n= 22)	24 weeks	4F/15 M 5F/ 17M	3 F/1M (of 4 subjects with rash) 3 F/0M(of 3 subjects with rash)
1182.4	TPV/r 500/100 (n=25) TPV/r 1250/100 (n=25)	24 weeks	6F/19M 4F/21M	0 F/3M (of 3 subjects with rash) 1 F/4M (of 5 subjects with rash)
1182.6	TPV/r 1250/100 (n=58) TPV/r 750/100 (n=63) TPV/r 250/200(n=87)	28 days (with optional extension to 20 weeks)	13F/45M 9F/54M 11F/76M	0 F/2M (of 2 subjects with rash) 2 F/7M (of 5 subjects with rash) 1 F/3M (of 4 subjects with rash)
1182.51*	TPV/r (n=69) LPV/TPV/r (n=86) SQV/TPV/r (n=85) APV/TPV/r (n=86)	24 weeks	5F/64M 6F/80M 5F/80M 6F/80M	2 F/25M of 27 subjects with rash
1182.52	TPV/r 500/100(n=73) TPV/r 500/200 (n=72) TPV/r 750/200 (n=71)	32 weeks	10 F/63M 12F/60M 12F/59M	0 F's /7 M with rash 2 F/1M of 3 subj with rash 1F/10M of 11 subj with rash

*Please note that in 1182.51, this data was collected from week 2-4, when TPV/r added to all Tx arms. During week 0-2, no females reported rashes. (The add-on dose was TPV/r 500/100 mg bid)

Source: AE database MSOC in the general, immune and skin categories for any AEs related to the skin; Exit and Demographic datasets were searched for gender and discontinuations related to skin rash. Applicant's submission 12/29/04

The following were excluded: isolated lesions of the limb and scalp not judged as a drug reaction, flaky scalp, localized pruritis and skin reactions thought to be related to administration of ENF.

TABLE 5: SUMMARY TABLE OF TOTAL NUMBER OF SUBJECTS, AND GENDER OF SUBJECTS WITH RASH IN TPV/r Phase II TRIALS

Study	TPV Dose and Formulation	Gender of subjects with rash		Total number of subjects in trial (by gender)		% subjects with rash (by gender)	
		M	F	M	F	% males with rash	% females with rash
1182.2	TPV/r 500/100 TPV/r 1000/100	1 0	3 3	32	9	3.1%	66.7%
1182.4	TPV/r 500/100 TPV/r 1250/100	3 4	0 1	62	17	11.3%	5.8%
1182.6	TPV/r 1250/100 TPV/r 750/100 TPV/r 250/200	2 3 3	0 2 1	175	33	4.5%	9.1%
1182.51*	TPV/r LPV/TPV/r SQV/TPV/r APV/TPV/r	25	2	294	21	8.5%	9.5%
1182.52	TPV/r 500/100 TPV/r 500/200 TPV/r 750/200	7 1 10	0 2 1	182	34	9.9%	8.8%
Overall Total		59	15	745	114	7.9	13.2 %

** In trial 1182.51, data was collected from week 2-4 of the trial, when TPV/r was added to all treatment arms.*

[Source Data: Data set analysis 12/29/04 submission]

Table 6: TABLE SHOWING TOTAL # SUBJECTS WITH RASH BY DOSE OF TPV/r AND STUDY NUMBER

	TPV/r 250/200	TPV/r 500/100	TPV/r 500/200	TPV/r 750/100	TPV/r 750/200	TPV/r 1000/100	TPV/r 1250/100
1182.2		4/34 (11.8%)				3/ 36 (8.3%)	
1182.4		3/25 (12%)					5/ 25 20%)
1182.6	4/87 (4.6%)			5/63 (7.9%)			2/ 58 (3.4%)
1182.51		27/315 (8.6%)					
1182.52		7/73 (9.6%)	3/ 2 (4.2%)		11/71 (15.5%)		
Total n/N (%)	4/87 (4.6%)	41/447 (9.2%)	3/72 (4.2%)	5/ 3 (7.9%)	11/71 15.5%)	3/ 36 (8.3%)	7/83 (8.4%)

[Source Data: FDA Compilation of data submitted by Applicant - !2/29/04 submission]

Table 7: TABLE SHOWING SUBJECTS WITH POSSIBLE SUBJECTIVE IMPAIRMENT IN MENTAL CONCENTRATION

Study	Pt #	TPV Dose	Diagnosis	Days
1182.51	336	TPV/SQV	difficulty concentrating	d90 x 21d
1182.52	6011	500/200	amnesia	d25, d28 x 1d
1182.52	5012	500/200	loss of concentration	d8, cont
1182.52	1073	500/200	forgetfulness	d11 x 134d
1182.52	3003	750/200	impaired memory	d99, cont
1182.2	263	1000/100	forgetfulness	d402, cont
1182.2	191	500/100	impaired mentation	d2-35
1182.4	207	1250/100	impaired concentration	3-26
1182.4	1157	500/100	impaired concentration	d2, cont.
1182.6	196	250/200	impaired concentration	d14x15days

[Source Data: AE Dataset 12/29/04.]

/S/

Neville A Gibbs M.D, MPH
MO/DAVDP/ODEIV/FDA/HFD-530

Concurrence:
ODE-6/ DepDirector Ed Cox
HFD-530/DivDir/Birnkrant
HFD-530/TL/Johann-Liang
cc:
Orig. NDA 21-814
HFD-530/CSO/Sinha
HFD-530/MO/James
HFD-530/Statistics/Bhore/Zhou

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NDA 21-814
Tipranavir for the treatment of HIV infection
Reviewer: Melisse Baylor, MD

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SUMMARY

This analysis included reviews of studies of tipranavir in different populations. Twenty-six studies enrolled healthy adult volunteers. Review of these studies in healthy volunteers provides important information on the safety of tipranavir, since the safety analysis is not complicated by signs and symptoms associated with advanced HIV. Phase 1 data in HIV-infected subjects are limited. Two pharmacokinetic studies enrolled HIV-infected subjects. Finally, two ongoing studies enrolling HIV-infected subjects are also included in this review. Study 1182.33 is a 48 week, safety and efficacy study of tipranavir HIV-naïve subjects, and study 1182.14 is safety and efficacy study of tipranavir in pediatric patients. Preliminary results from both studies are included in this review. Safety findings from this review are summarized below.

- The most common toxicity associated with tipranavir use in HIV-infected subjects and in healthy volunteers was gastrointestinal, particularly diarrhea and nausea. Gastrointestinal adverse events were also the most common reason for study discontinuation.

- Increases in ALT and in triglycerides were frequently reported in healthy volunteers and in HIV-infected subjects.
  - Increases in ALT were reported in healthy volunteers after a single dose and after multiple doses of tipranavir. Eighteen percent of healthy volunteers in multiple dose studies had increases in ALT including 2% of subjects with Grade 4 increases.
  - Increases in triglyceride levels were also common; 27% of subjects in multi-dose healthy volunteer studies with normal triglyceride levels had increases in triglyceride to greater than the upper limit of normal. In addition, triglyceride increases were observed in the single dose studies of tipranavir.
  - Increases in ALT and in triglycerides were observed in studies using tipranavir alone and in those using tipranavir boosted with ritonavir.

- Rash was reported in both single and multiple dose studies and in studies of HIV-infected subjects. The description of rash varied from urticaria to tiny papules. Some episodes of rash were accompanied by other signs and symptoms such as joint pain and throat tightness. In Phase 1 multi-dose studies, rash was substantially more common in females than males; rash was reported in 13% of females compared to 3.6% of males. In study 1182.22, the study was terminated due to concerns of serum sickness when 17 of 51 subjects developed a rash, often associated with musculoskeletal signs and symptoms.

- A hypersensitivity-like reaction was observed in subjects receiving tipranavir. A small number of healthy volunteers had rash with associated symptoms like joint pain, tingling, pruritis, and throat tightness. In addition, one woman had generalized pruritis and tightness of her throat, which resolved after treatment with benadryl. Another male subject had slurring of speech and tongue swelling, which resolved after treatment with steroids and benadryl.

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

- The Phase 1 studies suggest that adverse events are dose related. In the studies in which subjects were randomized to receive tipranavir and ritonavir at 500 mg/100 mg or at 750 mg/200 mg, gastrointestinal adverse events and hepatotoxicity were more frequent and more severe in subjects in the higher dose groups.

- Insufficient data was provided to reach any conclusions about the safety and efficacy of tipranavir in HIV-infected, treatment-naïve subjects and in pediatric patients. These studies are ongoing and the final study reports will be submitted when complete.

REVIEW OF PHARMACOKINETIC STUDIES OF TIPRANAVIR IN HEALTHY ADULT VOLUNTEERS

Resume

There were 20 multiple dose, Phase 1 studies of tipranavir in more than 600 healthy adult volunteers. The majority of subjects were White and Male. However, 265 females were enrolled allowing for some analyses based on gender. In five of these studies, subjects received tipranavir and in the remaining 15, tipranavir was administered with low dose ritonavir. Several formulations of tipranavir were used in these studies. The majority of studies were done using the formulation to be marketed, the SEDDS formulation, but the hard filled capsules were used in five studies. In addition, there were five single dose Phase 1 studies in healthy volunteers; the safety results were similar in the single and multiple dose studies. This review is limited to the safety data from these studies. Please see Dr. Zheng's review for discussion of the pharmacokinetic data obtained in these trials.

Adverse events were seen in almost all subjects receiving tipranavir in these Phase 1 studies. Safety signals from these trials are described below.

- The most common toxicity was gastrointestinal, particularly diarrhea and nausea; in seven if the 20 multi-dose studies, three-fourths or more of subjects reported diarrhea. Gastrointestinal adverse events often began on the first day of dosing with tipranavir and sometimes continued throughout the study. Gastrointestinal adverse events were the most common reason for study discontinuation; 24 subjects discontinued due to nausea, vomiting, diarrhea, or abdominal pain.

- Increases in ALT and in triglycerides were frequently reported. See the table summarizing these events at the end of this review.
  - Eighteen percent of healthy volunteers in multi-dose studies had increases in ALT to greater than the upper limit of normal. Twelve subjects or 2% of the subjects in the Phase 1 studies had Grade 4 ALT values and 4% (n=24) had Grade 3 increases. Twelve subjects discontinued the study prematurely due to hepatotoxicity. One subject in a Phase 1 study had an increase in ALT from normal limits to 3.5 times the ULN after a single dose of tipranavir. Increases in total bilirubin were uncommon but were reported in three subjects including one subject with ocular jaundice.
  - Increases in triglyceride levels were also common and were reported in 18 of the 20 multi-dose studies and in two of the five single dose studies. A total of 178 subjects (27%) in the multi-dose studies with normal triglyceride levels had increases in triglyceride to greater than the upper limit of normal. This includes 27 subjects with Grade 2 increases in triglyceride and one with a Grade 3 increase. Three subjects discontinued a study due to elevated triglyceride levels. Ritonavir use is associated with lipid abnormalities, however, increased

triglyceride levels were reported in 24 subjects in the four studies in which ritonavir was not used.

- Rash was reported in 48 subjects in multiple dose studies and in one subject in a single dose study. Five subjects discontinued due to rash. Rash was substantially more common in females than males; rash was reported in 13% of females in Phase 1 compared to 3.6% of males. The description of rash varied from urticaria to tiny papules. Some episodes of rash were accompanied by other signs and symptoms such as joint pain and throat tightness.

- A few adverse events suggest that a hypersensitivity-like reaction was observed in subjects receiving tipranavir. Subjects had rash with associated symptoms like joint pain, tingling, pruritis, and throat tightness. In addition, one woman had generalized pruritis and tightness of her throat, which resolved after treatment with benadryl. Another male subject had slurring of speech and tongue swelling, which resolved after treatment with steroids and benadryl.

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

Finally, these Phase 1 studies also suggest that adverse events are dose related. In the studies in which subjects were randomized to receive tipranavir and ritonavir at 500 mg/100 mg or at 750 mg/200 mg, gastrointestinal adverse events and hepatotoxicity were more frequent and more severe in subjects in the higher dose groups.

In conclusion, several safety signals were observed in healthy volunteer studies of tipranavir. These included gastrointestinal signs and symptoms, rash, increased ALT, and increased triglyceride levels. Less common adverse events such as possible hypersensitivity reactions and changes in concentration or cognition were also reported. The severity of the hepatotoxicity in some subjects and the female predisposition to rash should be explored further in post-marketing commitments.

MULTIPLE DOSE PHASE 1 STUDIES OF TIPRANAVIR IN HEALTHY VOLUNTEERS

I. Studies Which Were Prematurely Discontinued

A. Study 1182.22

1. Study Design

Study 1182.22 was a randomized, open-label, parallel group, drug drug interaction study comparing plasma concentrations of ethinyl estradiol (EE) and norethindrone (NET) after

administration of Ortho-1/35, an oral contraceptive pill, when given alone versus concentrations of EE and NET after co-administration with tipranavir.

The study enrolled females between the age of 18 and 50 years, who had a body mass index between 18 and 29 kg/m^2. Subjects had to be healthy as determined by history, physical examination, laboratory measurements, electrocardiogram, and chest radiograph. Subjects had to have negative serologic tests for HIV, hepatitis B, and hepatitis C. Subjects could not have any allergies or illnesses that might interfere with the study results or place the subject at increased risk. Study subjects could not have participated in any other investigational trials within 30 days of the start of this trial.

Healthy female volunteers were randomized to receive single doses of Ortho 1/35 on days 1 and 15 of the study plus *either* TPV/r 500 mg/100 mg *or* TPV/r 750 mg/200 mg twice daily from study day 4 to 16. The SEDDS formulation of tipranavir was used in this study.

2. Study population / Study disposition

A total of 52 healthy female volunteers at a single study center were randomized to either Ortho-1/35 plus TPV/r at a dose of 500 mg and 100 mg (n=26) or to Ortho-1/35 plus TPV/r at 750 mg/200 mg (n=26). Ninety-percent of study subjects (n=47) were White. The mean age of women in this study was 35.2 years.

All 52 subjects received at least one dose of study drug. Twenty subjects (38%) discontinued the study early. One subject withdrew consent on day 3 before starting tipranavir. The other 19 (37%) discontinued due to adverse events (rash-11, musculoskeletal-5, GI-2, and hepatitis-1). The study was stopped early because of the unexpectedly high number of rashes and musculoskeletal adverse events and concern that subjects were developing serum sickness. The 32 remaining subjects on study did not receive the day 16 dose of tipranavir and ritonavir. See the analysis of safety for further discussion of these adverse events.

> *MO Comment:* Since one subject in the 750 mg/200 mg arm discontinued the study before receiving tipranavir, it is more appropriate to use a denominator of 51 when calculating the frequency of TPV-related adverse events.

The main protocol violation was non-compliance with TPV dosing, defined as taking less than 95% of the TPV doses. There were 7 (27%) non-complaint subjects in the 500 mg/100 mg arm and 13 (52%) in the 750 mg/200 mg arm. Five subjects reported taking less than 50% of their tipranavir.

> *MO Comment*: The rate of individual adverse events were fairly similar between the two treatment groups; see the Analysis of Safety in this review. There is no clear evidence of a single AE or multiple AEs with a higher incidence in the high dose arm that might have been associated with decreased tolerance of TPV and

more non-compliance in the high dose group. Therefore, it is unclear why there was such a marked difference in non-compliance.

3. Analysis of Safety

a. Exposure to Study Drug

Seven subjects discontinued the study prematurely in the TPV/r 500 mg/100 mg arm and 13 in the 750 mg/200 mg arm. The mean number of days of exposure was 13 in the 500 mg/100 mg arm and 12.5 in the 750 mg/200 mg arm. The total number of days of exposure in the two arms was 324 days in the low dose group and 284 in the high dose group.

b. Clinical adverse events

There were a total of 501 adverse events (AEs) in the study; all study participants reported at least one adverse event. The majority of clinical AEs were Grade 1 (93%); there were no Grade 3 or 4 clinical AEs. Clinical adverse events observed in at least two subjects (5%) are shown in the table below.

Table Clinical Adverse Events in ≥ 2 Subjects (5%) in Study 1182.22

Adverse Event	Number of subjects with AE	
	500 mg/100mg	750 mg/200 mg
loose stools	21	20
nausea	19	20
rash	10	13
headache	11	10
upper abdominal pain	7	7
lower abdominal pain	6	3
abdominal pain NOS	6	2
pruritis	7	6
generalized pruritis	1	2
fatigue	6	7
vomiting	1	11
dizziness	6	6
chest pain	4	3
limb pain	5	1
flatulence	2	4
epimennorhea	4	1
anorexia or decr appetite	2	2
arthalgia	1	3
back pain	3	1
burning sensation	2	2
hypoaestheia	3	1
constipation	2	2
eructation	2	2
hot flashes	3	0

conjunctivitis	2	0
GI irritation	0	2
weakness	1	2
hepatitis	1	1
catheter problems	1	1
muscle spasm	0	2
somnolence	2	0

Source: CSR vol 1.122, p 76-77, 134-142.

Because many subjects had more than one adverse event in the same organ system, the numbers of AEs in a single organ system cannot be derived from the table above. However, as shown in the table above, the most common adverse events in this study were gastrointestinal. Gastrointestinal (GI) adverse events were reported in 47 subjects (92%). Diarrhea was the most common GI AE; abdominal pain, nausea, and vomiting were also common. Pruritis and rash were also frequently reported; 29 subjects (57%) had AEs related to the skin including 23 (44%) with rash. The incidence of musculoskeletal pain was noteworthy; 12 subjects reported musculoskeletal AEs. Eight additional subjects had chest pain or pain under their breast that was consistent with musculoskeletal pain.

On subject (2052) had a photosensitivity reaction on day 11. This adverse event was not judged as study drug related.

> *MO Comment*: TPV is a sulfonamide, therefore, it is possible that the photosensitivity reaction *was* related to TPV. The possibility of photosensitivity reactions and other adverse events typical of sulfonamides will be conveyed in the package insert and patient package insert.

> *MO Comment*: GI adverse events temporally associated with TPV/r administration, i.e., those reported on or after day 4 of the study when TPV/r was started, are shown in the table below:

Table: Number of Study Subjects with GI Adverse Events During TPV/r Use

Adverse Event	500mg/100mg	750mg/200mg	Total
Abdominal pain or burning	7	5	12
Dry mouth	0	1	1
Constipation	1	2	3
Flatulence	1	4	5
Diarrhea	13	9	22
Nausea	7	7	14
Vomiting	0	2	2

Source: CSR: Appendix 16.2. p:1849-1854, 1861-1866.

> As shown in this table, GI AEs were common in subjects receiving TPV/r. A total of 22 (43%) reported diarrhea, 14 (27%) nausea, and 12 (23.5%) abdominal

pain. This is not surprising since TPV has been associated with GI AEs in other studies, and GI AEs are listed as the most common type of AE in the proposed package insert for tipranavir.

The study was stopped early because of the unexpectedly high number of rashes and musculoskeletal adverse events; the investigators were concerned about the possibility of serum sickness. At the time of study closure, 20 subjects had prematurely discontinued the study. As discussed above, one subject in the 750 mg/200 mg arm withdrew her consent on day 3 before receiving tipranavir. Of the 19 subjects discontinuing the study due to adverse events, 7 (27%) were receiving TPV/r at 500mg/100 mg and 12 (48%) were receiving TPV/r 750 mg/200 mg. The reasons for premature study discontinuation included: 11 due to rash, 5 due to musculoskeletal pain, 2 due to vomiting, and 1 due to hepatitis. The 32 subjects remaining on study at the time of study closure only missed the final day of TPV/r dosing (day 16).

MO Comment: The applicant describes all adverse events resulting in study discontinuation as TPV/r related. However, as shown in the table below, there were additional subjects who reported rashes or musculoskeletal pain while receiving TPV that might have also been related to the use of TPV/r.

Table: Number of Subjects with Rash or Musculoskeletal AEs While Receiving TPV/r

	500/100	**750/200**	**Total**
Rash	7	10	17
Musculoskeletal AE	4	6	10

Source: CSR, Appendix 16.2 Subject Data Listings, p. 1922-1977.

As shown in this table, 17 subjects or 33% of all study subjects developed a rash while receiving TPV and 20% had musculoskeletal pain. Three subjects had both skin and musculoskeletal findings. An additional three subjects not included in this table reported symptoms that can be associated with drug hypersensitivity while receiving TPV; one had generalized pruritis and conjunctivitis on day 11, one had conjunctivitis on day 11, and the other had intermittent numbness and tingling in the leg on day 11. Therefore, the most conservative analysis, defined as all subjects with a *possible* drug hypersensitivity, would include 26 subjects (51%).

A rheumatologist and dermatologist were consulted, and additional studies were performed to determine if the rashes and musculoskeletal pain were due to serum sickness. Subject 2100 had a skin biopsy of her rash, which revealed an urticarial eruption with lymphocytes and eosinophils; this pathology was interpreted as non-specific but consistent with a drug reaction. ASO, CRP, and ESR titers were also performed for a subset of subjects; 8 of 13 subjects had an abnormal ASO, none of 12 had an abnormal CRP, and 8 of 13 had an abnormal ESR. Microscopic urinalyses were also performed and no subjects had renal casts. The applicant states that serum sickness

in these subjects was unlikely due to the lack of consistent elevations of ASO,CRP, ESR; the absence of renal casts, and the lack of lymphadenopathy on examination.

> *MO Comment*: Although no subjects were diagnosed with serum sickness, clearly a form of drug hypersensitivity occurred in a number of study subjects. There were 4 subjects with one organ system involvement plus two increased laboratory measure, and there were 5 subjects with two organ system involvement and at least one increased laboratory measure.

There were no severe or serious adverse clinical events or deaths reported in this study.

c. Laboratory adverse events

The only laboratory abnormalities that were determined to be clinically significant were increases in ALT and AST and decreases in hemoglobin.

Two subjects, one in each treatment group, experienced clinical adverse events called hepatitis. Both had Grade 4 elevations in ALT, which occurred on day 16. One subject also had a Grade 4 elevation in AST and the other had a Grade 3 elevation in AST. Both had normal hepatic transaminases at baseline and negative serology for hepatitis B and C.

> *MO Comment*: Increases in ALT are shown in the table below.

Table: Increases in ALT in Study Subjects While Receiving TPV/r

	500mg/100mg	**750mg/200mg**	**Total**
Grade 1	4	7	11
Grade 2	4	3	7
Grade 3	1	4	5
Grade 4	1	1	2
Total	**10**	**15**	**25**

Source: CSR, Line Listing 8.2.2 p. 2789-2811 and definition of ALT Grades in study protocol, p 320.

> As shown in this table, increased ALT was common and reported in 49% of subjects. Grade 3 or 4 elevations in ALT were reported in 14% of subjects. Increases in hepatic transaminases have been reported in other studies of TPV, however, Grade 4 increases in ALT in two healthy volunteers is concerning. The package insert for TPV will contain a boxed warning regarding hepatotoxicity.

The applicant could not find any correlation between the development of rash and increased ALT. One patient with Grade 4 had no signs or symptoms of a drug hypersensitivity reaction while the other had rash, chest pain, increased ASO, and increased ESR. In the applicant's analysis, the incidence of rash correlated with peak plasma TPV levels; all subjects with Grade 3 or 4 increases in ALT had TPV C_{max} levels in the highest one-third of the study population.

Two subjects, one in each study group, had decreases in hemoglobin that were considered clinically significant. Neither were Grade 3 or 4 laboratory abnormalities.

4. Conclusion

Study 1182.22 was stopped prematurely due to an unexpectedly high number of rashes and musculoskeletal adverse events. Thirty-three percent of all subjects reported a rash while 20% had a musculoskeletal adverse event. Although the sponsor concluded that these adverse reactions were not consistent with serum sickness, it is clear that a type of drug hypersensitivity reaction occurred in these healthy female volunteers. The incidence of such reactions in women should be confirmed by other studies in healthy volunteers and in studies of HIV-infected, treatment naïve subjects before the true risk can be determined.

There was a high incidence of increased hepatic transaminases in this study. It was of note that two subjects with without risk factors for hepatic dysfunction developed Grade 4 increases in ALT. In addition, Grade 3 and 4 increases in ALT were reported in 14% of subjects. According to the applicant, the risk of increased transaminases correlated with peak TPV levels. Because TPV levels are higher in females (proposed package insert), women receiving TPV should have hepatic transaminases monitored frequently.

B. Study 1182.42

1. Study Design

Study 1182.42 was a randomized, open-label, parallel group, drug-drug interaction study of two doses of TPV/r (500 mg/100 mg and 750 mg/200 mg) and didanosine (ddI) in healthy adult volunteers. TPV and RTV were administered twice daily on study days 2 to 15. Didanosine, 400 mg of the enteric coated formulation, was administered as a single dose on days 1 and 15. The SEDDS formulation of TPV was used.

2. Results

Twenty-three healthy volunteers were received at least one dose of TPV/r: 11 in the 500 mg/100 mg arm and 12 in the 750 mg/200 mg arm. Eighteen subjects were male and five female. All 23 were White.

Twenty-two of the 23 subjects (96%) experienced adverse events. The most common adverse events were gastrointestinal, which were reported by 21 or 91% of study subjects. The most frequently reported GI AE was diarrhea (74%); others were nausea (65%), flatulence (43.5%), and abdominal pain (30%). Three subjects had impaired concentration that was severe enough to interfere with their ability to drive. All subjects had normal neurological examinations.

> *MO Comment*: Although these subjects had normal examinations, this AE was of sufficient concern that the study was changed from an outpatient to an inpatient

study. The reason for impaired concentration in subjects receiving TPV is not known. Small amounts of TPV do cross the blood-brain barrier in animals (see Dr. Bigger's Pharmacology/Toxicology review), but it is not known if detectable TPV in the CNS correlates with any signs or symptoms in humans or in animals.

Increases in ALT greater than the upper limit of normal were reported in 14 (63%) subjects. Changes in ALT are shown in the table below.

Table: ALT Abnormalities in Study 1182.42

ALT	500/100 n=11	750/200 n=12	Total n=23
>ULN	4	10	14 (63%)
Grade 1	2	6	8
Grade 2	0	2	2
Grade 3	0	0	0
Grade 4	0	1	1

Although increases in ALT were common, only one subject had an increase of ALT to Grade 3 or 4. This subject had a baseline ALT of 10 U/L; the ALT value peaked at 261 U/L (Grade 4) on study day 7. The subject discontinued the study prematurely. The study reports that ALT values continued to increase after TPV was stopped in 7 subjects; however, the degree of increase and the time to resolution were not provided.

MO Comment: As shown in the table above, the frequency of ALT increases was dose-related. In addition, there were increases in ALT after stopping TPV in 7 subjects. No details of these subjects were provided, but the possibility of continued liver injury after stopping TPV is concerning.

Twelve subjects had Grade 1 increases in cholesterol. In general, cholesterol levels began to increase early in the study and continued to rise throughout treatment. In some subjects, cholesterol levels did not return to normal levels for several months. Six subjects had increases in triglyceride levels to greater than the upper limit of normal. One subject had an increase in triglyceride from 56 mg/dL at baseline to Grade 2 (588 mg/dL) on day 6. This subject discontinued the study due to increased triglyceride levels.

MO Comment: Increases in cholesterol and triglycerides have been reported in other studies of TPV in both healthy volunteers and in HIV-infected subjects. Lipid levels must be followed closely in all patients receiving TPV/r.

Eight subjects (35%) prematurely discontinued the study due to AEs. This included four for clinical AEs: diarrhea, poor concentration, chest pain and palpitations in a subject with a history of heart disease, and migraine. Another four subjects discontinued the study due to laboratory AEs: one with increased ALT and three with increased triglyceride levels. All study discontinuations, except for the one subject with a migraine, were from the 750 mg/200 mg arm. The entire study was stopped early because of the

high number of premature study discontinuations and the difficulty in interpreting results after a loss of 35% of the study subjects.

> *MO Comment*: TPV was difficult to tolerate, primarily because of GI AEs, increases in ALT, and lipid abnormalities. Patients taking TPV will need adequate monitoring and support.

II. Study in Special Population – Study 1182. 32

A. Study Design

Study 1182.32 was an open-label, pharmacokinetic, and safety study of TPV/r in adults with mild and moderate hepatic impairment. Subjects were assigned to treatment group by the degree of hepatic impairment. Subjects with mild hepatic impairment were assigned to Group A; mild hepatic impairment was defined as a Childs-Pugh score of ≤ 6. Subjects in Group A received TPV/r (500 mg/200 mg) twice daily on study days 1 to 7. Pharmacokinetic measurements were obtained on days 1 and 7. Subjects with moderate hepatic impairment were assigned to Group B; moderate hepatic impairment was defined as a Childs-Pugh score of 7 or 8 and moderate disease for less than 4 years duration. Matched controls were enrolled for each subject; matches were based on gender, race, age, weight, and cigarette smoking. Subjects were excluded for a history of bacterial peritonitis, advanced hepatic cirrhosis, Childs-Pugh score > 8, active esophageal variceal disease, asterixis, positive alpha fetoprotein, active or untreated hepatocellular carcinoma, active coagulopathy, HIV infection, or sulfa allergy. Matched controls had to have baseline ALT and AST values $\leq$ Grade 2. Liver function tests were obtained at screening and at days 0, 2, 5, 7, 10, and 12 in Group A. Liver function tests were obtained at screening and at days 2, 3, 4, 5, and 6 for subjects in Group B.

B. Study Results

1. Study Population and Study Conduct

A total of 24 subjects received at least one dose of study drug: 9 subjects with mild hepatic impairment with 9 matched controls and 3 subjects with moderate hepatic impairment with 3 matched controls. Twenty subjects were male and four female. All were White. The mean age was 51.4 years. All nine subjects in Group A had a Childs-Pugh score of 5 or 6; all subjects had a prolonged PT. All subjects in Group B had a Childs-Pugh score of 7 or 8; one subject had a total bilirubin > 3 mg/dL, two had albumin levels ≥ 2.8 but < 3.5 g/dL, one subject had an albumin level < 2.8 g/dL, and three subjects had an increased PT.

Sixteen protocol violations in 14 subjects were reported. Four were due to poor matching of control subjects. Five had abnormal entry laboratory values including one subject with a platelet count $< 75{,}000$ mm^3 and one with an alkaline phosphatase value more than two times the upper limit of normal. Four subjects had a history of drug or alcohol abuse

within the previous six months. Two had received drugs for hepatic disease within the previous 30 days.

> *MO Comment*: It is possible that the protocol violations impacted the outcome of the study. Specifically, poor matching would affect the ability to compare treatment arms, recent drug or alcohol abuse could compromise hepatic function, and recent treatment of hepatic disease could affect hepatic response to another drug.

2. Analysis of Safety

All 12 of the study subjects with hepatic impairment and 11 of the 12 matched controls reported adverse events. Twenty subjects (83%) had GI AEs including 19 with diarrhea (79%), seven with abdominal pain (29%) and seven with nausea (29%). The differences between GI AEs in the hepatic impairment group compared to the controls are shown in the table below.

Table: Gastrointestinal Adverse Events Reported More Commonly in Subjects with Hepatic Impairment than in Matched Controls

	Hepatic Impairment n=12	**Matched Controls n=12**
Any GI AE	12 (100%)	8 (67%)
Nausea	6 (50%)	1 (8%)
Flatulence	6 (50%)	0
Abdominal pain	5 (42%)	2 (12%)

> *MO Comment*: As shown in the table above, GI adverse events were reported slightly more often in subjects with hepatic impairment than in the matched controls. However, the study numbers are so small and six subjects received only one dose of TPV, therefore, it is difficult to reach any conclusions regarding these data.

There were no severe, life-threatening, or serious adverse events reported in the study. However, there were more subjects in the hepatic impairment arm with moderate AEs (8) compared to the control arm (1). The only moderate AE in the control arm was headache. Eight subjects with hepatic impairment had moderate AEs, and some subjects had more than one. Moderate AEs in subjects with hepatic impairment were diarrhea (3), nausea (2), increased liver function tests (2), headache (2), fatigue (1), decreased appetite (1), dizziness (1), and musculoskeletal stiffness (1). The two subjects with moderate increases in hepatic transaminases were in Group A. One had an increase in GGT from 214 U/L at screening to 619 U/L on TPV. The second subject had an increase in AST and ALT from within normal limits to Grade 1 on TPV.

Increases in ALT of more than one grade during the study period were reported in five subjects in the hepatic impairment group and five in the control group. One grade or more increases in total bilirubin were reported in 2 subjects with hepatic impairment and

in none of the controls. One grade or more increases in GGT were reported in four subjects in the hepatic impairment group and in two in the control arm.

> *MO Comment:* These data suggest that hepatic AEs are more common in subjects with hepatic impairment. Again, the study population was too small to reach any definitive conclusions. Further studies are needed to define the risks of TPV use in subjects with hepatic impairment.

In conclusion, results from this small study suggest that gastrointestinal and hepatic AEs may be more common in subjects with hepatic impairment. However, with only 12 total subjects with hepatic impairment, including only three with moderate impairment who received a single dose of TPV only, there are too little data to reach any conclusions about the safety of TPV in subjects with hepatic impairment.

III. Drug Drug Interaction Studies

A. Study P&U 03

Study P&U 03 was a multidose, randomized, double-blind, dose escalating study of tipranavir in 48 healthy adult volunteers. Tipranavir was administered three times daily at the following doses: 300 mg, 600 mg, 900 mg, 1200 mg, 1600 mg, and 2000 mg. Six subjects in each cohort received tipranavir and two received placebo. A single dose was administered on day 1; tipranavir was then administered every 8 hours from days 3 to 12. The TPV hand filled capsules with free acid were used in this study. Subjects infected with HIV, HBV, and HCV were excluded from study participation.

A total of 48 subjects were enrolled; 36 received TPV and 12 placebo. Of the 36 subjects who received TPV, 31 were male and 5 female; and 31 were White, 2 Black, 1 Hispanic, and 1 other. The age ranged from 19 to 55 years.

Only AEs for subjects receiving TPV are described in this review. Ninety-four percent of subjects reported at least one AE. The most common AEs were gastrointestinal, which were reported in 32 of 36 subjects (89%). Diarrhea and nausea were each reported in 23 subjects (64%). Seven subjects reported vomiting and five reported decreased appetite. Six reported abdominal cramping and six reported either localized or generalized abdominal pain. Headache was reported in 17 subjects (47%). Cognitive impairment and decreased concentration were reported in one subject each. Rash was reported in three subjects and was described as papulovesicular in one male subject, macular in another male subject, and macular in a female subject. One of the male subjects developed a mild macular rash of his forearms and trunk on day 11 then complained of a strange sensation and fullness in the throat. This subject was discontinued from the study due to throat irritation.

Severe adverse events were reported in four subjects; all four were in the 2000 mg arm. These AEs included vertigo (2), headache (1), and nausea (1).

One subject had Grade 1 increase in AST and Grade 2 increase in ALT on study day 3. The subject discontinued the study due to increased ALT and AST. His ALT and AST returned to normal limits on follow-up.

There were four premature study discontinuation due to AEs: one in the 1600 mg arm (throat irritation) and three in the 2000 mg arm (anxiety and slowed thinking; altered mood, psychomotor retardation, and vertigo; and increased ALT and AST). There were no serious AEs.

> *MO Comment:* Vertigo is not a common complaint in other Phase 1 studies of TPV. However, dizziness has been reported in multiple other TPV trials. In addition, other CNS AEs, such as cognitive impairment, have been reported in other trials.

B. Study P&U 08

Study P&U 08 was an open label, multi-dose, drug drug interaction study of tipranavir and delavirdine (DLV) in eight healthy adult volunteers. Subjects received delavirdine 400 mg t.i.d. on days 1 to 7 and on days 21 to 30. A single 1200 mg dose of TPV was administered on day 7, and TPV 1200 mg b.i.d. was given on days 14 to 30. The TPV hard filled capsule was used. Subjects infected with HIV, HBV, or HCV were excluded from the study.

Of the eight study subjects, 6 were male and 2 were female. All subjects were White. The mean age was 40.7 years (range of 26.3 to 49.7 years). One subject withdrew consent before receiving tipranavir.

Only adverse events, which occurred while subjects were receiving TPV, are included in this review. All study subjects reported at least one AE while receiving TPV. The most common AEs were gastrointestinal: diarrhea was reported in all 7 subjects, abdominal pain or stomach ache was reported in 4 subjects, nausea in 3 subjects, and vomiting in one subject. Two subjects reported a headache. It is notable that the two female study subjects experienced signs and symptoms consistent with an hypersensitivity reaction. Subject 7 was a 53 year old white female who had urticaria on her back, groin, and legs; tightness of her throat; and pruritis on day 10. She was discontinued from the study, treated with benadryl, and recovered. Subject 8 was a 46 year old white female who developed general pruritis, tightness of the throat, and tingling of the skin on day 23. She was treated with benadryl but continued to receive TPV. She also recovered.

There were no laboratory abnormalities reported as adverse events. In the line listings, there were 6 subjects with normal triglyceride levels at baseline and increases in triglyceride levels to greater than the upper limit of normal (ULN) while on study. One subject had increased ALT (88U/L) and GGT levels while receiving TPV.

There were no severe, life-threatening, or serious adverse events.

C. Study P&U 09

Study P&U 09 was an open label, multidose drug drug interaction study of tipranavir and ritonavir in 14 healthy adult volunteers. Subjects received TPV 1350 mg using the hard filled capsules twice daily from day 1 to day 7 and again on days 16 to 31. Ritonavir, 200 mg twice daily, was started on day 8 and gradually increased to 500 mg twice daily by day 16; RTV 500 mg twice daily was continued from day 16 to 31. Subjects infected with HIV, HBV, and HCV were excluded from study participation.

Of the 14 study subjects, 13 were male and 1 was female. Demographic data were provided for the 10 subjects who completed the study. Nine subjects were White and one Black. The mean age was 27.9 years. Four subjects prematurely discontinued the study: two due to AEs, one due to difficulties with transportation, and one due to non-adherence.

Thirteen subjects (93%) reported at least one AE during the study. The most common AEs were gastrointestinal: diarrhea (11 subjects), abdominal pain or cramping (7), nausea (5), and vomiting (3). Other adverse events of interest were headache (5), dizziness (2), amnesia (1), pruritis (1), and rash (1). There were five severe AEs reported: nausea (2), abdominal cramp (1), headache (1), and hypertriglyceridemia (1).

There were two premature study discontinuations due to an AE: one on day 9 due to memory loss and the other on day 18 due to gastrointestinal adverse events. There were no serious AEs and no deaths.

The majority of laboratory abnormalities that were included as an AE were episodes of hypertriglyceridemia (8, including one Grade 3 and one Grade 4), increased GGT (2), and increased ALT (1 subject with ALT of 211 IU). The applicant notes that the onset of all of the laboratory AEs was during the ritonavir dosing period.

> *MO Comment*: On review of the line listings a total of 11 subjects had increases in triglyceride levels including four with Grade 2 triglycerides. Although lipid abnormalities and hepatotoxicity are associated with ritonavir use, they have also been reported in subjects receiving TPV without ritonavir.
>
> *MO Comment*: Tipranavir and ritonavir are both protease inhibitors and have some similar adverse events. In this study, it is difficult to distinguish the relative contribution of each drug to gastrointestinal AEs, lipid abnormalities, and hepatotoxicity.

D. Study P&U 012

Study P&U 012 was an open label, randomized, parallel group, drug drug interaction study of tipranavir and ritonavir in 19 healthy adult volunteers. Study subjects were randomized to receive either 600 mg or 900 mg of the TPV hard filled capsule twice daily on days 1 to 24. Subjects received ritonavir 100 mg b.i.d. on days 6-13, 300 mg

b.i.d. on days 13-17, and 500 mg b.i.d on days 18-24. Subjects infected with HIV, HBV, or HCV were excluded from study participation.

Of the 19 study subjects, 16 were male and 3 were female. Eighteen subjects were White and one Black. The mean age was 30 years. Six subjects discontinued the study prematurely: 4 due to AEs, one due to noncompliance, and one withdrew consent.

Eighteen of the 19 subjects (95%) reported at least one adverse event. Diarrhea was the most common AE (14 subjects or 74%), followed by nausea (12, 63%), and headache (11, 58%). Other AEs included rash, which was observed in four subjects (three males and one female). Pruritis was reported in two subjects. Most AEs were mild; moderate AEs reported included headache (6), diarrhea (4), nausea (4), and vomiting (2).

There were 16 AEs related to clinical chemistries. Fourteen were due to increased triglyceride levels, one to increased CPK, and one to increased ALT. Both the CPK level and the ALT level were Grade 2 and both returned to normal after discontinuation of the study drug. The study subject with increased ALT levels discontinued the study prematurely. All 14 triglyceride levels were Grade 2 or less; some subjects had elevated triglyceride levels at baseline. The overall median triglyceride level at baseline was within the normal range but by the end of the study was 2.2 times the upper limit of normal. Twelve of the subjects with elevated triglyceride levels had triglyceride levels within normal limits at follow-up; the remaining two subjects were lost to follow-up.

The reasons for premature study discontinuation due to AEs were abdominal pain and emesis, emesis, increased ALT level, and rash. There were no severe, life threatening, or serious adverse events reported in this study.

E. Study P&U 013

Study P&U 013 was an open label, randomized, parallel group, multidose drug drug interaction study of tipranavir, ritonavir, and nevirapine in 24 healthy adult volunteers. Subjects in Group 1 received 1250 mg of TPV twice daily and nevirapine 200 mg twice daily; subjects in Group 2 received TPV 1250 mg twice daily, nevirapine 200 mg twice daily, and ritonavir 200 mg twice daily. Subjects received TPV or TPV/r from day 1 to 7 and from day 34 to 43. Nevirapine was administered from day 8 to 43. The soft elastic capsule with free acid formulation of TPV was used. Subjects with a history of castor oil hypersensitivity or infected with HIV, HBV, or HCV were excluded.

Of the 24 study subjects, 21 were male and three were female; 11 completed the study. Demographic data were provided for these 11 study subjects: all 11 were male and 10 were White. The mean age was 27.5 years.

Gastrointestinal AEs were common during TPV administration. The following GI AEs were reported during the TPV phase: nausea (20 subjects), diarrhea (17), abdominal pain or upset stomach (11), vomiting (8), and decreased appetite (2). Other AEs reported during TPV use included headache (10 subjects), dizziness (2), increased liver function

tests (3), rash (2) and jaundice (1). Subject #4 had an increase in ALT on day 34 and rash on day 36; both while on nevirapine, just after TPV was added on day 34. This male subject also developed pruritis, jaundice, and abdominal pain during the same time period.

> *MO Comment:* It is very likely that these AEs are an example of symptomatic hepatotoxicity that is observed with nevirapine use. Another subject had increased liver function tests on day 37, while on nevirapine and TPV, and the third subject had increased LFTs on TPV alone.

A total of 13 subjects discontinued the study prematurely. Two subjects withdrew consent. Only three subjects discontinued due to an AE while receiving TPV; the other eight discontinued due to AEs reported while receiving nevirapine alone. The three subjects on TPV discontinued due to increased liver function tests on day 6, due to increased liver function tests on day 37, and due to nausea and retching.

No laboratory abnormalities that were not captured as adverse events were reported in the study report. In the study line listings, 11 subjects with normal triglyceride levels at baseline had an increase in triglyceride to more than the ULN including one subject with a Grade 2 triglyceride level.

F. Study P&U 014

Study P&U 14 was a randomized, open-label, parallel group study comparing the bioavailability of the SEDDS formulation (1200 mg) and the hard filled capsule (2400 mg) in 18 healthy adult volunteers. All subjects received a single dose of TPV on day 1 then received TPV twice daily on days 2 to 10. Subjects with a history of castor oil hypersensitivity or infected with HIV, HBV, or HCV were excluded.

Of the 18 subjects, 16 were male and two were female. Thirteen subjects were White and five Black. The mean age was 28.5 years.

Fifteen of the 18 subjects (83%) had at least one adverse event. Diarrhea was the most common AE and was observed in six subjects. Nausea was reported in six subjects and vomiting in three. Three subjects, two males and one female, had a rash while on TPV. All three were treated with diphenhydramine. One male was discontinued due to urticaria. Four subjects had pruritis including one that was graded as severe. Cognitive impairment was reported in one subject and impaired concentration in two.

Two subjects discontinued the study early: one because of a gum infection and the other, a white male, due to a severe urticarial rash on day 10. There were no serious or life-threatening adverse events.

On review of the line listings, one subject had an increase in triglyceride levels from within normal limits at baseline to greater than the ULN on study. Six subjects with

normal total cholesterol levels at baseline had increases in cholesterol to greater than the ULN.

G. Study P&U 19

Study P&U 19 was an open-label, randomized, parallel group, drug drug interaction study of tipranavir and efavirenz in 24 healthy adult volunteers. Subjects in Group 1 received tipranavir 1250 mg twice daily on days 1 to 7 and on days 22 to 31; EFV was administered on days 8 to 31. Subjects in Group 2 received TPV/r 1250 mg/200 mg twice daily with EFV on the same schedule. All subjects received the SEDDS formulation of TPV. Persons with a history of castor oil hypersensitivity or infected with HIV, HBV, or HCV were excluded from study participation.

A total of 24 subjects were enrolled in the study. Demographic data were provided for subjects with evaluable pharmacokinetic data only. Of these 13 subjects (8 males, 5 females), 12 were White. The mean age was 39.0 years.

Twenty-two of the 24 subjects (92%) reported at least one AE. Gastrointestinal AEs were common: nausea was reported in 16 subjects, vomiting in 10, diarrhea in 11, and loose stools in 5. All episodes of vomiting were of moderate intensity. The frequency of vomiting was higher in subjects receiving TPV/r (8 subjects) compared to those receiving tipranavir alone (2). Abdominal cramping was reported in 6 subjects, abdominal pain in 4, and abdominal distention in 2. Other adverse events included headache (19 subjects) and dizziness (17 subjects). In addition, a large number of subjects reported an AE related to cognition or concentration: impaired cognition (3), disorientation (2), impaired concentration (1), and confusion (1). Desquamation of the skin was reported in one subject and pruritis in one subject.

> *MO Comment*: The use of efavirenz is associated with CNS changes such as those reported in this study. It is difficult to determine the relative contribution of TPV to these AEs.

Of the 24 subjects, there were nine premature study discontinuations; five were due to AEs. The reasons for premature study discontinuation were nausea/vomiting (3, one also with dizziness and flank pain), fever (1), headache, fatigue, and abdominal cramping (1).

Six subjects had increased ALT levels during study participation; three had Grade 3 increases in hepatic transaminases while receiving tipranavir. Eleven subjects with normal triglyceride levels at baseline had increased to greater than the ULN including one subject with a Grade 2 triglyceride level.

H. Study 1182.5

Study 1182.5 was an open label, parallel group, pharmacokinetic study of the effect of TPV/r on CYP isoenzymes in 113 healthy adult volunteers. TPV was given twice daily alone for the first 11 days and then twice daily with ritonavir from day 11 to 32. The

following doses were used; (the TPV dose was given throughout the study and ritonavir was started on day 11): 250 mg/200 mg, 500 mg/100 mg, 500 mg/200 mg, 750 mg/100 mg, 750 mg/200 mg, 1000 mg/100 mg, 1000 mg/200 mg, or 1250 mg/100 mg. The SEDDS formulation of TPV was used. Subjects with a history of sulfonamide hypersensitivity and those infected with HIV, HBV, or HCV were excluded.

Of the 113 study subjects, 45 were male and 68 were female. Ninety-four subjects (83%) were White and 19 were Black (17%). The mean age was 48.0 years. Eighteen subjects discontinued the study prematurely: 11 due to AEs, 4 withdrew consent, 2 for non-compliance, and one was lost to follow-up.

AEs were reported in 109 or 96% of study subjects. Ninety percent of subjects reported a GI AE including diarrhea (75%), nausea (53%), vomiting (41%), and abdominal pain (19.5%). Most of these GI AEs were mild, and there were six GI AEs of moderate intensity (nausea-5, vomiting-1) Non-GI AEs reported in more than 5% of subjects included headache (30%), dizziness (17%), and vertigo (6%). Rash was also reported in two subjects; one of the subjects with rash and a second with pruritis were female. In subject 4017, the rash began after the first dose of TPV with RTV, was located on the back, chest, arms, and abdomen and was described as maculopapular. This subject discontinued the study prematurely, was treated with diphenhydramine and methylprednisolone, and recovered.

The applicant compared the plasma concentration of TPV in subjects with vomiting or diarrhea to those without vomiting or diarrhea, and there was no trend or statistical difference between TPV plasma concentrations between the groups.

> *MO Comment*: The correlation of diarrhea or vomiting with TPV levels was performed using trough levels and total exposure only. Since peak levels were not used in this analysis, the possibility of a relationship between diarrhea or vomiting and plasma TPV levels cannot be ruled out.

Eleven subjects discontinued the study prematurely due to an AE. Ten of the 11 discontinued during the TPV only phase and one discontinued after the addition of RTV. AEs reported during TPV only were 5 due to nausea and vomiting, 2 with respiratory infections, one with asthma exacerbation, one with dizziness, nausea and vomiting, and one with Grade 3 increase in ALT. The one subject discontinuing on TPV/r discontinued due to a rash. There were no severe or serious AEs and no deaths.

There were no Grade 4 laboratory values reported. The most common abnormal laboratory value was increase in prothrombin time, which was reported in 20 subjects (18%). Increased PT values ranged from 12.0 seconds to 23.5 seconds (Grade 3). Thirteen of the 20 had only one increased PT with normal PT values at follow-up. Two subjects had one increased value at the final study evaluation only. There were 12 subjects with increased GGT, but none had Grade 3 or 4 increases. Increased ALT was reported in three subjects (3%) including one subject with a Grade 3 increase in ALT. Nine subjects had increases in amylase including one subject with Grade 3 amylase and

lipase levels. There were 24 subjects with normal triglyceride levels at baseline who had increases in triglycerides to greater than the ULN. Three of these were Grade 3. Similarly, there were four subjects with increased LDL levels during treatment, but all four had elevated LDL levels at baseline.

MO Comment: A high proportion of study subjects had increases in prothrombin time. The reason for this is unclear. There were no clinical episodes of bleeding that correlated with this laboratory finding. Most of the elevations occurred at a single visit only and resolved without discontinuation of study drug. This frequency of increased PT has not been reported in other studies.

I. Study 1182.10

Study 1182.10 was an open-label, multidose, drug drug interaction study of tipranavir, ritonavir, and fluconazole in 20 healthy adult volunteers. All subjects received fluconazole (200 mg loading dose followed by 100 mg daily) on days 1 to 13. Subjects then received TPV/r 500 mg/200 mg twice daily on days 7 to 13; the SEDDS formulation of TPV was used. Persons with a history of sulfonamide hypersensitivity or infected with HIV, HBV, or HCV were excluded from study participation.

Of the 20 subjects 18 were male and 2 female. Nineteen subjects were White and one was Black. The mean age was 42.4 years.

Eighty percent of subjects (16) reported at least one AE while receiving TPV. The most common organ system involved (65%) was gastrointestinal. Seven subjects reported loose stools, seven abdominal pain, three nausea, and two anorexia. Headache was reported in three subjects and dizziness in two.

The only Grade 3 or 4 laboratory abnormality was a Grade 3 lipase, which was reported for two subjects on day 14. There were two Grade 1 increases in GGT and four Grade 1 increases in APTT. Twelve subjects with normal triglyceride levels at baseline had increases in triglyceride levels to greater than the ULN. The median change from baseline for triglycerides was+1.88 mg/dL (maximum increase of 5.09), for total cholesterol was +1.23 mmol/L (maximum increase of 2.95), and for ALT was +35 U/L (maximum increase of 116).

There were no premature discontinuations due to an AE. There were no severe, life-threatening, or serious AEs.

J. Study 1182.11

Study 1182.11 was an open label, multidose drug drug interaction study of TPV/r and clarithromycin in 24 healthy adult volunteers. The SEDDS formulation of TPV was used. TPV/r (500 mg/200 mg twice daily) was administered on days 6 to 13 while clarithromycin (500 mg twice daily) was administered on days 1 to 13. Persons with a

history of sulfonamide hypersensitivity or infected with HIV, HBV, or HCV were excluded.

Of the 24 study subjects, 17 were male and 7 were female. Twenty-two subjects were White and two Black. The mean age was 33.2 years.

Fifty-four percent of subjects reported an AE while receiving TPV. One subject had chest wall pain, one had a maculopapular rash, and one had swelling of the face.

There were no premature study discontinuations due to AEs, serious AEs, or deaths.

Changes in ALT from baseline were observed in 12 subjects: Grade 1 in 7, Grade 2 in 4, and Grade 3 in one subject on day 7 of TPV/r. The median change in ALT from baseline was +45 U/L with a maximum increase of 258. Nine subjects with normal triglyceride levels at baseline had an increase in triglyceride levels to greater than the ULN. The median change in triglycerides from baseline was +114 mg/dL (maximum increase of 214) and the median change in LDL was +4 mg/dL (maximum increase of 122). Total cholesterol values were not obtained.

There were no premature discontinuations due to an AE. There were no severe, life-threatening, or serious AEs.

K. Study 1182.21

Study 1182.21 was an open-label, multidose, drug drug interaction study of tipranavir, ritonavir, antacid, and atorvastatin in 23 healthy adult volunteers. Subjects received a single dose of TPV/r (500 mg/200mg) on day 8 and on day 13, then received TPV/r at the same dose twice daily on days 14 to 21. The SEDDS formulation of TPV was used. Subjects also received a single dose of atorvastatin on days 1 (40 mg) and 20 (10 mg). Finally, subjects received a single dose of Maalox antacid (20 ml) on day 13. Persons with a history of sulfonamide hypersensitivity or infected with HIV, HBV, or HCV were excluded from study participation.

Twenty-three healthy adults were enrolled in study 1182.21. Eleven were male and 12 female. The majority of subjects were White (22 or 96%). The mean age was 32.7 years.

Adverse events discussed are those which were reported during the time periods in which the subjects received TPV. All subjects experienced at least one AE. The most common adverse events were gastrointestinal, which were reported in 96% of subjects and included diarrhea (83%), loose stools (22%), nausea (56.5%), abdominal pain or tenderness (52%), and flatulence (30%). One subject reported moderate nausea, and GI AEs were mild in the remaining subjects. Headache was reported in 10 subjects and muscle weakness in four. Two subjects had AEs reported as "adverse drug reactions," however, these AEs were not described further. There was one serious AE, an ankle injury suffered while running.

There were 10 subjects with a Grade 1 increase in ALT, one with a Grade 2 increase and one with a Grade 3 increase (303 U/L on day 22). The median change in ALT was +30 U/L with the maximum change of +200. One subject had a Grade 2 total bilirubin; this subject had mild ocular icterus while on TPV/r alone. There was one Grade 2 triglyceride level and two Grade 1 cholesterol levels.

There were no premature study discontinuations due to AEs. There were no life-threatening adverse events.

L. Study 1182.24

Study 1182.24 was an open label, single arm, pharmacokinetic study of tipranavir and ritonavir absorption, distribution, metabolism, and elimination in 12 healthy male volunteers. Subjects received TPV/r 500 mg/200 mg twice daily for 14 days. The SEDDS formulation was used. Females and persons infected with HIV, HBV, or HCV were excluded from study participation.

All 12 study subjects were male. Ten (83%) were white, one was Black, and one was Asian. The mean age was 36.2 years. Four subjects discontinued the study prematurely: two due to AEs, one withdrew consent, and one was not chosen to receive radiolabeled TPV.

Seven of the 12 subjects experienced an adverse event. All seven reported a GI AE including nausea (4), loose stools (4), and vomiting (1). One subject discontinued the study on day 6 due to nausea; this subject also had an increased ALT to 566 U/L and increased AST (277 U/L). The nausea and increased ALT and AST resolved on follow-up. Headache was reported in one subject. A rash was reported in one subject.

All subjects had normal ALT values at baseline. Ten of the 12 subjects had increases in ALT to above the ULN. Three subjects had Grade 1or 2 increases in ALT. Increased ALT and in AST were reported as clinical AEs in two subjects: a Grade 3 increase in ALT (227 U/L on days 1 and 7) in one and a Grade 4 increase (566 U/L on day 6) in another. Subject 106 discontinued the study on day 14 due to increases in ALT and AST (165 U/L and 60 U/L respectively). The subject was lost to follow-up, therefore, it is not known if the elevations in ALT and AST resolved. Increases in cholesterol and in triglycerides were reported as clinical AEs in one subject each. Three subjects had Grade 2 increases in triglycerides. The median increase in total cholesterol from baseline to last dose of study drug was 40 mg/dL and for triglycerides was 163 mg/dL. Three of nine subjects had elevations in prothrombin time above the upper limit of normal, but none had a Grade 1 increase in PT and all resolved.

There were two premature study discontinuations due to an AE: one due to nausea and vomiting and the other due to increased ALT. There were no serious AEs or deaths reported.

M. Study 1182.37

Study 1182.37 was an open label, randomized, parallel group, drug drug interaction study of TPV/r and zidovudine in 60 healthy adult volunteers. Study subjects were randomized to receive TPV/r twice daily at a dose of 500 mg/100 mg or 750 mg/200 mg from days 2 to 12; a single dose of tipranavir and ritonavir was administered on day 13. A single 300 mg dose of zidovudine (ZDV) was administered on days 1 and 13. The SEDDS formulation of TPV was used. Persons infected with HIV, HBV, or HCV were excluded from study participation.

Thirty subjects were enrolled in each treatment arm (TPV/r 500 mg/100 mg and TPV/r 750 mg/200 mg). Twenty-eight were male and 32 were female. Fifty-two subjects (87%) were White, and eight were Black. The mean age was 38.7 years. There were six premature study discontinuations; the reasons for study discontinuation were non-adherence (2), consent withdrawn (2), family emergency (1), and an adverse event (1).

Fifty subjects or 85% reported at least one AE. The frequency of AEs was higher in the TPV/r 750 mg/200 mg arm (97%) than the TPV/r 500 mg/100 mg arm (73%). Gastrointestinal AEs were common in both arms and were reported in 90% of high dose compared to 70% of low dose subjects. GI AEs for both arms included nausea (48%), diarrhea (30%), abdominal pain (27%), and vomiting (20%); each of these AEs was reported more commonly in the 750 mg/200 mg arm than the 500 mg/100 mg arm. Other common AEs included dizziness (37%) and headache (22%); both were more common in the high dose arm compared to the low dose arm. Most AEs were of mild intensity. There were two moderate AEs (diarrhea and abdominal pain); both occurred in subjects receiving 750 mg/200 mg of TPV/r.

> *MO Comment*: Clinical adverse events were substantially more frequent in the 750 mg/200 mg arm than the TPV/r 500 mg/100 mg arm. It also appears that AEs were more severe at the higher dose. As shown in other studies of TPV, higher doses of TPV are difficult to tolerate.

Less common AEs of interest included palpitations in three subjects. All three were in subjects who were also experiencing GI AEs. One of the subjects complained of chest pressure but had a normal electrocardiogram. All three AEs were mild and resolved within 24 hours while on study drug. Rash and pruritis were reported in one female study subject. Arthralgia was reported in one female subject. One subject (28 year old female) had nausea, vomiting, diarrhea, and an upset stomach on day one of TPV/r; she discontinued the study on day 3 because of dizziness, loose stools, and weakness on day 3.

> *MO Comment*: It is unclear why the 3 subjects experienced palpitations. This has not been commonly reported in other studies of TPV. It is highly possible that the subject who withdrew experienced symptoms due to dehydration.

Increases in ALT from baseline were common and were reported in 11 subjects (5 in the 500 mg/100 mg group and 6 in the 750 mg/200 mg group). Overall, there were 7 subjects with Grade 1 ALT values, 2 with Grade 2 values, one with Grade 3, and one with Grade 4. The majority of increases in ALT (4 of 5) in the 500 mg/100 mg arm were Grade 1 and the remaining increase was a Grade 2. Three subjects in the 750 mg/200 mg arm had Grade 1 increases, and one each had a Grade 2, Grade 3, and Grade 4 increase. ALT levels returned to Grade 1 levels or less within 3 weeks for all subjects. No subjects were symptomatic and none had increases in total bilirubin. Eighteen subjects with normal triglyceride levels at baseline had increases in triglyceride to greater than the ULN while receiving study drug.

> *MO Comment*: The severity of ALT increase appeared to be more common in the higher dose arm.

There was one premature study discontinuation due to an adverse event (dizziness, loose stools, and weakness). There were no severe AEs, no serious AEs, and no deaths.

N. Study 1182.41

Study 1182.41 was an open label, randomized, parallel group, drug drug interaction study of TPV/r and efavirenz (EFV) in 68 healthy adult volunteers. Study subjects were randomized to receive TPV/r twice daily at a dose of 500 mg/100 mg *or* 750 mg/200 mg. Study subjects received EFV 600 mg as a single dose on day 1 and day 5 and then once daily from days 7 to 21. Subjects received a single TPV/r dose on days 3, 5, and 14 and TPV/r twice daily from day 15 to day 21. The SEDDS formulation of TPV was used. Persons infected with HIV, HBV, or HCV were excluded from study participation.

Of the 68 study subjects, 45 were male and 23 were female. Forty-three subjects (63%) were White, 21 Black, and 4 Asian. The mean age was 33.1 years. Twenty subjects discontinued the study prematurely: two discontinued before receiving TPV, 15 due to AEs, 3 withdrew consent, and 2 for other reasons.

Sixty-two of the 66 subjects (94%) who received TPV reported at least one AE. The number of subjects with an AE was 31 in each TPV/r arm. Gastrointestinal AEs were the most common AE and were reported in 86% of all subjects, however, the percentage of subjects with GI AEs was higher in the 750 mg/200 mg arm (97%) than the 500 mg/100 mg arm (76.5%). The most common GI AEs in the study were nausea (67%), diarrhea (54.5%), vomiting (35%), and abdominal pain (24%). Each of these GI AEs was more common in the 750 mg/200 mg arm than the 500 mg/100 mg arm. Other common AEs were dizziness (41%), euphoria (35%), and headache (32%). A rash was reported in one female study subject.

> *MO Comment:* Dizziness and euphoria have been reported with EFV use, however, dizziness has also been reported in other Phase 1 studies of TPV.

There were three severe AEs in the 500 mg/100 mg arm and two in the 750 mg/200 mg arm. The severe AEs were oral numbness, hypotension, pyelonephritis, blurred vision, and dystonic reaction. Hypotension was reported in a 18 year old female (subject 125) on her first day of TPV/r (after 7 days of EFV). She also complained of nausea and a mild dazed feeling; all signs and symptoms resolved after a bolus of intravenous fluids. Subject 212 was a 23 year old male who developed severe oral numbness, mild slurring of speech, and moderate swelling at the base of the tongue on day 5 after single doses of TPV/r and EFV. The subject was given benadryl and symptoms resolved. Both subjects discontinued the study prematurely. There was one serious AE, which was reported in a 38 year old female receiving TPV/r 500 mg/100 mg. This subject had a history of nephrolithiasis and was hospitalized with pyelonephritis ten days after finishing TPV/r.

> *MO Comment*: The episodes of hypotension and of an hypersensitivity-like reaction are of concern. Health care providers should be aware that such episodes may occur in their patients taking TPV/r.

Fifteen subjects discontinued the study due to an adverse experienced after receiving at least one dose of TPV/r. One subjects was discontinued due to anxiety, which began during EFV administration and continued. Six of the remaining 14 subjects who discontinued due to an AE were in the 500 mg/100 mg arm and eight were in the 750 mg/200 mg arm. These premature discontinuations included subjects 125 and 212 who are described above. Other discontinuations in the 500 mg/100 mg arm were due to nausea; nausea, vomiting, and fatigue; lice; and pyelonephritis. Discontinuations in the 750 mg/200 mg arm were due to fatigue, abdominal pain, epigastric pain, diarrhea, vomiting, cardiac palpitations, dystonic reaction with tongue abnormality, and anxiety.

There were 16 Grade 1 ALT values (5 in the 500 mg/100 mg arm and 11 in the 750 mg/200 mg arm). All Grade 2 and 3 increases in ALT were in the 750 mg/200 mg arm and included 5 Grade 2 ALT values and 2 Grade 3 ALT values. There were no Grade 4 ALT abnormalities. Three subjects had Grade 3 increases in amylase. There were no Grade 3 or 4 increases in lipase. Twenty-nine subjects with normal triglyceride levels at baseline had increases in triglyceride levels to greater than the upper limit of normal, including four with Grade 2 levels.

O. Study 1182.44

Study 1182.44 was a multidose, open label, drug drug interaction study of tipranavir, ritonavir, and rifabutin in 24 healthy adult volunteers. Subjects received TPV/r 500 mg/200 mg from days 8 to 20. Subjects received a single 150 mg dose of rifabutin on days 1 and 15. The SEDDS formulation of TPV was used. Persons with a history of sulfonamide hypersensitivity or infected with HIV, HBV, or HCV were excluded from study participation.

Of the 24 study subjects, 20 were male and four were female. Twenty-two (92%) were White, two were Black, and two were Hispanic. The mean age was 32.8 years. Four subjects discontinued the study prematurely; all due to adverse events.

Eighteen of the 24 subjects (75%) experienced at least one AE. The most common AEs were gastrointestinal (58%) including nausea (8 subjects), vomiting (6), abdominal pain (4), and loose stools (3). Headaches (33%) and dizziness (12.5%) were also frequently reported.

Three subjects had drug-related hepatitis during the study. Two had Grade 3 ALT levels and one had Grade 4 ALT value. The subject with a Grade 4 increase in ALT had a Grade 1 increase in PT at the same study visit. All three were asymptomatic. All three were detected seven days after starting TPV/r. All three subjects had resolution of ALT abnormalities within 33 days. Another subject was discontinued prematurely due to a generalized rash with pruritis on study day 19.

Four subjects prematurely discontinued the study. Three subjects discontinued due to drug-related hepatitis; all were asymptomatic and were previously described. One male subject discontinued due to generalized rash and pruritis. Two other subjects had papular rashes.

In addition to the three subjects with Grade 3 and 4 abnormalities in ALT described above, there were 5 subjects with Grade 1 increases in ALT and two with Grade 2 increases in ALT. One subject had a Grade 3 increase in lipase on day 21, which was normal on follow-up seven days later. This subject had a Grade 1 amylase, but no clinical symptoms at the same study visit. There were no Grade 3 or 4 increases in amylase. Another subject had a Grade 3 increase in PT on day 8 prior to TPV dosing, which was normal on day 14; however, this subjects could not be identified in the line listings.

There were no severe and no serious AEs. There were no deaths.

P. Study 1182.46

Study 1182.46 was an open-label, randomized, parallel group, drug drug interaction study of tipranavir, ritonavir, and tenofovir (TDF) in 49 healthy adult volunteers. Study subjects were randomized to receive TPV/r twice daily for 14 days at a dose of 500 mg/100 mg or 750 mg/200 mg. Study subjects received a single 300 mg dose of TDF on days 1 and 13. The SEDDS formulation of TPV was used. Persons infected with HIV, HBV, or HCV were excluded from study participation.

Of the 49 study subjects, 26 were male and 23 female. All subjects were White. The mean age was 35.4 years. Two subjects prematurely discontinued the study: one due to an AE and one due to a change in his work.

Ninety-six percent of subjects in both study arms experienced at least one AE. Gastrointestinal AEs were the most common type of AE and were reported in 84% of subjects (88% of subjects in the750 mg/200 mg and 79% of subjects in the 500 mg/100 mg arm). GI AEs for both arms included 27 subjects with diarrhea, five with loose

stools, 20 with nausea, eight with abdominal pain, and four with vomiting. Other common AEs included abnormal liver function tests (14 subjects) and headache (12).

Skin AEs included urticaria in three female subjects, severe erythematous rash in a female, and generalized pruritis in one female. Four of the five subjects with rash were receiving TPV/r at the 750 mg/200 mg dose. All cases of urticaria started nine to 10 days after starting TPV/r and resolved in 10 to 12 days. The severe erythematous rash began on day 4 and resolved 19 days later. This rash was described as painful, pruritic tiny papules extending from both knees to the breast and arms. This subject was discontinued from the study prematurely. Other less common AEs of interest included chest tightness (1 subject), syncope (1), and epistaxis (1).

All subjects had ALT values with normal limits at baseline. After dosing with TPV/r, there were ten subjects with Grade 1 ALT values, five with Grade 2, and one with Grade 3. Of these 16 subjects with abnormal ALT values, 11 were receiving the higher dose of TPV/r including four of the five Grade 2 ALT values and the one Grade 3 value. Twenty-one subjects had increases in triglyceride levels; none were Grade 3 or 4. Seventeen subjects with normal triglyceride levels at baseline had increases to greater than the ULN including three with Grade 2 triglyceride levels.

> *MO Comment:* Both the frequency and severity of hepatotoxicity associated with TPV/r were dose related in this trial.

One subject discontinued the study prematurely due to a rash. There were no serious adverse events and no deaths.

Q. Study 1182.55

Study 1182.55 was a multidose, drug drug interaction study of TPV, ritonavir, and loperamide in 24 healthy adult volunteers. Subjects were randomized to receive either TPV 750 mg or 500 mg from days 4 to 9 and 12 to 22. Study subjects also received ritonavir from days 12 to 22; subjects originally receiving 750 mg of TPV added 200 mg of RTV while subjects receiving TPV 500 mg added 100 mg of RTV. All subjects received loperamide on day 1, day 9, and day 22. Persons with a history of sulfonamide hypersensitivity or infected with HIV, HBV, or HCV were excluded from study participation.

Of the 24 study subjects, 14 were male and 10 female. Nineteen subjects were White, four Black, and one Asian. The mean age was 33.5 years.

Seventeen (71%) of subjects reported AEs while receiving TPV. The most common class of AEs reported was gastrointestinal (67%), which included loose stools (37.5%), nausea (33%), abdominal pain (29%), and vomiting (17%). Headache was reported in 25% of study subjects. Skin AEs were reported in 12.5% of subjects. Maculopapular rashes were reported in three subjects (two females and one male), and pruritis was reported in two subjects. Two of the rashes were of mild intensity and one was moderate. Onset of

rash ranged from day 3 to day 21. Less common AEs of interest included anorexia (2 subjects), musculoskeletal pain (1), confusion (1), sensation of chest pressure (1), and erythema (1).

Most AEs were mild in intensity. Moderate AEs included vomiting (17%), nausea (12.5%), and headache (8%).

Three subjects had Grade 3 increases in ALT values and five had Grade 4. All eight subjects had ALT values within normal limits at baseline. ALT values started to increase on day 9 for 2 subjects and on day 17 for six. All ALT values returned to normal limits on follow-up. There were no other Grade 3 or 4 laboratory abnormalities. However, two subjects had Grade 2 triglyceride levels.

There were no severe AEs. No subjects discontinued the study prematurely due to an adverse event. There were no serious AEs.

Rash, Hepatotoxicity, and Lipid Abnormalities in Phase I, Multidose, PK Studies of Tipranavir in Healthy Volunteers

Study	TPV Dose and Formulation	TPV Duration	Gender	Rash	Hepatotoxicity	Number of subjects with Triglyceride Levels >ULN*
P&U 3	300-2000 mg tid, HFC	10 days	31M / 5F	rash (M) macular rash (F)	--	6
P&U 8	1200 mg bid, HFC	17 days	5M / 2F	urticaria, throat tightening, puriritis (F) throat tightness, generalized pruritis (F)	--	6
P&U 9	1350 mg bid, HFC	17 days	13M / 1F	--	1 – Grade 3 ALT	11
P&U 12	600 mg or 900 mg bid, HFC, 100-500 mg RTV after d5	24 days	16M / 3F	4 w/rash – (3M, 1F)	9 – ALT >ULN (nl BL)	6
P&U 13	1250 mg, SEC, ½ of subjects received RTV 200 mg NVP drug interaction study	17 days	21M / 3F	5 w/ rash (4M, 1F)	3 -Grade 3 ALT 1 - Grade 4 ALT 2 subjects with Gr 2 bili	11
P&U 14	1200 mg, SEDDS and 2400 mg, HFC bid	10 days	16 M / 2F	urticaria (M) rash (M) rash, pruritis, tingling (F)	--	1
P&U 19	TPV/r 1250/200 bid SEDDS	17 days	18M / 6F	--	2 – Grade 3 ALT	11
1182.5	TPV/r 250-1250 mg/100-200 bid, SEDDS	32 days	45M / 68F	rash (M) rash (F)	1- Grade 3 ALT	24
1182.10	TPV/r 500/200 bid, SEDDS	7 days	18M / 2F	--	--	12
1182.11	TPV/r 500/200 bid, SEDDS	7 days	17M / 7F	MP rash (F) lip swelling (M)	1 – Grade 3 ALT	9
1182.21	TPV/r 500/200 bid, SEDDS	18 days	11M / 12F	--	1 – Grade 3 ALT 1 – Grade 2 bili and jaundice	1
1182.22	TPV/r 500/100 or 750/200 bid, SEDDS	13 days	51 F	17 females w/ rash 1 photosensitivity	5 – Grade 3 ALT 2 – Grade 4 ALT	0
1182.24	TPV/r 500/200 bid, SEDDS	7 days	12M	rash (M)	1 – Grade 3 ALT 1 – Grade 4 ALT 8 – ALT > ULN (nl BL)	6
1182.32	TPV/r 500/200 bid, SEDDS	7 days	16M / 6F	--	--	2
1182.37	TPV/r 500/100 or 750/200 bid,	11.5 days	28M / 32F	rash and pruritis (F)	1 – Grade 3 ALT	18

	SEDDS				1 – Grade 4 ALT 11 – ALT > ULN (nl BL)	
1182.41	TPV/r 500/100 or 750/200 bid, SEDDS	7 days	45M / 23F	rash (F)	2 – Grade 3 ALT 23 – ALT > ULN (nl BL)	29
1182.42	TPV/r 500/100 or 750/200, SEDDS	14 days	18M / 5F	--	1 – Grade 4 ALT 14 – ALT > ULN (nl BL)	6
1182.44	TPV/r 500/200 bid, SEDDS	13 days	20M / 4F	generalized rash and pruritis (M) papular rash (F)	3 – drug induced hepatitis (2 Grade 3 ALT, 1 – Grade 4 ALT)	#
1182.46	TPV/r 500/200 or 750/200 bid, SEDDS	11.5 days	26M / 23F	severe erythematous rash (F) 3 w/ urticaria (all F) generalized pruritis (F)	1 – Grade 3 ALT 16 – ALT > ULN (nl BL)	17
1182.55	TPV/r 500/200 or 750/200 bid, SEDDS (subgroup w/5d TPV only)	10.5-16 days	14M / 10F	3 w/ maculopapular rash (2F, 1M)	3 - Grade 3 ALT 5 - Grade 4 ALT	2

* Only subjects with normal TG levels at baseline were included in this table. Overall, there were 27 Grade 2 increases in TG and one Grade 3 increase. There were no Grade 4 increases.

#No electronic line listings were provided for this study, and this data could not be captured from the clinical study report.

SINGLE DOSE PHASE 1 STUDIES OF TIPRANAVIR IN HEALTHY VOLUNTEERS

This review is limited to the safety data from these studies. Please see Dr. Zheng's review for discussion of the pharmacokinetic data obtained in these trials.

I. Study P&U 001

Study P&U 001 was a randomized, double-blind, placebo-controlled, single dose escalation study in healthy adult volunteers. The hand-filled TPV capsule was used. Four subjects received TPV and two received placebo at each dose level (100, 300, 500, 700, 900, 1200, 1600, and 2000 mg). Subjects with HIV, HBV, or HCV were excluded.

A total of 48 subjects were enrolled. Thirty-six were male and 12 female. Forty-six were White and 2 Black. The age at enrollment ranged from 20 to 55 years.

Adverse events (AEs) were reported in 19 of 32 TPV subjects (59%) compared to 2 of 16 placebo subjects (13%). There were no severe, life-threatening, or serious AEs. Individual AEs are shown in the table below.

A. Table: Percentage of subjects with AEs in Study P&U 004

AE	TPV	PBO
headache	19%	12.5%
eructation	19%	0
nausea	19%	12.5%
diarrhea	12.5%	0
abd pain	19%	0

Four subjects had an one grade shift from Grade 0 to Grade 1: one in PT, one in total bilirubin, and two in lipase (both of these were in the PBO group).

II. Study P&U 002

Study P&U 002 was a randomized, open-label, four-way crossover study to compare four formulations of TPV (hand-filled capsule with disodium salt, oral solution, hard-filled capsule, and [redacted] compressed capsule) in healthy adult volunteers. The hand-filled capsule was used in study 001. All subjects received a single 800 mg dose of each TPV formulation with a wash-out period between doses. Subjects could not be infected with HIV, HBV, or HCV.

Twelve subjects received at least one dose of TPV. Eleven subjects were male; one was female. Eleven subjects were White, and one was Black. The mean age was 29 years with a range of 18 to 49 years.

The mean bioavailability of the other formulations compared to the oral solution was hand filled 87%, hard filled 125%, and [illegible] 83%.

Adverse events were reported in 11 of 12 (92%) subjects. There were no severe, life-threatening, or serious AEs. There were no discontinuations due to an adverse event. Selected individual adverse events by formulation, including all adverse events reported more than once, are shown in the table below.

Table: Selected Adverse Events Reported in Study P&U 002

AE	Hand filled	Oral Solution	Hard filled	[illegible] capsule	Total
bitter taste	1	8	1	2	12
diarrhea	3	3	1	1	8
eructation	1	1	3	0	5
abd cramping	1	1	1	0	3
nausea	1	1	1	1	4
flatulence	1	1	0	0	2
constipation	1	0	1	1	3
headache	1	1	2	1	5
epistaxis	0	0	1	0	1

As shown in the table above, gastrointestinal AEs were common, particularly diarrhea. The only AE which was reported noticeably more frequently in one formulation was bitter taste with the oral solution.

There were two laboratory abnormalities of note. One subject with serum creatinine of 1.0 at BL, had an increase of creatinine to 1.4 after one dose of TPV. The second dose delayed for one week. The creatinine returned to normal values, and the subject tolerated other 3 doses without problems. Another subject experienced an increase in ALT from 11 at baseline to 49 before the fourth and last TPV dose; these values are both within the normal limits.

III. Study P&U 005

Study P&U 005 was an open-label, randomized, single dose, three way crossover study in healthy adults to assess the effects of food and antacid administration on absorption of TPV. A 900 mg dose of the hard-filled capsule of TPV was administered after fasting, after an high fat meal, and 10 minutes after 20 ml of Maalox. Subjects could not be infected with HIV, HBV, or HCV.

A total of 12 subjects received at least one dose of TPV; all completed the study. Six subjects were male and six female. Eleven were White, and one was Black. The mean age was 34.9 years with a range of 20 to 51 years.

Adverse events were reported in nine of 12 subjects (75%). There were no severe, life-threatening, or serious AEs. There were no study discontinuations due to AEs.

Table: Adverse Events Reported in Study P&U 005

AE	Fast	Fed	Maalox	Total
nausea	2	1	3	6
headache	0	3	2	5
diarrhea	2	1	1	4
flatulence	0	2	0	2
eructation	1	0	0	1
abd pain	0	1	0	1
constipation	0	1	0	1
rash	0	1	0	1
tinnitus	0	1	0	1
lightheaded	0	0	1	1

As shown in the table above, gastrointestinal adverse events were common. One subject experienced a rash. There were no serious or severe AEs.

One subject had an amylase value greater than the upper limit of normal while on study. Two subjects with normal triglyceride levels at baseline had triglyceride levels greater than the upper limit of normal while on study.

IV. Study P&U 007

Study P&U 007 was an open-label, randomized, single dose, five way crossover study in healthy adults to assess the bioavailability of five formulations of TPV. A single 1200 mg dose of the following formulations was administered to each subject: hard-filled capsule, coated beads in capsule, coated beads in applesauce, [redacted] tablet, and self-emulsifying drug delivery system (SEDDS). Subjects could not be infected with HIV, HBV, or HCV.

A total of 10 subjects received at least one dose of study drug; all completed the study. Eight were male; two were female. All were White. The mean age was 32.9 years with a range of 21 to 51 years.

Adverse events were reported in all 10 study subjects. There were no severe, life-threatening, or serious AEs. There were no study discontinuations due to AEs. Individual AEs are shown in the table below.

Table: Adverse Events Reported in Study P&U 007

AE	hard filled	coated beads	beads in applesauce	[redacted] capsule	SEDDS	Total
diarrhea	3	3	1	2	5	14
headache	2	4	2	2	2	12
abd pain/cramps	1	3	1	3	3	11

taste perversion	0	0	9	0	0	9
nausea	1	3	1	0	2	7
lightheaded	2	1	1	1	2	7
eructation	0	0	1	0	0	1
pallor	1	0	0	0	0	1
increased saliva	0	0	1	0	0	1
fatigue	0	0	0	0	1	1
indigestion	0	0	0	0	1	1

As shown in the table above, gastrointestinal AEs were common, particularly diarrhea and abdominal pain or cramps. Headache was also commonly reported. Taste perversion was unique to the beads administered in applesauce.

One subject had an increase in white blood cell count from baseline to before the fifth dose of 7.55 to 12.8 with a left shift (neutrophils increased from 5.71 to 10.66). On review of the AE line listings, this laboratory change was not associated with an infection.

V. Study P&U 011

Study P&U 011 was a randomized, open label four way crossover study comparing the bioavailability of three SEDDS formulations of TPV and the effect of food on these formulations. Subjects were randomized to receive single 1200 mg doses of the TPV formulations in different sequences with a seven day washout period between doses. The formulations were the hard filled capsule, SEDDS without base, SEDDS and Tris with GDO/GMO, and SEDDS and Tris with Capmul MCM. In addition, subjects were randomized to receive a second dose of one of the four formulations with a high fat meal in a fifth study period. Persons were excluded from study participation for a history of castor oil hypersensitivity infection or for infection with HIV, HBV, or HCV.

Sixteen subjects were enrolled. Thirteen subjects were male and three female. All subjects were White. The mean age was 34.6 years. One subject prematurely discontinued the study due to otitis media.

Fifteen of the 16 subjects experienced at least one adverse event. Gastrointestinal AEs were common; the following GI AEs were reported: 15 episodes of diarrhea, eight nausea events, four abdominal events, and two episodes of vomiting. Other AEs included nine reports of headache and four of dizziness.

One subjects, a 47 year old White male had an increase in ALT from 23 U/L at baseline to 219 U/L (3.5 times ULN) on day 3. He also had an increase in AST but none in bilirubin. This subject continued on study and the ALT level decreased to normal limits. Two subjects had increased amylase levels, two had increased total cholesterol levels, and five had increased triglyceride levels.

There was one premature discontinuation for otitis media. There were no severe or serious AEs.

VI. Study 1182.45

Study 1182.45 was an open label, randomized, single dose, three way crossover study comparing the TPV oral solution after fasting, the TPV oral solution after a high fat meal, and the TPV SEDDS capsule after fasting. Each formulation was administered with 200 mg of ritonavir. Subjects were randomized to receive the TPV formulations with ritonavir in different sequences with a seven day washout period between each dose. There were no clinically significant entry criteria.

Thirty subjects were enrolled. Eighteen were male and 12 female. All were White. The mean age was 34.5 years.

Twenty-five subjects (83%) reported at least one adverse event. The most common AEs were gastrointestinal (57%). Upper abdominal pain was reported in 33% of subjects, diarrhea in 23%, and nausea in 17%. In addition, 30% of subjects reported headache and 13% dizziness. One subject is reported as having mild hypotension in the line listings, but this AE is not described further.

There were no Grade 3 or 4 laboratory abnormalities and no clinically significant laboratory abnormalities.

PHASE 1 STUDIES OF TIPRANAVIR IN HIV-INFECTED SUBJECTS

I. Resume

Two Phase I studies were conducted in HIV-infected subjects. In study P&U 004, 40 HIV-experienced subjects on stable two NRTI regimens added TPV to their regimen. Twenty-four PI naïve subjects were sequentially enrolled to receive TPV at one of three increasing doses (900 mg, 1200 mg, or 1500 mg three times daily); these subjects continued their two NRTIs and TPV for 24 weeks. Sixteen subjects infected with protease inhibitor resistant HIV received two NRTIs and TPV 1500 mg three times daily for four weeks. In study P&U 015, 31 treatment-naïve subjects received TPV (TPV 1200 mg, TPV/r 300 mg/200 mg, or TPV/r 1200 mg/200 mg) twice daily for 14 days. Pharmacokinetic, safety, and antiviral activity data were collected in both studies.

Short-term antiviral activity was demonstrated in both studies. In study, P&U 004, most subjects experienced virologic rebound, which was expected due to the addition of TPV to a failing two NRTI regimen.

The most common adverse events were gastrointestinal; GI AEs were reported in all study subjects in both studies. Diarrhea was particularly common and frequently occurred throughout the dosing period. Less common AEs of concern were rash, joint stiffness, decreased concentration, increased triglyceride levels, and increased hepatic enzymes. These AEs have been observed in other studies of TPV.

II. Study P&U 004

A. Study Design

Study P&U 004 was a Phase 1, open-label, non-randomized study of TPV added to two NRTIs in 40 HIV-infected adults with CD4+ cell counts > 50 cells/mm^3. All subjects must have been on a stable NRTI regimen for at least 2 months prior to study entry. PI-naïve subjects were sequentially enrolled in the first three cohorts while PI-experienced subjects were enrolled in Cohorts 4 and 5. Subjects in Cohort 4 must have received either IDV or RTV for more than 6 months, while subjects in Cohort 5 must have received more than two PIs for at least three months each. The treatment arms are shown in the table below.

Table: Treatment Arms in Study P&U 004

Cohort	Baseline HIV RNA (copies/ml)	PI History	TPV dose	Duration	Treatment Options
1	>10,000	PI naïve	900 mg tid	24 weeks	after 12 weeks can change NRTI
2	>10,000	PI naïve	1200 mg tid	24 weeks	

3	>10,000	PI-naïve	1500 mg tid	24 weeks	
4	>5,000	IDV or RTV	1500 mg tid	4 weeks	after 2 weeks can change
5	>5,000	multiple PIs	1500 mg tid	4 weeks	NRTI or add hydroxyurea

Source: CSR U01-3010, Volume 1.28, Submitted 12/29/04.

> *MO Comment*: The study design allowed subjects receiving two NRTIs and who had ongoing viremia to add TPV; this design was consistent with clinical practice at the time in which the study was conducted. However, subjects were adding TPV to a failing ARV regimen resulting in functional TPV monotherapy, and guaranteeing short term antiviral effect at best. In addition, this was a Phase 1 study, and no definitive conclusions regarding safety and antiviral activity can be derived from the study results due to the open-label, non-randomized design, the option of changing NRTIs during the study, and the small study numbers.

PI naïve subjects were inpatients for the first 11 days of the study and were seen at weeks 3, 4, 8, 12, 16, and 24 after discharge. PI experienced subjects were seen as outpatients on days 1, 2, 4, 7, 9 and 10 and at weeks 2, 3, and 4.

B. Study Results for Cohorts 1-3

Results for Cohorts 1-3 (PI-naïve) and 4-5 (PI experienced) are presented separately because of the differences in study design and study populations between these cohorts.

A total of 24 subjects (8 in each dosing cohort) were enrolled in Cohorts 1-3. The mean age was 36.5 years with a range of 24 to 49 years. Eighty-three percent were male; 54% were Black and 46% White. Nine subjects had a history of an AIDS defining event. The mean viral load at baseline was 4.34 $\log_{10}$ copies/ml and the mean CD4+ cell count at baseline was 408 cells/mm^3. Subjects in Cohort 3 had the lowest median baseline viral load (3.74 $\log_{10}$ copies/ml vs. 4.53 in the other two cohorts) and highest median baseline CD4+ cell count (431 cells/mm^3 vs. 349 and 350 in Cohorts 1 and 2 respectively).

> *MO Comment*: The differences in baseline viral load and CD4+ cell count may have biased the study results.

The most common previously used NRTI was 3TC (96%) followed by ZDV (83%), d4T (37.5%), and ddI (25%). The mean duration of exposure to NRTIs at study entry ranged from 3.5 months exposure to ddC to 23.6 months exposure to ZDV. Fifty-eight percent of subjects were receiving ZDV and 3TC at baseline; 33% were receiving d4T and 3TC.

Six of the 24 subjects or 25% discontinued the study prior to 24 weeks: two subjects in Cohort 1 (both due to lack of efficacy), two in Cohort 2 (loss to follow-up and an AE), and two in Cohort 3 (loss to follow-up and patient request).

There were 10 protocol violations noted by the applicant. These included 6 subjects who had a viral load less than 10,000 copies/ml at baseline, two with abnormal chest radiographs at baseline, and two with abnormal baseline laboratory values. In addition,

the applicant also reported in a separate section of the study report that four subjects changed their NRTI regimen from ZDV/ddI to d4T/3TC at study entry.

> *MO Comment*: This was a small Phase 1 study with a substantial number of premature study discontinuations and protocol violations, which limit the usefulness of the data collected.

Antiviral Activity in Cohorts 1-3 An approximately one log decrease in plasma HIV RNA was observed at day 11 but was not maintained. The mean change in plasma HIV RNA from baseline to week 24 was –0.525 $\log_{10}$ copies/ml in Cohort 1, -0.368 in Cohort 2, and +0.079 in Cohort 3. Six subjects had viral loads less than 400 copies/ml at some point during the study, but only two subjects had HIV RNA less than 400 copies/ml at week 24. The mean change in CD4+ cell counts was –25 cells/mm^3 in Cohort 1, +18 cells/mm^3 in Cohort 2, and –43 cells/mm^3 in Cohort 3.

> *MO Comment*: The lack of antiviral activity in all three cohorts is not surprising since TPV was added to a failing two NRTI regimen.

Genotype testing for mutations was performed at week 24 for 10 subjects who initially responded then had virologic rebound. The new mutations reported at week 24 are listed below by cohort.

Table: New PI Mutations Noted in Virologic Failures in Study P&U 004

Cohort	Positions with New PI Mutations
1	Q2H, R8Q, E35D, I625S, V82A
2	N37S, Q58E, I64T
3	R8Q, T12R, I15V, A71T

Source: CSR U01-3010, Volume 1.28, Submitted 12/29/04.

P&U concluded that these mutations were not known to be associated with PI resistance and that lack of virologic response was likely due to noncompliance.

> *MO Comment*: Since this was an early study of TPV, the *in vivo* mutation pattern was not completely understood. Several of these mutations were reported in the large Phase 3 trials of TPV. Clearly, genetic mutations will develop with use of TPV as functional monotherapy.

Analysis of safety for Cohorts 1-3
The mean exposure to TPV was 20.1 weeks and ranged from 2 to 25 weeks; there was little difference in exposure by cohort with median exposure of 23 weeks, 25 weeks, and 24 weeks for Cohorts 1, 2, and 3 respectively.

At least one AE was reported for each of the 24 subjects. The total number of AEs was highest in the 900 mg tid cohort (91 compared to 80 in Cohort 2 and 70 in Cohort 3). AEs were most frequently reported in the GI system; GI AEs were reported in all study subjects. The most common individual AEs were headache (17), diarrhea (16), nausea

(16), vomiting (12), loose stools (10), abdominal cramps (7), abdominal pain (6), rash (4), maculopapular rash (4). There was no dose relationship observed for any of the AEs. One subject in Cohort 2 discontinued the study prematurely due to Grade 2 diarrhea.

> *MO Comment*: Diarrhea was commonly reported and impacted subject quality of life. Forty-four percent of subjects continued to have diarrhea after week 12; 30% still had diarrhea at week 24. Thirty-eight percent of subjects took over the counter drugs to treat the diarrhea.

Additional adverse events included rash in seven subjects, including one female subject, and impaired concentration in four subjects.

There was one serious AE reported during the 24 week study; a subject in Cohort 1 was diagnosed with pseudomembranous colitis that was not judged as drug related. There were no new AIDS defining events reported during the study. One subject died after week 24 due to a methadone overdose. One female subject became pregnant during study participation but chose to terminate the pregnancy.

Laboratory values were analyzed for shifts in two grades; three subjects had two grade or more shifts. One subject's platelet count decreased from Grade 1 to Grade 4 but resolved without change in study drug. One subject had an increase to Grade 3 in GGT and another subject who was coinfected with HCV had an increase to Grade 3 in AST and ALT.

C. Study Results for Cohorts 4-5

Sixteen PI-experienced subjects participated in Cohort 4 (n=5) and Cohort 5 (n=11) of Study P&U 004. The mean age of PI experienced subjects was 40 years with a range of 28 to 61 years. The majority of subjects were White (75%), and all were male. Fourteen of the 16 subjects had a prior AIDS defining events. The median baseline plasma HIV RNA level was 4.36 $\log_{10}$ copies/ml for Cohort 4 and 4.76 for Cohort 5. The median baseline CD4+ cell count was 195 cells/mm^3 for Cohort 4 and 181 for Cohort 5.

All subjects in these two cohorts had previously received ZDV. In addition, 87% had received 3TC, 87% indinavir, 81% d4T, 56% ddI, and 44% ddC. Other PIs previously used by subjects in Cohort 5 included nelfinavir (64%), saquinavir (54.5%), and ritonavir (54.5%). Two subjects in Cohort 5 and none in Cohort 4 had prior use of a NNRTI.

Two subjects discontinued the study prematurely: one in Cohort 4 due to Grade 3 diarrhea and one in Cohort 5 due to an increase in both pre-existing arm pain and anxiety. There were two protocol deviations noted by the applicant: one subject had a viral load less than 5,000 copies/ml at baseline and another had not been on a stable NRTI regimen for at least two months prior to study entry.

Antiviral Activity in Cohorts 4-5: The mean change in HIV RNA from baseline to week 4 was +0.34 $\log_{10}$ copies/ml for Cohort 4 and –0.52 for Cohort 5. The maximum change

in viral load was reported at day 7 for subjects in Cohort 4 and at week two for subjects in Cohort 5. One subject in cohort 5 had a viral load measurement less than 400 copies/ml. The mean change in CD4+ cell counts was 0 for subjects in Cohort 4 and +4 cells/mm^3 in Cohort 5.

> *MO Comment*: Rebound after early response is not surprising given that study subjects were receiving functional monotherapy. It is difficult to distinguish any treatment differences between Cohorts 4 and 5 given the very small number of subjects.

Twelve subjects had genotype resistance testing at baseline and at week 4. No new mutations were reported in seven subjects. Genetic mutations reported in the other five subjects after four weeks of TPV were R8Q, M36V, N37D, and R41K; all were reported in an HIV isolate from a single subject. In addition, one subject's isolate had three new mutations: V82A, R87G, and I193L. The applicant concluded that there was no pattern of mutations and that most were not known to be associated with PI use.

> *MO Comment*: Again, this study was performed early in the development of TPV, and several of these mutations were observed in later Phase 2 and Phase 3 studies of TPV.

Analysis of Safety for Cohorts 4-5

All subjects in Cohorts 4 and 5 reported at least one AE during the four week study period. GI AEs were reported in all subjects: 64% experienced diarrhea, 50% nausea, 36% loose stools, and 19% vomiting. In addition, seven subjects (44%) reported abdominal pain, cramping, or distension. One subjects had Grade 3 diarrhea and discontinued the study during week 3. Four subjects continued to have diarrhea throughout the study period. Sixty-four percent used over-the-counter medications to treat the diarrhea.

> *MO Comment*: As seen in other studies and in Cohorts 1-3 of this study, GI AEs, particularly diarrhea, are common with the use of TPV.

Other adverse events reported in Cohorts 4 and 5 included rash (1), cognitive impairment (2), and disorientation (1).

> *MO Comment*: Confusion has been noted in other studies of TPV, the reason for this is unclear. Rash has also been reported in other studies of TPV.

One serious AE was reported in both cohorts: the Grade 3 diarrhea described above and a subject with an increase in pre-existing anxiety and arm pain to Grade 3. Both subjects discontinued the study prematurely. There were no AIDS defining events reporting the study. One subject died after the four week study period of a pulmonary embolus, which was verified on autopsy.

Two grade shifts in laboratory values were noted for absolute neutrophil counts (two subjects), and for ALT (one subject). Grade 3 laboratory abnormalities were reported for three subjects with Grade 3 triglyceride levels; all three subjects had elevated triglyceride levels at baseline. There were no Grade 4 laboratory abnormalities.

D. Study Conclusions

Study P&U 004 was a small Phase 1 study of TPV added to a stable two NRTI regimen in 40 treatment experienced subjects with ongoing viremia. Although there was early antiviral activity, virologic rebound and the development of new genetic mutations in the protease gene were reported. This lack of sustained antiviral activity is consistent with the use of TPV as functional monotherapy. The safety profile was consistent with other studies of TPV. All study subjects reported gastrointestinal AEs; diarrhea was observed through out the dosing period and often required over the counter medications for treatment. Rash, decreased concentration, increases in hepatic enzymes, and increases in triglycerides were reported in a small number of subjects.

III. Study P&U 015

A. Study Design

Study P&U 015 was an open-label, randomized, pharmacokinetic, safety, and antiviral activity study of TPV in treatment-naïve, HIV-infected subjects with CD4+ cell counts ≥ 50 cells/mm3 and HIV RNA levels ≥ 5,000 copies/ml. Study subjects were randomized to TPV alone 1200 mg, TPV/r 300 mg/200 mg, or TPV/r 1200 mg/200 mg twice daily for 14 days. The SEDDS formulation was used in all treatment arms.

Study subjects were seen in the study clinic on days 1, 3, 5, 8, 11, and 15. Pharmacokinetic measurements were collected over 12 hours on day 11.

Subjects completing the study were offered a 46 week extension with delavirdine, zidovudine, and lamivudine but not TPV.

B. Study Results

1. Study population

Thirty-one subjects were enrolled at three very different sites: Virginia, Puerto Rico, and South Africa. Of the 31 subjects, 10 received TPV 1200 mg, 10 received TPV/r 300 mg/200 mg, and 11 received TPV/r 1200 mg/200 mg. Nineteen subjects (61%) were male and 55% were Black. The mean age was 37 years with a range of 23 to 65 years. Fifteen subjects were enrolled in South Africa, 12 in Puerto Rico, and 4 in the United States. Five subjects had a prior AIDS defining event. The median viral load at baseline was 4.96 $\log_{10}$ copies/ml and the median CD4+ cell count was 244 cells/mm^3. The treatment arms were similar with the following exceptions: more females were enrolled in the TPV/r 300 mg/200 mg arm (6) than in the other 2 arms (3 each) and the median

CD4+ cell count was lower in the TPV/r 300 mg/200 mg arm (165 cells/mm^3) compared to the TPV 1200 mg arm (421 cells/mm^3) and the TPV/r 1200 mg/200 mg arm (244 cells/mm^3).

> *MO Comment*: This was a randomized but small study, therefore it is not surprising that there was some variation in baseline characteristics.

Three subjects discontinued the study prematurely: two in the TPV/r 300 mg/200 mg arm (dizziness, lost to follow-up) and one in the TPV/r 1200 mg/200 mg arm (increased ALT on day 1 pre-treatment laboratory monitoring, taken off study drug after received results). There were ten protocol deviations in nine subjects: 5 due to abnormal laboratory values at screening (Grade 2 hemoglobin, Grade 2 platelet count, CD4+ cell count <50 cells/mm^3, and Grade 2 GGT in two subjects), two due to screening outside of window period, and three without a screen 1 CD4+ cell count.

> *MO Comment*: The premature study discontinuations and protocol deviations in all probability had little effect on the study outcome.

2. Pharmacokinetic Analysis

Please see Dr. Zheng's clinical pharmacology review.

The median trough, AUC, and Cmax for TPV were lowest in the unboosted TPV arm and highest in the TPV/r 1200 mg/ 200 mg arm. The ritonavir trough was higher in the 300 mg/200 mg arm than in the 1200 mg/200 mg arm; this was likely due to the effect of TPV on the CYP450 enzymes.

3. Analysis of Efficacy

Plasma HIV RNA levels and CD4+ cell counts were measured at baseline and on days 3, 5, 8, 11, and 15. The median change in viral load and CD4+ cell count from baseline to day 15 is shown in the table below.

Table: Median Change in HIV RNA Level (log_{10} copies/ml) and in CD4+ Cell Count (cells/mm^3) from Baseline to Day 15 in the As Treated Population

Cohort	Baseline HIV RNA	Baseline CD4+ cell count	Change in HIV RNA	# < 400 copies/ml	Change in CD4+ cell
TPV 1200 mg bid	4.9	421	-0.768	0	+41.5
TPV/r 300/200 bid	5.2	165	-1.431	1	+74.5
TPV/r 1200/200 bid	4.79	244	-1.637	2	+83

Source: CSR U01-3009, Volume 1.141, submitted 12/29/04

> *MO Comment*: Antiviral activity over 15 days appeared to be exposure related since it increased with increasing doses of boosted TPV. However, the numbers

are too small to reach any definitive conclusions. In this study, TPV showed short term activity in treatment-naïve, HIV-infected subjects.

4. Analysis of Safety

The mean duration of exposure was similar between treatment arms (14, 13.5, and 13.5 days).

Twenty-five subjects (81%) had treatment-emergent adverse events. The frequency of AEs increased as TPV exposure increased. There were 17 AEs in the unboosted TPV arm, 21 in the TPV/r 300 mg/200 mg arm, and 25 in the TPV/r 1200 mg/200 mg arm. The most common AEs were diarrhea (52%), nausea (23%), vomiting (13%), increased ALT (10%), and headache (10%). All episodes of nausea were Grade 1 in intensity; one episode of diarrhea was Grade 3 while the remaining events were Grade 1.

> *MO Comment*: Diarrhea and nausea were slightly more common in the arm with the highest TPV exposure; diarrhea was reported in 6 subjects in the unboosted TPV arm, 3 in the TPV/r 300 mg/200 mg arm, and 7 in the TPV/r 1200 mg/200 mg arm, while nausea was reported in 1 subject in the unboosted TPV arm, 0 in the TPV/r 300 mg/200 mg arm, and 6 in the TPV/r 1200 mg/200 mg arm. These results suggest that GI toxicity may be related to TPV exposure but study numbers are too small to reach any definitive conclusions.

Other AEs reported in this study included abdominal pain in one subject in each arm, joint stiffness (1 subject), rash (1 subject), disorientation (1 subject).

> *MO Comment*: Rash and pruritis were reported in a 30 year old, South African female on study day 11; the rash lasted five days. Joint stiffness was reported in the arms of a 35 year old South African female on day 11. Symptoms, gender, and time of onset are similar to those observed in HIV-uninfected females participating in study 1182.2; data from these studies suggest that an hypersensitivity-like reaction can occur with TPV use in females.

Three Grade 3 adverse events were reported in two study subjects. On subject in the TPV 1200 mg arm had Grade 3 diarrhea and vomiting. One subject in the TPV/r 1200 mg/200 mg arm had a Grade 3 increase in ALT. There were no Grade 4 AEs. There was one serious adverse event due to dizziness associated with a migraine; this subject was discontinued from the study. There were no other premature study discontinuations due to AEs. There were no deaths on study.

As stated above, one subject had a ALT value within normal limits at screening and his ALT peaked at Grade 3 on day 15; this subject discontinued the study prematurely. Another subject, #322 in the 1200 mg/200 mg arm and one in the unboosted arm had an increases in ALT to Grade 2. A subject in the TPV/r 300 mg/200 mg arm had an increase in GGT to Grade 2. One subject in the TPV/r 300 mg/200 mg arm had an increased

bilirubin; this subject was HCV coinfected and had a bilirubin within normal limits at baseline that increased to Grade 2 on day 15.

There were no other Grade 3 or 4 increases in laboratory values. However, there was an increase in the median cholesterol and triglyceride levels for all three groups. These increases were highest in the TPV/r 1200 mg/200 mg arm.

> *MO Comment*: Hepatotoxicity was observed in this study. An increase in ALT to Grade 3 after just 14 days of treatment with TPV was observed in one subject. A Grade 2 increase in bilirubin in a HCV coinfected subject was also reported. Finally, increases in lipid levels were reported in all study groups, boosted and unboosted.

C. Conclusion

Tipranavir exposure increased with ritonavir boosting and with increase of TPV dose, while ritonavir levels decreased with increasing tipranavir levels. This pharmacokinetic finding allowed determination of dose response for activity and for safety. Tipranavir showed antiviral activity over 14 days in this small, Phase 1 study of HIV-infected adults. The median decrease in HIV RNA and the median increase in CD4+ cell count was exposure related. Gastrointestinal adverse events, particularly diarrhea and nausea were common. Less common AEs of significance were increased ALT values and increases in lipid values; the frequency of these AEs were exposure related.

STUDY OF TIPRANAVIR IN TREATMENT- NAÏVE HIV INFECTED SUBJECTS

Study 1182.33 - "A randomized, open-label, active controlled trial to evaluate the antiviral efficacy and safety of treatment with 500mg Tipranavir plus 100mg or 200mg Ritonavir p.o. BID in combination with standard background regimen in antiretroviral therapy naïve patients for 48 with extension up to 156 weeks."

I. Resume

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

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

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

II. Study Design

Study 1182.33 is an ongoing, phase IIb study comparing TPV/r at 500mg/100mg or 500mg/200mg with lopinavir ritonavir 400mg/100mg BID in approximately 540 treatment naïve adult subjects. Subjects in all three arms are receiving tenofovir 300mg and lamivudine 300mg once a day as additional ARV therapy. The randomization is being stratified by CD4 cell count > 200 cells/μL at screening.

Eligible subjects include HIV-1 infected men and women $\geq$ 18 years of age with no prior ARV therapy, HIV viral load of $\geq$ 5000 copies/mL and CD4+ T lymphocyte count < 500 cells/μL.

The primary efficacy endpoint of the study is the proportion of treatment responders at week 48 (defined as subjects with viral loads less than 50 copies/mL) without prior

treatment failure (defined as viral rebound or change of ARV therapy for reasons other than toxicity or intolerance).

III. Study Results

Study 1182.33 was initiated in May 2004. Information on serious adverse events and deaths was submitted in the two month safety update (2MSU). Additional line listings for demographics, AEs and laboratory values were requested by the Division and submitted in SNs 037 and 042. The study is open-label for subjects and investigators but blinded to the applicant, so some of the data submitted are blinded to treatment group.

At the time of database closure for the 2MSU on September 30, 2004, 323 subjects had been randomized and received at least one dose of study drug. The number of subjects was higher in the two subsequent submissions because of continued data collection. As of SN 37, there were 170 subjects in the TPV/r 500/100 arm, 166 in the TPV/r 500/200 arm, and 162 in the LPV/r arm. Of these, 76% are male. The average age is 36 years.

Seventy-two percent of subjects have had at least one adverse event. As in other studies of TPV, the most common AEs were gastrointestinal. GI AEs have been reported in 56% of subjects and include those shown in the table below.

Table: Gastrointestinal Adverse Events Reported in >2 Subjects in Any Treatment Arm in Study 1182.33

	TPV/r 500/100 n=170	**TPV/r 500/200 n=165**	**LPV/r n=162**
Abdominal discomfort /pain/stomach discomfort	15	31	17
Abdominal distension	3	7	7
Diarrhea/loose or watery stools/ frequent bowel movements	62	66	68
Flatulence	9	9	7
Gastritis	2	2	3
Nausea	54	54	38
Vomiting	20	13	8

Source: SN 37, Table of Adverse Events.

MO Comment: The number of subjects with diarrhea was similar between treatment groups. GI AEs in the TPV/r arms were not clearly dose related, but abdominal pain, nausea, and vomiting were more common in the TPV/r arms.

Other AEs that were reported in ≥5% of subjects of any treatment arm were fatigue, pyrexia, dizziness, and headache. All were reported in less than 11% of subjects in any treatment arm.

Adverse events of interest that were reported in fewer than 5% of subjects are shown in the table below.

Table: Adverse Events of Interest in Study 1182.33

	TPV/r 500/100 n=170	**TPV/r 500/200** **n=165**	**LPV/r** **n=162**
Hepatitis	0	1	0
Increased ALT	0	4	0
Increased transaminases	0	1	1
Increased hepatic enzymes	1	0	0
Abnormal LFT	1	0	0
Increased GGT	0	1	0
Increased serum creatinine	1	0	0
Acute renal failure	1	0	0
Allergic dermatitis	0	1	1
Drug eruption	1	0	1
Erythema	0	3	1
Exanthem	1	2	1
Generalized pruritis	1	0	0
Rash	4	5	8
Macular rash	0	0	1
Maculopapular rash	0	1	1
Urticaria	1	2	0

Source: SN 37, Table of Adverse Events.

MO Comment: Liver AEs were more common in subjects receiving TPV than LPV, and hepatotoxicity was most frequent in the higher dose arm of TPV/r. The number of subjects with rash was similar between study arms.

Serious adverse events were reported for 33 subjects including 16 in the TPV/r 500/100 mg arm, 13 in the TPV/r 500/200 arm, 2 in the LPV/r arm, and 2 receiving TPV without the dose of RTV identified. Serious AEs were varied but the majority were infectious (for example: TB, Shigella, dengue fever, and bronchitis) or illnesses associated with HIV disease (Kaposi's sarcoma, lymphoma, and PCP). Serious AEs that were reported in more than one subject were syphilis, PCP, Kaposi's sarcoma, fever, pneumonia, and abdominal pain.

Five deaths have been reported thus far in this study. These include four in the TPV arms (PCP and respiratory failure, septic shock and multi-organ failure, interstitial pneumonia, and urosepsis with renal failure) and one in the LPV/r arm (disseminated TB).

MO Comment: It is unclear why there were more serious AEs in subjects receiving TPV compared to those receiving LPV. There was no one AE that predominated. Infectious AEs were common but so were AEs in other organ systems such as cardiovascular, neurologic, and gastrointestinal. It is also unclear why there are more deaths in the TPV arms, but the number of deaths is small and there were twice as many TPV subjects as LPV/r.

The applicant submitted line listings for ALT, bilirubin, and serum creatinine values. The ritonavir dose in the TPV arms was not identified. There were 8 Grade 3 and 7 Grade 4 increases in ALT in the TPV/r arms. There were 2 Grade 3 and 3 Grade 4 increases in ALT in the LPV/r arm. The median maximum ALT value was 362 U/L (range of 208-1791) in the TPV/r arms and 562 U/L (range of 233-1838) in the LPV/r arm. There was only one subject with a Grade 3 or 4 increase in bilirubin; this subject was receiving LPV/r and had a Grade 3 increase in bilirubin on day 13. There were no Grade 2 or higher increases in serum creatinine. The last value provided for the subject who died of renal failure was Grade 1.

MO Comment: Laboratory abnormalities in ALT, bilirubin, and creatinine were similar between the two study arms.

IV. Study Conclusions

Limited data from study 1182.33 has been submitted to the Agency. It is clear that subjects enrolling in this trial are treatment naïve but also have advanced HIV disease as demonstrated by the types of serious AEs recorded. Nausea and vomiting were more common in subjects receiving TPV compared to LPV. There were also more serious AEs and deaths in subjects receiving TPV than in those receiving LPV. Since the types of serious AEs and causes of death varied, the reason for this disparity is unclear. This finding should be analyzed thoroughly and correlated with baseline characteristics and treatment effect when the final study report is reviewed.

PEDIATRIC STUDY OF TIPRANAVIR

Clinical Study Report: Study 1182.14 - Multiple-dose, open-label, randomized, safety and pharmacokinetic study of tipranavir in combination with low-dose ritonavir in HIV-infected pediatric patients

I. Resume

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

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

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

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

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

In conclusion, [redacted]. No new safety signals have been identified in this pediatric study, but the tolerability of the oral solution was poor.

II. Study Design

Study 1182.14 is an ongoing phase I/IIa, randomized, multicenter, 24 week trial of two doses of the TPV/r oral solution (100 mg/ml) in 100 HIV-1 positive, treatment-naïve and treatment experienced pediatric patients between the ages of 2 and 18 who have a viral load >1500 copies/ml. Subjects are being stratified by age and then randomized into one of two dosage groups, which are targeted to achieve a target trough level of $\geq$ 20μM (see table below). The dose of TPV/RTV should not exceed 500mg/200mg.

Table 1: Treatment Groups in Pediatric Study of Tipranavir

Cohort	Age	Dose of TPV/r	# for PK
I	2 to < 6 years	Group A: 290 mg/m^2/115 mg/m^2 b.i.d.	12
		Group B: 375 mg/m^2/150 mg/m^2 b.i.d.	12
II	6 to 12 years	Group A: 290 mg/m^2/115 mg/m^2 b.i.d.	8
		Group B: 375 mg/m^2/150 mg/m^2 b.i.d.	8
III	12 to 18 years	Group A: 290 mg/m^2/115 mg/m^2 b.i.d.	6

		Group B: 375 mg/m^2/150 mg/m^2 b.i.d.	6

MO Comment: TPV oral solution contains 116 IU of vitamin E per milliliter. High concentrations of vitamin E are associated with GI, immune, and hematologic toxicity, but Dr. Lo has determined that the vitamin E in the TPV oral solution is at nontoxic levels. Please see Dr. Lo's chemistry review.

Treatment-naïve subjects are receiving two NRTIs plus TPV/RTV; experienced subjects are being treated with a background antiretroviral regimen chosen based on screening genotype plus TPV/RTV or have substituted TPV/RTV for their existing PI. No protease inhibitors besides TPV and RTV can be used in the study.

A subgroup of 52 subjects are having pharmacokinetic sampling (see above table) at week 2. Trough sampling is also being performed every 2 weeks through Week 8, every 4 weeks through Week 16, and then every 8 weeks through Week 48.

Subjects ≥12 years of age are allowed to switch from the liquid formulation to the SEDDS formulation of TPV after Week 4. These subjects will have an "intensive PK profile" performed at Weeks 2 and 6 to compare the relative bioavailability of the TPV liquid and capsule formulations.

The remaining 48 subjects, who are not included in the PK substudy, are also being stratified by age, however, an equal number of subjects are not being stratified to each group and up to 38 of the 48 may be in Cohort III (12 to 18 years of age).

III. Study Results

Safety, pharmacokinetic, and efficacy results for 37 subjects during the first four weeks of the study were provided in the original NDA submission. Safety results for the first 12 weeks were provided for a total of 74 study subjects were provided in the two month safety update (2MSU); the number of study subjects by age and TPV dose are shown in the following table.

Table: Subjects Enrolled in Study 1182.14 as of the Two Month Safety Update

Age Group (yrs)	Low Dose	High Dose	Total
2 - <6	3	3	6
6 - <12	15	13	28
12-18	20	20	40
Total	**38**	**36**	**74**

Source: Two Month Study Update, Volume 1, Table 9.1.1:1.

MO Comment: Clearly, there have not been sufficient subjects younger than 6 years of age enrolled in this study to reach any conclusions about dosing, safety, or efficacy in this age group.

Fifty-one percent of the subjects are male and 49% female. Sixty-five percent are White, 31% Black, and 3% Asian. There is a higher proportion of White subjects in the low dose group (74%) compared to the high dose group (56%).

> *MO Comment*: At this time, there is no known racial or ethnic difference in drug metabolism or in the safety of tipranavir, so this imbalance may not be clinically significant.

The median baseline viral load for all subjects was 4.69 $\log_{10}$ copies/ml and the median CD4+ cell count was 359 cells/mm^3. Twenty-four subjects (44%) had symptomatic HIV disease at entry. Only three subjects were treatment naïve at study entry, however, information on previous treatment is missing for 20 subjects (27%).

Seven subjects prematurely had discontinued the study at the time of database cut off for the 2MSU. These included five who discontinued for adverse events (one subject in the low dose group due to vomiting and four subjects in the high dose group due to poor palatability of solution, abdominal pain, and nausea; GI discomfort and retching; increased ALT; and rash). One subject was discontinued prematurely due to non-compliance and another subject withdrew consent. Both of these subjects complained about the taste of the oral solution.

> *MO Comment*: The two month safety update states that 4 subjects have discontinued due to adverse events. However, there were three discontinuations in the first study report (subjects 1054, 1211, 1213) and two additional in the safety update (5401, 5505). A high percentage (9%) of subjects discontinued due to intolerance to the oral solution or adverse events; this indicates that the oral solution was difficult for children to tolerate, primarily due to the poor palatability and the GI adverse events.

Information on protocol deviations was provided for the first 37 subjects. In this subset of subjects, there were nine protocol violations. Six subjects had laboratory abnormalities that did not meet the entry criteria. Three subjects changed from oral solution to capsules prior to four weeks (on days 9, 13, and 15).

> *MO Comment*: Because of the small number of study subjects, the early change to capsules has a significant impact on PK results. Two of these subjects had all of their PK analyses while receiving capsules, and the third had PK for the oral solution at one timepoint only.

IV. Analysis of Pharmacokinetics

Please Dr. Zhang's review.

The applicant supplied pharmacokinetic results for the first 37 study subjects, 18 in the low dose group (TPV/r at 290 mg/m^2 / 115 mg/m^2 b.i.d.) and 19 in the high dose group (TPV/r at 375 mg/m^2/150 mg / m^2 b.i.d.). Unfortunately, only 4 subjects were in the 2 to

<6 year age group; 14 subjects were from 6 to <12 years of age and 19 subjects were 12 to 18 years of age.

The median trough value at 28 days in the low dose group was 29.7 μM and 44.6 μM in the high dose group. Median trough values at 28 days by dose and age groups are shown in the table below.

Table: Tipranavir Trough Values at Day 28 by Age and Dose

Age	Low Dose			High Dose		
	N	Median (μM)	Range	N	Median (μM)	Range
2-<6 yrs	2	43.2	23-64	2	18.9*	--
6-<12 yrs	5	31.4	18-70	7	70.5	35-98
12-18 yrs	11	18.8	BLQ-198	10	14.1	BLQ-131

*Only one value was collected in this age group at 28 days.
Source: CSR, Volume 157, Tables 11.5.2.1:1 and 11.5.2.1:2.

The median trough levels and ranges for adult studies of TPV and ritonavir using the proposed dose for marketing are shown in the following table for comparison to the pediatric values.

Table: Median Trough Values for HIV-Infected Adults Receiving Tipranavir and Ritonavir for 28 Days

Study	N	Median (μM)	Range
1182.12	198	38.2	BLQ-136.2
1182.48	298	30.6	BLQ-184.4
1182.51	19	33.1	10.3-66.6

Source: CSR, Vol 147, table 11.5.3:1

MO Comment: Plasma TPV concentrations in study 1182.14 appeared to be inversely correlated to age. While the median TPV levels in children 2 to <12 years, who are receiving the low dose of TPV/r, are similar to those in adult studies, the levels in adolescents are much lower. This may reflect problems with compliance in adolescents (see safety section of this review).

The applicant recognizes that there were too few subjects less than two years of age to identify a dose for this age group, and has proposed dosing information for TPV/r use (290 mg/m^2/115 mg/m^2 b.i.d.) in subjects 6 years of age and older. However, it appears doubtful that an appropriate dose can be identified for children older than 6 years of age. Of the 12 subjects in the 6 to <12 year age group, none were younger than 7.9 years and only six of the 12 subjects were younger than 10 years of age. In the low dose group, which is the dose proposed for use in pediatric patients, there are three trough values for the subjects less than 10 years of age at day 28: 18.8, 29.5, and 33.4 μM. There are PK data for the three subjects less than 10 years of age in the high dose group; the trough values for these subjects ranged from 54.6 to 95.9 μM.

In addition, in analysis of all 21 subjects listed in the PK results tables (11.5.2.1:1 and 11.5.2.1:2) the total number of subjects with measurable PK values is low. Two subjects in the low dose group and one in the high dose group discontinued the study prior to completing PK sampling. Two subjects in the low dose group switched from the oral solution to the capsule prior to 28 days. Four subjects in the high dose group have trough values at both days 14 and 28 that are below the limit of quantification. Overall, trough values for day 28 are missing or BLQ for 7 subjects in the low dose group and four in the high dose group; as a result, there are only 3 subjects in the low dose group and five in the high dose group with measurable trough levels on day 28. Finally, the applicant also states that two of the subjects with measurable values in the low dose group had PK measurements that were outliers (i.e., more than 1.5 times the interquartile range). Therefore, it appears to this clinical reviewer, that there are too few PK data points available for accurate identification of a TPV dose in HIV-infected children. Please see Dr. Zhang's review for further comment.

V. Analysis of Efficacy

VI. Analysis of Safety

Twelve week safety information was provided for the first 74 subjects. The median duration of exposure, 131.5 days, was identical for the low and high dose arms at the

point of database closure. Eighty-one percent of subjects have had at least 12 weeks of study drug, and 66% have had at least 16 weeks.

The number of subjects with adverse events are shown in the table below.

Table: Number and Percent of Subjects with Adverse Events in Study 1182.14

	Low Dose Arm n=38	**High Dose Arm n=36**	**Total n=74**
Any AE	23 (60.5%)	25 (69%)	48 (65%)
Drug related AE	12 (32%)	17 (47%)	29 (39%)
Serious AE	2 (5%)	1 (3%)	3 (4%)
AE leading to study discontinuation	1 (3%)	4 (11%)	5 (7%)

Source: Two Month Safety Update, Volume 1, Table 9.1.2:1

Adverse events were most common in the gastrointestinal (38%) and infections and infestations (19%) classes. GI adverse events were more common in the high dose group compared to the low dose as shown in the table below.

Table: GI Adverse Events in Study 1182.14

	Low Dose Arm	**High Dose Arm**
Nausea	4 (10.5%)	6 (17%)
Vomiting	3 (8%)	9 (25%)
Retching	1 (3%)	2 (6%)
Diarrhea/loose stools	2 (5%)	8 (22%)
Fecal incontinence	0	1 (3%)
Abdominal pain/GI upset	3 (8%)	4 (11%)

Source: Two Month Safety Update, Volume 15, line listings.

MO Comment: The applicant has a similar table (Table 9.1.2:2) in the text of the 2MSU, but the numbers are lower than shown in the table above for two reasons: the applicant's table includes AEs which were reported in 3 or more subjects only and this reviewer combined the AEs diarrhea and loose stools and abdominal pain, GI upset, and stomach ache. In both this table and in the applicant's table, it is clear that all types of GI AEs were more common in the high dose group than in the low dose group.

Other AEs that were observed in at least three study subjects included headache (2 subjects each arm, drug eruption (2 each arm), and rash (2 in the low dose group and 1 in the high dose group).

MO Comment: On review of the line listings, rash was observed in 10 subjects (7 in the low dose group and 3 in the high dose group). Facial swelling was observed in an additional subject. Four of the 10 subjects with rash were female. Eight of the 10 rashes appeared in the first 14 days after starting TPV. Four rash AEs were of moderate intensity and the remaining 6 were mild. One subject in

the high dose group had study drug held then reintroduced due to rash, and another stopped study drug due to a maculopapular rash and the rash returned after rechallenge, so the subject discontinued the study.

Five subjects discontinued the study prematurely; one in the low dose group and four in the high dose group. The reasons for study discontinuation were previously listed in this review. Of note, 3 of 5 subjects discontinued for GI AEs.

There were 12 serious AEs, eight in the low dose group and four in the high dose group. The only serious AE that was reported in more than one subject was herpes zoster, which was observed in two subjects in the low dose arm. Serious AEs in the low dose group also included anemia, pneumonia, hallucinations and nightmares, increased bilirubin, and increased GGT. Serious AEs in the high dose group included renal failure and dehydration, nausea and abdominal pain, rash, and increased ALT.

There have been no deaths in this study.

Grade 3 or 4 laboratory values observed in at least 2 subjects included increased GGT (2 subjects in each treatment arm), increased amylase (2 subjects in each treatment arm), and increased ALT (2 subjects in the high dose treatment arm). No subjects had Grade 3 or 4 increases in lipase. Two of these laboratory abnormalities were also drug-related serious AEs: an increased GGT and increased ALT (Grade 3). The subject with a Grade 3 increase in ALT had his TPV held but the ALT increased to Grade 2 after TPV reintroduction, so the subject was discontinued from the study. A Grade 1 or 2 increase in serum creatinine was observed in two subjects in treatment arm, but these laboratory abnormalities cannot be identified in the line listings provided by the applicant.

The applicant is collecting information on compliance as part of this study. According to the study report in the original NDA submission, 20 of the 37 subjects had greater than 95% compliance with dosing.

> *MO Comment*: On review of the line listings provided in the 2MSU, compliance was often poor. Ten subjects took 75% or less of their study drug, including three in the high dose group who took 25% or less and three in the low dose and one in the high dose arm who took 50% or less of study drug. Comments were available for four subjects with poor compliance and included complaints such as bad taste and smell, hates taste, and nausea with oral solution. The reason for three subjects changing from oral solution to capsules earlier than planned was not provided but may also be related to the poor tolerability of the oral solution.

VII. Conclusions

Preliminary results for study 1182.14 were provided in the NDA and in the 2MSU.

Pharmacokinetic data was also provided for the first 37 subjects; however, there were few data points available for analysis

making identification of an appropriate pediatric dose difficult. The decision of pediatric dosing will be determined after consultation with the clinical pharmacology reviewer.

Safety data was provided for 74 subjects with a median exposure of 131.5 days. As in adults, GI AEs were the most common adverse events and the most common reason for premature study discontinuation. Rash was also common and was reported for 10 (13.5%) of subjects; rash occurred at similar rates in males and females. Hepatotoxicity was also observed. One subject discontinued due to an increased ALT and two subjects had Grade 3 or 4 increases in ALT. GI AEs and hepatotoxicity were dose related and were more common in high dose subjects; rash was not dose related but the only discontinuations or interruptions in treatment due to rash were in the high dose group. Finally, tolerability of the oral solution appears to be poor due to the poor taste and smell and the GI toxicity associated with the drug. Ten subjects or 13.5% took 75% or less of their study drug and two subjects discontinued the study due to the poor palatability of the oral solution.

The applicant has proposed [redacted]

[redacted]

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