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 A subject in the high-dose group was withdrawn from the study due to severe dizziness, diarrhea, nausea, tachycardia, and vivid dreams and vomiting.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.

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[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.

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[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]