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.

10.2 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:

10.3 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 ≤ 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