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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-814**

**Clinical Pharmacology and Biopharmaceutics  
Review**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS  
TEAM LEADER MEMO**

**NDA:** 21-814

**DRUG:** Aptivus (Tipranavir)

**FORMULATION:** 250 mg capsules

**SPONSOR:** Boehringer Ingelheim

**TEAM LEADER:** Kellie Schoolar Reynolds, Pharm.D.

**SUBMISSION DATE:** December 21, 2004

Tipranavir is an HIV protease inhibitor. Tipranavir (500 mg) co-administered with 200 mg ritonavir twice-daily is indicated for combination antiretroviral treatment of HIV-1 infected adults with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

The clinical pharmacology information reviewed in support of this application describes tipranavir pharmacokinetics with and without ritonavir co-administration, the effect of food on tipranavir/ritonavir (TPV/r), mass balance, in vitro metabolism, drug-drug interactions, the effect of hepatic impairment, and the effect of gender and race. I concur with the conclusions of Dr. Derek Zhang's Clinical Pharmacology and Biopharmaceutics Review. He concludes that the sponsor provided adequate clinical pharmacology and biopharmaceutics information with this NDA. His review states that the management of known and potential drug-drug interactions emerged as a challenging issue during the review. Another important clinical pharmacology topic for this NDA was the role of exposure-response evaluations and the potential role of therapeutic drug monitoring (TDM). Dr. Jenny J. Zheng's Pharmacometric Review (Appendix to Dr. Derek Zhang's review) provides details of the exposure-response evaluations. I concur with Dr. Zheng's conclusions.

Drug-drug interactions

Many of the drug-drug interactions observed or predicted with TPV/r are similar to those with other protease inhibitors administered with ritonavir. However, there are several unique issues with TPV/r. These issues were discussed at the Antiviral Drugs Advisory Committee Meeting on May 19, 2005.

1. TPV/r is a net inhibitor of CYP3A and a net inducer of P-gp. Thus, it is difficult to predict the effect of TPV/r on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drug for CYP3A and P-gp, and the extent of intestinal first pass metabolism and efflux.
2. Studies in human liver microsomes indicate TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP2D6. The in vitro results suggest an in vivo interaction with substrates of each enzyme is likely. However, follow-up in vivo evaluations were not conducted. Due to the known effect of ritonavir, the administration of TPV/r is expected to inhibit CYP2D6. The net effects of TPV/r on CYP1A2, CYP2C9, and CYP2C19 are not known.

The drug interaction table included in the PRECAUTIONS section of the APTIVUS label reflects the uncertainty noted above.

Clinical Pharmacology team leaders for other therapeutic areas will be notified of all drugs that are included in the CONTRAINDICATIONS and PRECAUTIONS section of the APTIVUS label. Because most of the interactions are similar to interactions described in other labels, we did not have detailed discussions with the team leaders prior to approval. Although there is some information in the APTIVUS label that differs from other protease inhibitor labels, all

CONTRAINDICATIONS and recommendations for dose adjustments are the same as information in other labels.

There are some post marketing commitments for drug-drug interaction studies, as described in the last section of this memo.

#### Exposure-response evaluations

Dr. Jenny J. Zheng's review includes a detailed exposure-response evaluation. Dr. Zheng evaluated exposure-response information from the Phase 2 dose finding study (1182.52) and the pivotal Phase 3 studies (1182.12 and 1182.48). Her analyses indicate a relationship between inhibitory quotient ( $IQ = C_{min}/adjusted\ IC_{50}$ ) and the probability of a  $\geq 1$  log drop in HIV RNA at week 24. A higher IQ value is associated with a higher probability of response. The analyses also indicate a lower IQ value is associated with response if TPV/r is administered with enfuvirtide.

Variability in  $C_{min}$  and  $IC_{50}$  contribute to variability in IQ values across patients. The observed variability in IQ values indicates there may be a role for therapeutic drug monitoring to optimize tipranivir therapy for individual patients. Dr. Zheng presented her findings at the Advisory Committee Meeting. The Aptivus label includes a description of the relationship between IQ and proportion of patients with a  $\geq 1$  log drop in HIV RNA at week 24. The applicant will continue to evaluate the exposure-response relationship and the potential role of therapeutic drug monitoring.

#### Post-marketing commitments

The applicant agreed to conduct the following drug-drug interaction studies as phase 4 commitments. Some of the studies are ongoing or completed. All of the drug-drug interaction studies were on the applicant's original list of proposed phase 4 commitments, prior to Division of Antiviral Drug Products (DAVDP) and Office of Clinical Pharmacology and Biopharmaceutics (OCPB) discussion. For each drug, there is potential for an interaction, but the interaction cannot be adequately predicted. Each drug is important to some segment of the HIV population and the drug-drug interaction information will help the health care providers give better advice to patients.

1. Atazanavir
2. Buprenorphine/naloxone
3. Carbamazepine
4. Tadalafil
5. Ribavirin/pegylated interferon alpha 2a
6. Methadone

The applicant also committed to conduct a CYP/P-gp mechanistic study to determine the effect of TPV/r on individual CYPs. This study will indicate whether further drug-drug interaction studies are needed.

Special population studies include:

1. Studies in pediatric patients
2. Study in subjects with Child-Pugh B liver disease (Application included acceptable information for Child-Pugh A, but not Child-Pugh B)
3. 48-week study in patients coinfecting with HIV and HBV or HCV. The applicant will discuss a potential therapeutic drug monitoring substudy for this protocol with the FDA.

In addition to phase 4 commitments, the applicant indicated their intention to conduct drug-drug interaction studies with a number of investigational HIV drugs. They also intend to evaluate intracellular triphosphate levels of zidovudine and abacavir when co-administered with TPV/r.

The applicant will meet with DAVDP and OCPB within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIV-infected patients receiving TPV/r. The study will be conducted and the results will be used to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for patients taking TPV/r.

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**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

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NDA: 21-814	Submission Date(s): December 21, 2004
Brand Name	APTIVUS
Generic Name	Tipranavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Boehringer Ingelheim
Relevant IND(s)	IND 51,979
Submission Type; Code	
Formulation; Strength(s)	Capsule (250 mg)
Dosing regimen	500 mg tipranavir co-administered with 200 mg ritonavir, b.i.d.
Indication	Treatment of HIV-1 infection in protease inhibitor-experienced adults

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## 1 Executive Summary

### 1.1 Recommendation

The clinical pharmacology and biopharmaceutics information submitted to NDA 21-814 is acceptable.

1. The management of known and potential drug-drug interactions emerged as a challenging issue for tipranavir (TPV) administered with ritonavir (r). The label will include extensive drug interaction information. The interaction potential for 500 mg TPV in combination with 200 mg ritonavir is summarized below:

#### Potential for TPV/r to affect other drugs:

1. TPV, co-administered with low-dose ritonavir at the recommended dosage, is a net inhibitor of CYP3A. Thus, TPV/r may increase plasma concentrations of agents that are primarily metabolized by CYP3A and could increase or prolong their therapeutic and adverse effects. Thus, co-administration of TPV/r with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring
2. Studies in human liver microsomes indicated TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Follow-up in vivo evaluations using probe substrate drugs for these enzymes have not been conducted to rule out or confirm these potential interactions. Ritonavir is a moderate CYP2D6 inhibitor, and likely an inducer of CYP1A2, CYP2C9 and glucuronosyl transferases. The potential net effect of TPV/r on CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. Data are not available to indicate whether TPV inhibits or induces glucuronosyl transferases and whether TPV induces CYP1A2, CYP2C9 and CYP2C19.
3. Data suggest that the net effect of TPV/r at the proposed dose regimen (500 mg/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.
4. Based on items 1 and 3 above, it is difficult to predict the net effect of TPV/r on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

#### Potential for other drugs to affect TPV/r:

1. TPV is a CYP3A substrate as well as a P-gp substrate. Therefore, co-administration of TPV/r and drugs that induce CYP3A and/or P-gp may decrease TPV plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of TPV/r and drugs that inhibit P-gp may increase TPV plasma concentrations and increase or prolong its therapeutic and adverse effects.

2. Co-administration of TPV/r with drugs that inhibit CYP3A may not further increase TPV plasma concentrations, because the level of metabolites is low following steady-state administration of tipranavir/ritonavir 500/200 mg twice daily.
- II. Exposure response analysis indicated that there was a relationship between inhibitory quotient (IQ) and probability of efficacious response (> 1 log reduction in plasma viral RNA at week 24) in the two phase III clinical trials (1182.12 and 1182.48) and the phase II clinical trial (1182.52).

A methodologically sound study needs to be conducted with the aim of determining an optimized target IQ and a dosing strategy to adjust dose based on the IQ in patients for whom tipranavir/ritonavir is indicated.

## 1.2 Post Marketing Commitments

The following post marketing commitments (PMCs) are justified because the requested studies will provide information that will improve the safe and effective use of TPV/r in the target population. These PMCs address drug interaction potential with individual CYP enzymes and P-gp (PMC 1), quantitative drug interaction information (PMCs 2-7), PK and safety information in special populations (PMC 8) and optimized dosing strategy (PMC 9).

1. To conduct a CYP/P-gp mechanistic study to determine effect of TPV/r on individual CYPs
2. To conduct a human drug-drug interaction study of TPV/r twice daily and atazanavir
3. To conduct a human drug-drug interaction study of TPV/r twice daily and buprenorphine/naloxone
4. To conduct a human drug-drug interaction study of TPV/r twice daily and carbamazepine
5. To conduct a human drug-drug interaction study of TPV/r twice daily and tadalafil
6. To conduct a human drug-drug interaction study of TPV/r twice daily and ribavirin/pegylated IFN alpha 2a.
7. To conduct a human drug-drug interaction study of TPV/r twice daily and methadone
8. To assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease
9. To conduct a 48-week prospective observational cohort study with TPV/r twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

#### ***Absorption, Distribution, Metabolism and Elimination***

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. TPV is a substrate for CYP3A and P-gp, so the limited absorption may be due to the effect of the intestinal CYP3A4 and the intestinal P-gp efflux transporter. Peak plasma concentrations are reached approximately 2-3 hours (range from 1 to 5 hours) after dose administration. The proposed dose of TPV 500 mg with RTV 200 mg bid (CYP3A4 inhibitor) at steady-state resulted in an increase of the mean plasma TPV  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  by 45-fold, 4-fold, and 11-fold respectively, compared to TPV 500 mg bid given alone. The mean plasma TPV  $C_{min}$ ,  $C_{max}$ ,  $AUC_{0-12h}$  and elimination half-life was 32.6  $\mu$ M, 131  $\mu$ M, 859  $\mu$ M-h, 4.8 h, respectively, at steady state following a TPV/r dose of 500 mg/200 mg twice daily with a light meal. For SEDDS capsule formulation, the  $AUC_{0-12h}$  and  $C_{max}$  of TPV increased 31% and 16%, respectively, with a high-fat meal compared to that with a light snack.

TPV protein binding is very high (ca. 99.9% at 20  $\mu$ M) in human plasma. The degree of binding is similar over a wide concentration range from 10 to 100  $\mu$ M. TPV binds to both human serum albumin and  $\alpha$ -1-acid glycoprotein.

In vitro metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP enzyme involved in tipranavir metabolism.

Tipranavir is a P-gp substrate.

A mass-balance study in healthy male subjects demonstrated that, at steady-state, a median of 82.3% of the radioactivity of the  $^{14}$ C-TPV dose (TPV 500 mg/RTV 200 mg) was recovered in feces. The excretion of tipranavir via the feces could be due to a combination of unabsorbed drug as well as the biliary excretion of absorbed drug and its metabolites. Tipranavir trough concentrations at steady-state are about 60-80% lower than those on Day 1. Unchanged tipranavir accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity).

#### ***Special Populations***

**Hepatic Impairment:** After 7 days of 500mg/200mg bid dosing, the mean systemic exposure of tipranavir was higher for 9 subjects with mild hepatic insufficiency compared to that of 9 matched controls and the ranges of 90% CI were quite large, e.g., geometric mean ratios with 90% CIs for  $AUC$ ,  $C_{max}$  and  $C_{min}$  were 1.30 (0.88, 1.92), 1.14 (0.83, 1.56) and 1.84 (0.81, 4.20), respectively. A similar change in ritonavir exposure was observed. Dosage adjustment may not be warranted for this group of patients based on the moderate change in tipranavir and ritonavir systemic exposure and safety profiles observed in this study. There were insufficient data (lack of data at the steady-state) from moderate hepatic insufficiency group to reach any conclusion. Since liver is the major organ that eliminates tipranavir from systemic circulation, for anticipated safety

concerns, tipranavir/ritonavir should be contraindicated for patients with moderate or severe hepatic insufficiency.

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

**Gender and Race:** The range of tipranavir exposure was similar for males and females and between the races. Concentrations are slightly higher in women.

**HIV-1 Patients:** A population pharmacokinetic analysis of steady-state TPV exposure in healthy volunteers and HIV-infected patients following administration of TPV/r 500 mg/200 mg bid suggested the mean systemic exposure of tipranavir was slightly lower for HIV-1 infected subjects compared to that of HIV-1 negative subjects. This observation does not change conclusions of studies conducted in healthy volunteers.

**Pediatric Patients:** The pharmacokinetic profile of tipranavir in pediatric patients has not been established.

### ***Drug interactions***

Potential for TPV/r to affect other drugs:

1. TPV, co-administered with low-dose ritonavir at the recommended dosage, is a net inhibitor of CYP3A. Thus, TPV/r may increase plasma concentrations of agents that are primarily metabolized by CYP3A and could increase or prolong their therapeutic and adverse effects. Thus, co-administration of TPV/r with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring
2. Studies in human liver microsomes indicated TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Follow-up in vivo evaluations using probe substrate drugs for these enzymes have not been conducted to rule out or confirm these potential interactions. Ritonavir is a moderate CYP2D6 inhibitor, and likely an inducer of CYP1A2, CYP2C9 and glucuronosyl transferases. The potential net effect of TPV/r on CYP2D6 is inhibition. The net effect of TPV/r on CYP1A2, CYP2C9 and CYP2C19 is not known. Data are not available to indicate whether TPV inhibits or induces glucuronosyl transferases and whether TPV induces CYP1A2, CYP2C9 and CYP2C19.
3. Data suggest that the net effect of TPV/r at the proposed dose regimen (500 mg/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.
4. Based on items 1 and 3 above, it is difficult to predict the net effect of TPV/r on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Potential for other drugs to affect TPV/r:

1. TPV is a CYP3A substrate as well as a P-gp substrate. Therefore, co-administration of TPV/r and drugs that induce CYP3A and/or P-gp may decrease TPV plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of TPV/r and drugs that inhibit P-gp may increase TPV plasma concentrations and increase or prolong its therapeutic and adverse effects.
2. Co-administration of TPV/r with drugs that inhibit CYP3A may not further increase TPV plasma concentrations, because the level of metabolites is low following steady-state administration of tipranavir/ritonavir 500/200 mg twice daily.

The following tables highlight drugs that are contraindicated and not recommended for co-administration with tipranavir/ritonavir (Table 1) and some other established or potential drug interactions (Table 2). The information in both tables is based on drug interaction studies or is predicted based on expected mechanisms of interactions.

**Table 1: Drugs that Should Not be Co-administered with TPV/r**

<b>Drug Class/Drug Name</b>	<b>Clinical Comment</b>
<b>Antiarrhythmics:</b> Amiodarone, bepridil, flecainide, propafenone, quinidine	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
<b>Antimycobacterials:</b> rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>Ergot derivatives:</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	<b>CONTRAINDICATED</b> 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.
<b>GI motility agents:</b> Cisapride	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal products:</b> St. John's wort	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>HMG CoA reductase inhibitors:</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptics:</b> Pimozide	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Sedatives/hypnotics:</b> Midazolam, triazolam	<b>CONTRAINDICATED</b> 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
<b>HIV-Antiviral Agents</b>		
Nucleoside reverse transcriptase inhibitors: Abacavir	↓Abacavir concentrations by approx. 40%	Clinical relevance of reduction in abacavir levels not established. Dose adjustment of abacavir cannot be recommended at this time.
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.
Zidovudine	↓Zidovudine concentrations by approx. 50%	Clinical relevance of reduction in zidovudine levels not established. Dose adjustment of zidovudine cannot be recommended at this time.
Protease inhibitors (co-administered with low-dose ritonavir): Amprenavir Lopinavir Saquinavir	↓Amprenavir approx. 50%, ↓Lopinavir 50-70%, ↓Saquinavir 70-80%,	Combining amprenavir, lopinavir or saquinavir with TPV/r is not recommended.
Other PIs	Similar degree of interaction might be expected as that of amprenavir, lopinavir or saquinavir	No formal drug interaction data are currently available for the concomitant use of TPV, co-administered with 200 mg of ritonavir, with protease inhibitors other than those listed above.
<b>Other Agents</b>		
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	↑Tipranavir, ↔Fluconazole	Fluconazole increases TPV concentrations but dose

**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
Ketoconazole Voriconazole	Expected ↑Itraconazole, Expected ↑Ketoconazole Cannot predict effect of TPV/r on voriconazole	adjustments are not needed. Fluconazole doses >200 mg/day are not recommended.  Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (200 mg/day) are not recommended.  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.
Calcium Channel Blockers: e.g., diltiazem, nifedipine and verapamil	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.
Antimycobacterials:		
Rifabutin	Tipranavir not changed, ↑Rifabutin ↑ Desacetyl-rifabutin	Single dose study. Dosage reductions of rifabutin by 75% are recommended (e.g. 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.
Clarithromycin	↑Tipranavir, ↑Clarithromycin, ↓14-hydroxy metabolite	No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary.  For patients with renal impairment the following dosage adjustments should be considered: <ul style="list-style-type: none"> <li>• For patients with CL<sub>CR</sub> 30 to 60 mL/min the dose of</li> </ul>

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\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

**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
		clarithromycin should be reduced by 50%. For patients with CL <sub>CR</sub> < 30 mL/min the dose of clarithromycin should be decreased by 75%.
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	Expect ↓Methadone	Dosage of methadone may need to be increased when co-administered with TPV/r.
Meperidine	Expect ↓Meperidine, ↑Normeperidine	Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures)
Oral contraceptives/Estrogens: Ethinyl-estradiol	↓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.
Despiramine	Expect ↑Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.

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**Exposure-Response** (Reviewed by Jenny J. Zheng, Ph.D.)

Exposure response analyses were conducted using the data from a dose-finding study (Study 1182.52, N=160) and the two pivotal clinical studies (1182.12 and 1182.48 studies; N=291).

1. Exposure-Viral Load Analysis: The exposure response analysis of phase 2 and phase 3 studies consistently demonstrated that the probability of a patient's response to tipranavir/ritonavir treatment is related to inhibitory quotient (IQ = C<sub>min</sub>/corrected IC<sub>50</sub>).

However, due to the variability in pharmacokinetics of the drug and infected virus, the range of resulting inhibitory quotient after the fixed doses are wide, which results in unpredictable virological response for individual patient. To maximize the likelihood of a patient's response, individualized dose adjustment based on IQ could be an alternative to the fixed dose regimen. In addition, phase 3 studies showed that enfuvirtide (ENF) use significantly increases the probability of patient's response to tipranavir/ritonavir treatment.

2. Exposure-ALT Analysis: The incidence of Grade 3/4 ALT elevation is associated with tipranavir exposure.

Yuanchao (Derek) Zhang, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

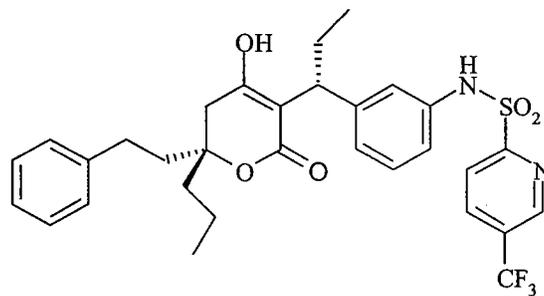
Kellie S. Reynolds, Pharm. D  
Team Leader, Antiviral Drug Products Section  
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## 2 Question based review (QBR)

### 2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Tipranavir is a non-peptidic protease inhibitor of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. The chemical name of tipranavir is 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl). Tipranavir is a white to off-white to slightly yellow solid. Tipranavir has the following structural formula:



$C_{31}H_{33}F_3N_2O_5S$  tipranavir Mol Wt. 602.7

The composition of the proposed to be marketed tipranavir 250 mg self-emulsifying drug delivery system (SEDDS) capsule is shown below:

Component	Amount per Capsule (mg)	% w/w
Tipranavir	250	!
Dehydrated Alcohol		
Propylene Glycol		
Polyoxyl 35 Castor Oil		
Mono/Diglycerides of Caprylic/Capric Acid		
Soft Gelatin Capsule		
Total		

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

The human immunodeficiency virus (HIV) encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV protease that inhibits viral replication by preventing the maturation of viral particles.

### 2.1.3. What is the proposed dosage and route of administration?

The proposed oral dose of tipranavir is 500 mg (two 250 mg capsules), co-administered with 200 mg ritonavir, twice daily with food.

## 2.2 General Clinical Pharmacology

### 2.2.1. What are the design features of the clinical studies used to support dosing or claims?

The applicant collected the important efficacy and safety information in the following clinical trials:

#### Phase III pivotal clinical trials

Studies RESIST-1 (1182.12) and RESIST-2 (1182.48): tipranavir/ ritonavir 500 mg/200 mg bid + optimized background regimen (OBR) vs. comparator PI/ritonavir bid + OBR.  
1182.12: (n= 311) tipranavir/ ritonavir 500 mg/200 mg bid + OBR; (n= 309) CPI/ritonavir bid + OBR  
1182.48: (n= 271) tipranavir/ ritonavir 500 mg/200 mg bid + OBR; (n= 268) CPI/ritonavir bid + OBR

1182.12 and 1182.48 are ongoing, randomized, open-label, multicenter studies in HIV-positive, triple class experienced patients, evaluating treatment with tipranavir co-administered with low-dose ritonavir plus an OBR individually defined for each patient based on genotypic resistance testing and patient history. The comparator regimen included a ritonavir-boosted PI (also individually defined) plus an OBR. All patients had received at least two PI-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90. Analysis of 24-week data for efficacy and safety were submitted with this NDA submission.

#### Phase II dose-ranging trials

Study 1182.52: Double-blind, randomized, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/r) in multiple antiretroviral drug-experienced subjects (n= 216)

The doses evaluated were 500mg/100 mg, 500mg/200mg and 750mg/200 mg TPV/r BID. The patient population of this study was treatment experienced in each of three classes of anti-retrovirals (NRTIs, NNRTIs, and PIs) for at least 3 months with NRTIs, NNRTIs, and  $\geq$  two PIs, had a viral load of  $\geq$  1000 copies/mL, and a genotype indicating at least one primary PI resistance mutation, including 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M with not more than one of 82L/T, 84V, or 90M.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The surrogate endpoints used in the clinical trials are HIV RNA level and CD4+ cell count. The HIV RNA level indicates the amount of virus present in the plasma. Previous studies indicate that reduction in HIV RNA level correlates with reduction in opportunistic infections and death. The CD4+ cell count indicates the status of the immune system. Changes in CD4+ cell count tend to lag behind changes in HIV RNA levels.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the applicant measured the appropriate moieties in clinical pharmacology studies. They measured tipranavir and ritonavir in most clinical pharmacology studies. They measured the concentrations of other moieties, as appropriate, in drug interaction studies. It was not necessary to measure concentrations of tipranavir metabolites, except for in the mass balance study. See Analytical section (2.6) for more details.

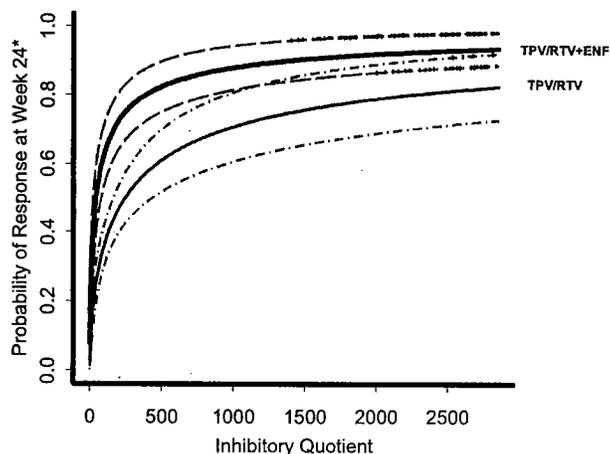
2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy?

In combined 1182.12 and 1182.48 studies, inhibitory quotients (IQ) were obtained from 291 patients, of which 91 patients received TPV/RTV with enfuvirtide (ENF). The relationship between IQ and ENF use on the probability of having  $\geq 1 \log_{10}$  reduction in HIV-1 RNA at week 24 are presented in Figure 2. The response rate is higher in patients who received ENF in addition to TPV/RTV. The odds ratios associated with  $\log_{10}(\text{IQ})$  and ENF use are 4.24 (90% CI: 2.52-7.12) and 2.98 (90% CI: 1.73-5.16), respectively. Probability of patients achieving  $\geq 1 \log_{10}$  viral load reduction at week 24 increases with higher inhibitory quotient.

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## Probability of Response to TPV/RTV Treatment in Related to ENF Use and Inhibition Quotient (IQ)



\* response is defined as  $\geq 1 \log_{10}$  viral load reduction from baseline at week 24.

Solid lines represent predicted probability of response when tipranavir was used alone and with ENF, respectively. The broken lines represent the 90% confidence interval.

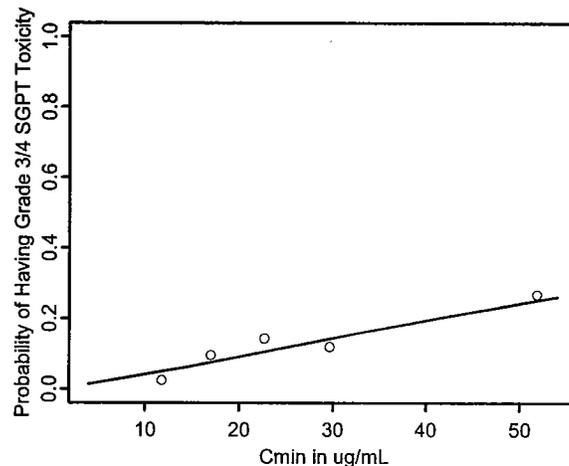
Inhibitory quotient = tipranavir trough concentration / corrected  $IC_{50}$

$$\text{corrected } IC_{50} = \frac{IC_{50, \text{tested}}}{IC_{50, \text{measured}}} \cdot 0.058 \cdot 3.75 (\mu M)$$

Tipranavir trough concentrations were measured between week 2 and 24. 0.058 is mean wild type HIV  $IC_{50}$  and 3.75 is the protein binding adjustment factor. An average trough concentration was determined in patients with multiple measurements.

### 2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety?

Results from a Phase II dose-finding trial (1182.52) indicate that the ALT abnormality is dose dependent. The logistic regression analysis was conducted between the incidence of Grade 3/4 ALT elevation and  $\log_2$  (tipranavir trough concentrations, TPV  $C_{\min}$ ), using the data from 210 patients with tipranavir concentrations. The results showed that the odds ratio associated with  $\log_2$  tipranavir trough concentration is 2.40 (95% CI: 1.43-4.02,  $p < 0.0001$ ). Probability of patients having a grade 3/4 ALT elevation is higher at higher tipranavir  $C_{\min}$ s (Figure below). Similar analysis was conducted for ritonavir trough concentration. The results showed that ritonavir  $C_{\min}$ s are not significantly correlated with grade 3/4 ALT elevation.



The solid line represents the regression fit. Subsequent to the logistic regression, the rates of having Grade 3/4 ALT elevation in 5 concentration groups (0-20 percentile, 20-40 percentile, 40-60 percentile, 60-80 percentile, 80-100 percentile of  $C_{min}$ ) were determined. The results are presented as symbols to assess the goodness-of-fit.

#### 2.2.4.3. Does tipranavir prolong QT or QTc interval?

All currently available data suggest that there is limited potential for QT prolongation in patients using TPV/r. All related information is in the Clinical and the Pharmacology/Toxicology reviews. A definitive study to assess the potential for QT prolongation in healthy volunteers using tipranavir co-administered with ritonavir is ongoing.

#### 2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dose and dosing regimen of tipranavir/ritonavir are consistent with the known relationship between dose-concentration-response, based on efficacy and tolerability considerations. However, a number of patients may not have adequate TPV concentration at this dose.

The sponsor selected the dose for phase III trials mainly based on phase II trial 1182.52. Three doses were studied in 1182.52: 500/100 TPV/r, 500/200 TPV/r, and 750/200 TPV/r. The median  $\log_{10}$  changes from baseline viral load were -0.85, -0.93, and -1.18, respectively, following 2 weeks of treatment with 500/100 TPV/r, 500/200 TPV/r, and 750/200 TPV/r, indicating anti-viral activity was dose-dependent. The safety analysis also demonstrated a dose related relationship (see table below). Based on the tolerability results from this study, the dose of 500/200 bid TPV/r was selected for phase III trials.

Percent of subjects with severe adverse event, discontinuation and grade 3 ALT elevation across treatments

	500/100 TPV/r	500/200 TPV/r	750/200 TPV/r
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%

Because the Phase III dose was selected based on tolerability, it is important to determine the proportion of patients who may not benefit from treatment at this dose. An analysis of study 1182.52 data can help determine the proportion of patients who may be underdosed at the 500/200 TPV/r dose level.

Due to the large between-subject variability in trough concentrations of TPV (range: [ ] ng/mL) observed from phase III trials, some patients who receive 500/200 TPV/r will have low TPV concentrations that are not likely to provide benefit if their virus has a high  $IC_{50}$ . Based on the logistic regression analysis of data from study 1182.52 (see figure in 2.2.4.1), an inhibitory quotient ( $C_{min}/IC_{50}$ ) of 100 would result in 1 log reduction at week 24 in 43% of the patients. Of the 293 patients with tipranavir  $C_{min}$  and  $IC_{50}$  data in two phase III trials, only 53% have an inhibitory quotient of 100 or greater at the 500/200 TPV/r regimen, due to the high between-subject variability in  $C_{min}$  and  $IC_{50}$ .

## 2.2.5. What are the PK characteristics of tipranavir?

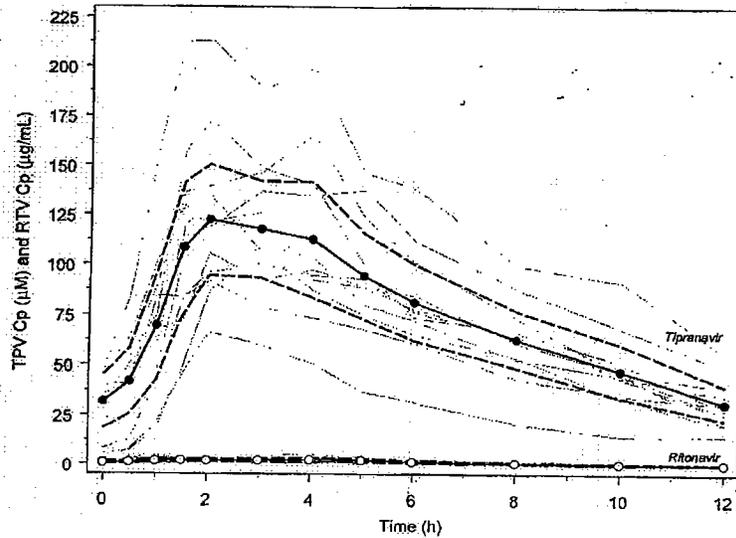
### 2.2.5.1. What are the single and multiple dose PK parameters?

The relevant TPV PK data were collected following co-administration of TPV and low dose RTV. Tipranavir is primarily metabolized in the liver. Studies in *in vitro* human liver microsomes demonstrated that CYP3A4 is the predominant enzyme involved in the metabolism of TPV. TPV is also a potent CYP3A4 inducer. Repeated dosing with TPV resulted in TPV levels 50 to 70% lower at steady-state than those after a single dose. Co-administration of TPV (250 to 1250 mg) with low doses of the CYP3A4 inhibitor, RTV (100 mg or 200 mg) bid resulted in an increase of the mean plasma steady-state TPV  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  by 19- to 99-fold, 3- to 4-fold, and 4- to 13-fold, respectively, at TPV/R doses studied compared to TPV given alone (Study 1182.5).

The proposed dose of TPV 500 mg with RTV 200 mg bid at steady-state resulted in the increase of the mean plasma TPV  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  by 45-fold, 4-fold, and 11-fold respectively, compared to TPV 500 mg bid given alone (Study 1182.5).

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

Mean steady-state tipranavir plasma concentrations (95% CI) with ritonavir co-administration (tipranavir/ritonavir 500 mg SEDDS capsules/200 mg bid) is shown in the figure below:



Tipranavir steady-state  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  with and without co-administration of ritonavir in healthy subjects (geometric mean with 90% confidence intervals) are shown the tables below:

TPV b.i.d. Dose (mg) RTV 0 m <sup>st</sup>		$C_{min}$ ( $\mu$ M)	$C_{max}$ ( $\mu$ M)	$AUC_{0-\tau}$ (h $\cdot$ $\mu$ M)
250	12	0.21 (0.16-0.29)	13.7 (8.7-21.6)	28 (16-49)
500	23	0.59 (0.5-0.68)	30.4 (26.8-34.4)	83.0 (73-95)
750	22	0.64 (0.53-0.79)	42.2 (35.2-50.5)	116 (94-143)
1000	22	1.08 (0.82-1.43)	62.5 (53.0-73.7)	199 (162-244)
1250	14	1.55 (1.06-2.27)	66.9 (54.4-82.2)	236 (179-311)

TPV b.i.d. Dose (mg) RTV 100 mg <sup>†</sup>		C <sub>min</sub> (μM)	C <sub>max</sub> (μM)	AUC <sub>0-τ</sub> (h•μM)
500	12	16.3 (8.0–33.3)	130.1 (105.5–160.5)	755 (530–1077)
750	11	12.4 (4.3–35.7)	110.1 (71.7–169.0)	636 (385–1050)
1000	10	40.2 (15.0–107.8)	232.7 (178.2–303.7)	1584 (1126–2228)
1250	14	18.0 (8.2–39.7)	175.4 (129.0–238.4)	1083 (737–1594)

TPV b.i.d. Dose (mg) RTV 200 mg <sup>†</sup>		C <sub>min</sub> (μM)	C <sub>max</sub> (μM)	AUC <sub>0-τ</sub> (h•μM)
250	12	12.3 (7.5–20.2)	58.5 (42.5–80.6)	376 (273–517)
500	11	26.3 (16.7–41.3)	129.2 (108.3–154.2)	934 (761–1145)
750	11	35.5 (18.4–68.2)	168.8 (122.7–232.3)	1235 (901–1696)
1000	12	26.8 (11.1–64.8)	135.8 (88.8–207.7)	963 (591–1569)

2.2.5.2. How does the PK of tipranavir in healthy volunteers compare to that in patients?

A population pharmacokinetic analysis of steady-state TPV exposure in healthy volunteers and HIV-infected patients following administration of TPV 500 mg /RTV 200 mg bid suggested the mean systemic exposure of tipranavir was slightly lower for HIV-1 infected subjects compared to that of HIV-1 negative subjects. This observation does not change conclusions of studies conducted in healthy volunteers.

The NONMEM model-derived pharmacokinetic parameters for female and male HIV+ patients and HIV- subjects.

Pharmacokinetic parameter	HIV+ patients		HIV- subjects	
	Females (N = 14)	Males (N = 106)	Females (N = 25)	Males (N = 42)
C <sub>ph,12h</sub> (µM)	30.94	31.63	43.26	32.97
C <sub>max</sub> (µM)	92.33	75.87	114.71	90.08
T <sub>max</sub> (h)	2.9	2.9	3.0	2.9
AUC <sub>0-12h</sub> (h*µM)	792.8	681.0	1005.3	781.8
CL (L/h)	1.05	1.22	0.83	1.06
V (L)	7.7	10.2	5.3	7.0
t <sub>1/2</sub> (h)	5.5	6.0	4.7	4.8
K <sub>a</sub> (h <sup>-1</sup> )	0.5142	0.5291	0.4406	0.4780
K <sub>e</sub> (h <sup>-1</sup> )	0.1354	0.1200	0.1560	0.1510

Note: Pharmacokinetic parameters are reported as geometric mean, except t<sub>1/2</sub> which is reported as the arithmetic mean. CL and V are apparent oral clearance and apparent volume of distribution, respectively.

#### 2.2.5.3. What are the characteristics of drug absorption?

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. Tipranavir is a substrate of P-gp and CYP3A, and the limited absorption may be a manifestation of the intestinal CYP3A4 as well as the intestinal P-gp efflux transporter. Peak plasma concentrations are reached approximately 2-3 hours (range from 1 to 5 hours) after dose administration. Tipranavir, co-administered with low-dose ritonavir, exhibits an increase of the plasma TPV exposure at steady state, compared to TPV given alone. See tables in section 2.2.5.1.

#### 2.2.5.4. What are the characteristics of drug distribution?

TPV protein binding is very high (ca. 99.9% at 20 µM) in human plasma. The extent of binding is concentration independent over a wide concentration range from 10 to 100 µM. It binds to both human serum albumin and α-1-acid glycoprotein. From clinical samples of healthy volunteers and HIV-positive patients who received tipranavir without ritonavir, the mean fraction of tipranavir unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV-positive patients 0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82 µM.

#### 2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass-balance study (1182.24) in healthy male subjects demonstrated that, at steady-state, a median of 82.3% of the radioactivity of the <sup>14</sup>C-TPV dose (TPV 500 mg/RTV 200 mg) was recovered in feces. Renal elimination appeared to be a minor route of excretion for tipranavir as

only a median of 4.4% radioactivity of the dose was recovered in urine and unchanged TPV was about 0.5% of total urine radioactivity. As the main route of excretion of tipranavir was via the feces, it could be due to a combination of unabsorbed drug as well as the biliary excretion of absorbed drugs and its metabolites. Furthermore, based on the observation that the predominant portion of fecal radioactivity was present as the unchanged TPV, and the data from an *in vitro* study that indicated that TPV is a P-gp substrate, part of the radioactivity could be due to "excretion" into the gastrointestinal tract mediated by this efflux transporter.

2.2.5.6. What are the characteristics of drug metabolism?

*In vitro* metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP isoform involved in tipranavir metabolism. Ketoconazole at concentrations of 1  $\mu$ M or 5  $\mu$ M inhibited the metabolism of tipranavir (50  $\mu$ M) by 90% and 95%, respectively. Correlation analysis also confirmed the strong involvement of CYP3A4. CYP2D6 was confirmed not to be involved in the metabolism of tipranavir by incubating tipranavir with cDNA-expressed human CYP2D6.

A mass-balance study (1182.24) in healthy male subjects demonstrated that, at steady-state, following a  $^{14}$ C-TPV dose (TPV 500 mg/RTV 200 mg), unchanged tipranavir was predominant and accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In feces, unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

2.2.5.7. What are the characteristics of drug excretion?

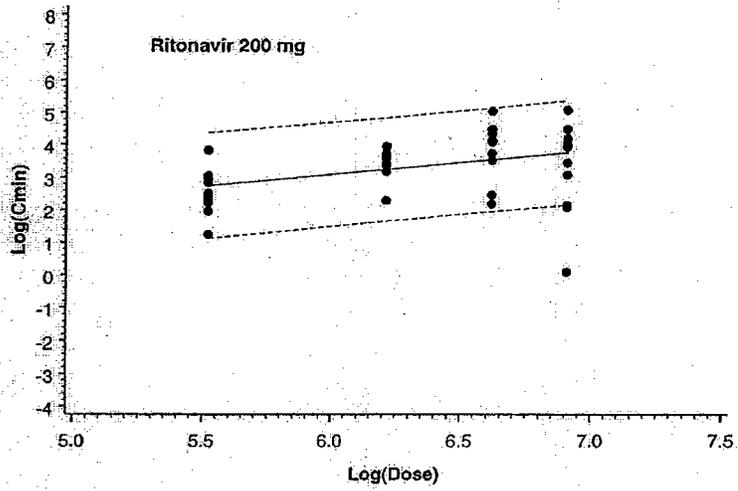
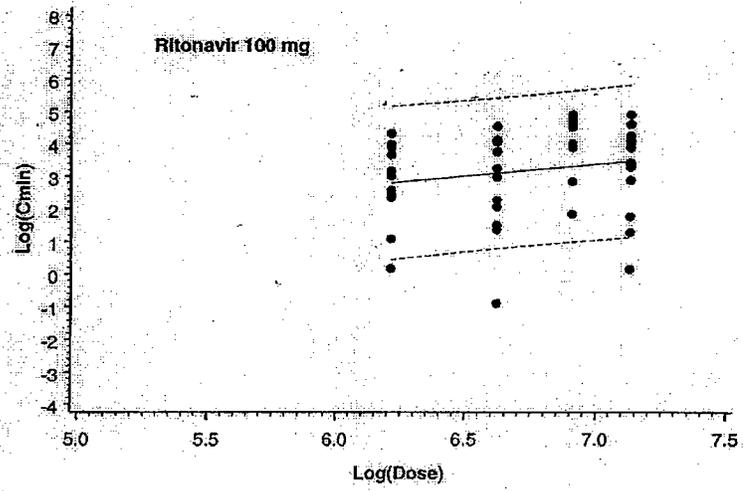
See Section 2.2.5.5.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

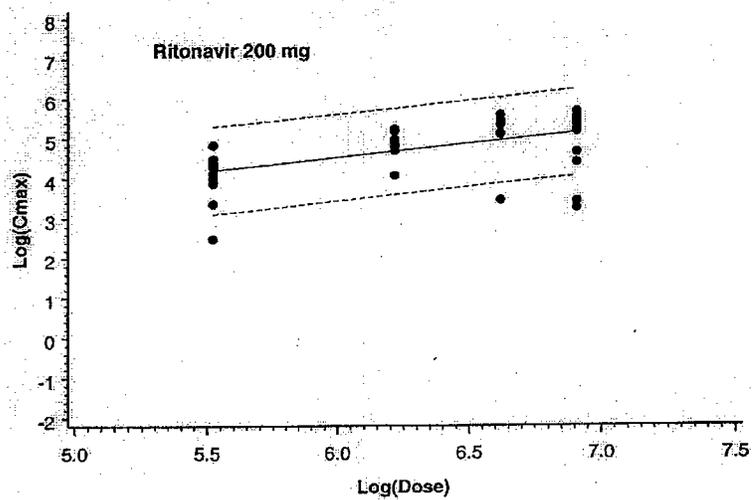
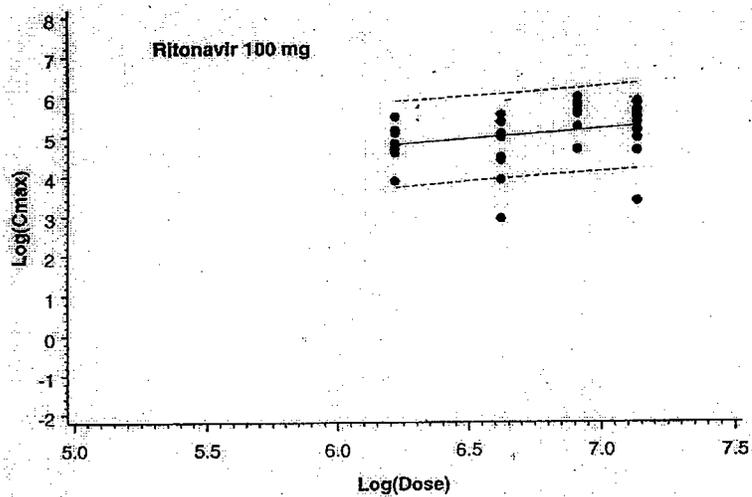
In general, an increase of TPV exposure is dose proportional with co-administration of same RTV dose though the variability is high.

Co-administration of TPV (250 to 1250 mg) with low doses of RTV (100 mg or 200 mg) bid at steady-state appears to result in linear pharmacokinetics of TPV, though the variability is high (Study 1182.5).

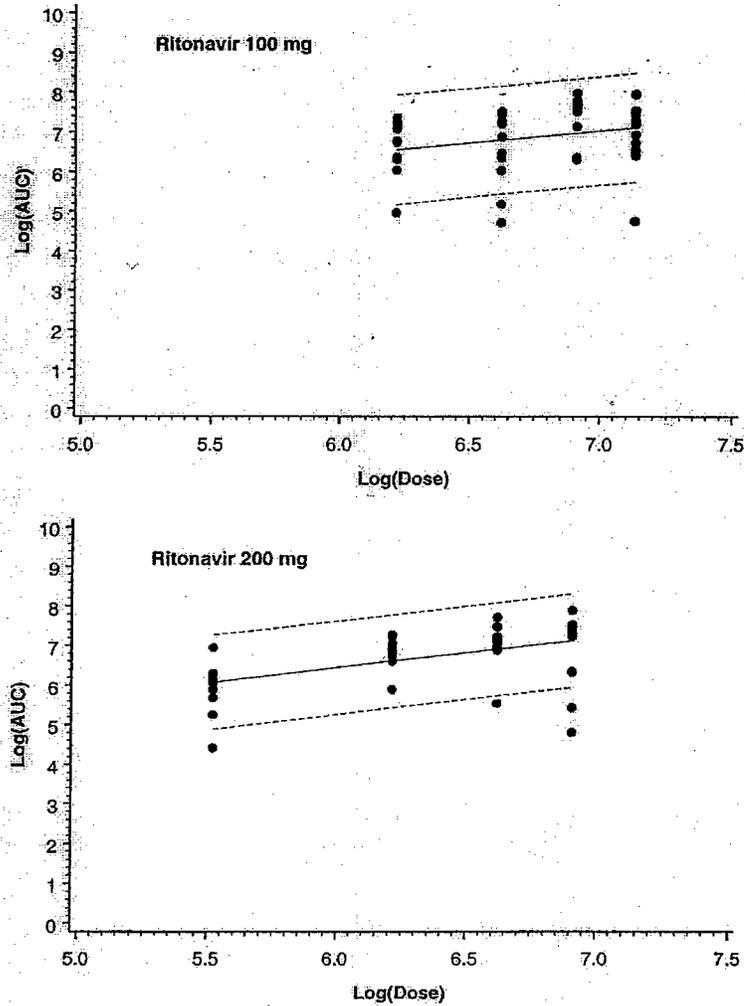
Regression analysis of plasma tipranavir  $C_{min}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)



Regression analysis of plasma tipranavir  $C_{max}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)



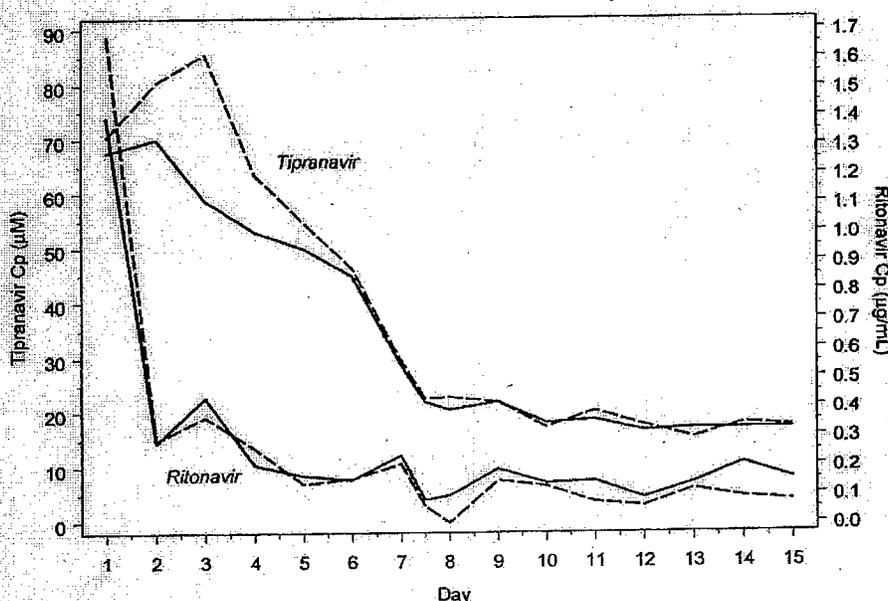
Regression analysis of plasma tipranavir  $AUC_{12h}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)



2.2.5.9. How do PK parameters change with time following chronic dosing?

Repeated dosing with TPV/R bid resulted in TPV levels 50-70% lower at steady-state than those after a single dose. Daily monitoring of TPV trough plasma concentrations in 7 subjects in the mass-balance study 1182.24 suggested that TPV concentrations decreased markedly until reaching steady-state in 7-10 days.

Comparison of daily plasma tipranavir and ritonavir trough concentrations for 7 subjects receiving TPV/r 500/200 mg bid for 14.5 days (Solid line: geometric mean, broken line: median)



2.2.5.10. What is the inter- and intra-subject variability in volunteers and patients, and what are the major causes of variability?

Data are not available to determine intra-subject or intra-patient variability. Following multiple doses of 500 mg TPV/200 mg RTV bid with food, inter-subject variability of TPV concentrations is approximately 30-60% in healthy volunteers and approximately 30-50% in HIV infected patients.

## 2.3 INTRINSIC FACTORS

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

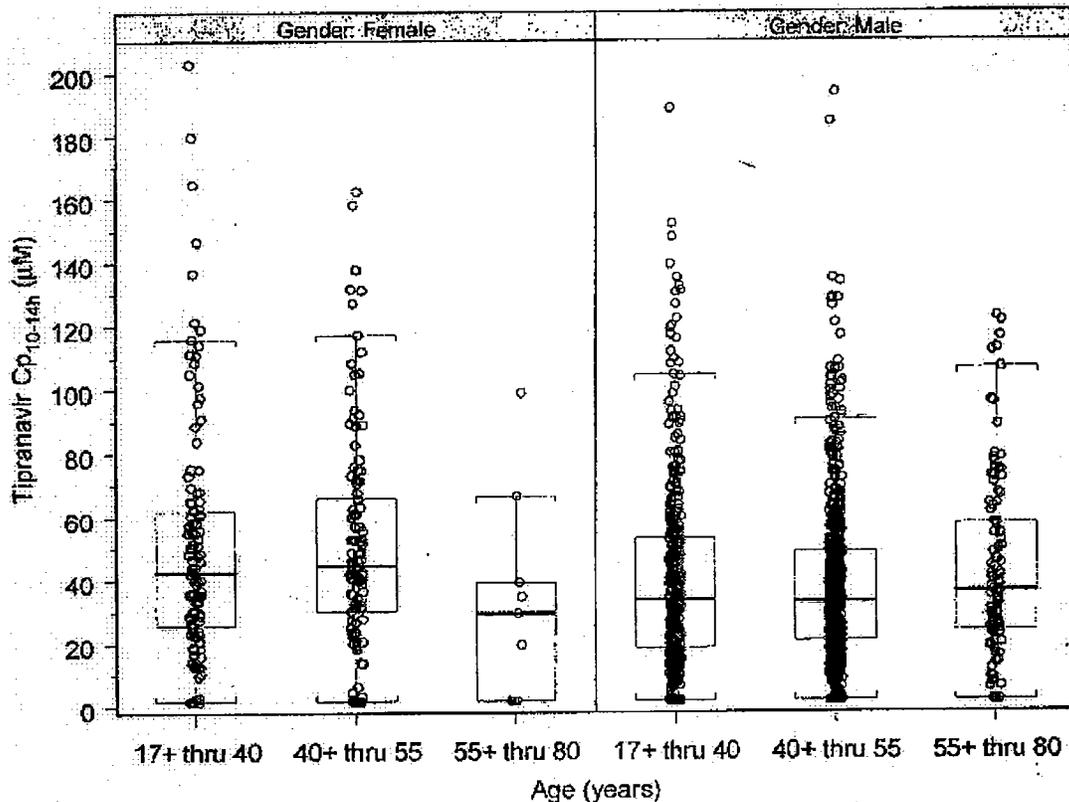
The applicant evaluated the effect of the following intrinsic factors on exposure to tipranavir: gender, race, body size, age and hepatic impairment. As described below, hepatic impairment may affect tipranavir exposure.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

### 2.3.2.1. Elderly

Evaluation of steady-state plasma tipranavir trough concentrations from two pivotal phase III clinical trials indicated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There was an insufficient number of women greater than age 65 years in the two trials to evaluate the elderly, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

Trough TPV concentrations (10-14 h post-dose) from the 1182.12 and 1182.48 trials  
paneled gender and age



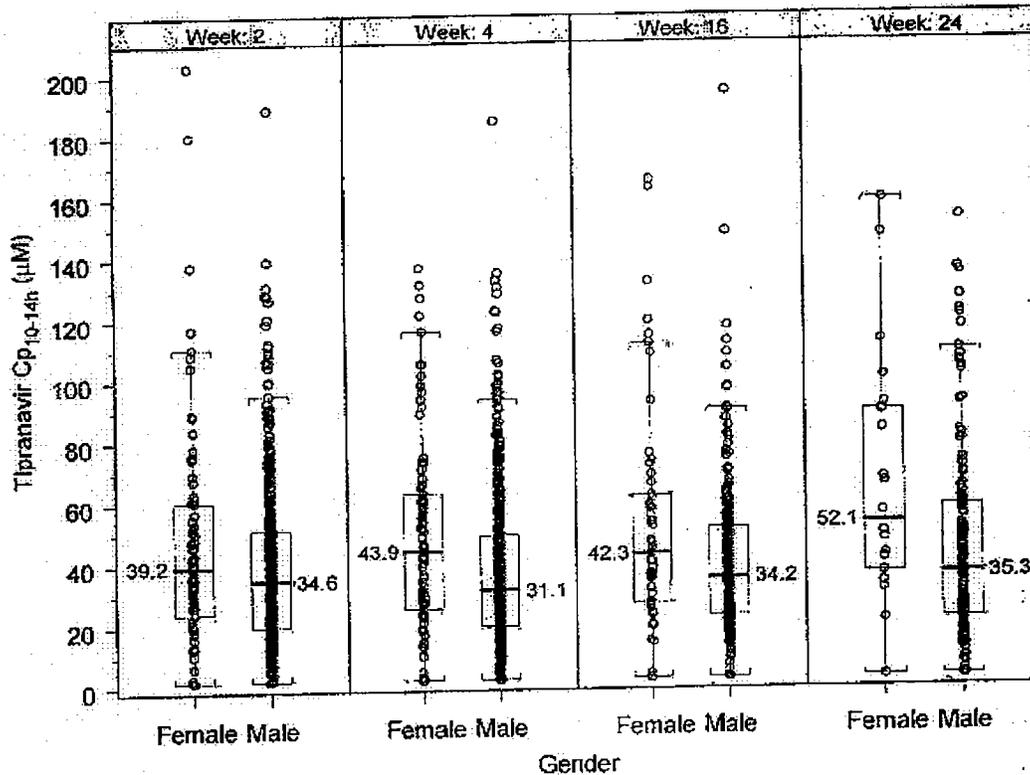
### 2.3.2.2. Pediatric Patients

Tipranavir, co-administered with low-dose ritonavir, is being studied in 100 pediatric HIV-1 infected children and adolescents between 2 and 18 years of age (Study 1182.14). The study is ongoing and the applicant does not seek pediatric indication in the NDAs submitted. No sufficient PK data are available for review.

### 2.3.2.3. Gender

Evaluation of steady-state plasma tipranavir trough concentrations from two pivotal phase III clinical trials indicated that females generally had higher tipranavir concentrations than males. After 4 weeks of tipranavir/ritonavir 500 mg/200 mg bid, the median plasma trough concentration of tipranavir was 43.9  $\mu\text{M}$  for females and 31.1  $\mu\text{M}$  for males. The range of exposure was similar for males and females.

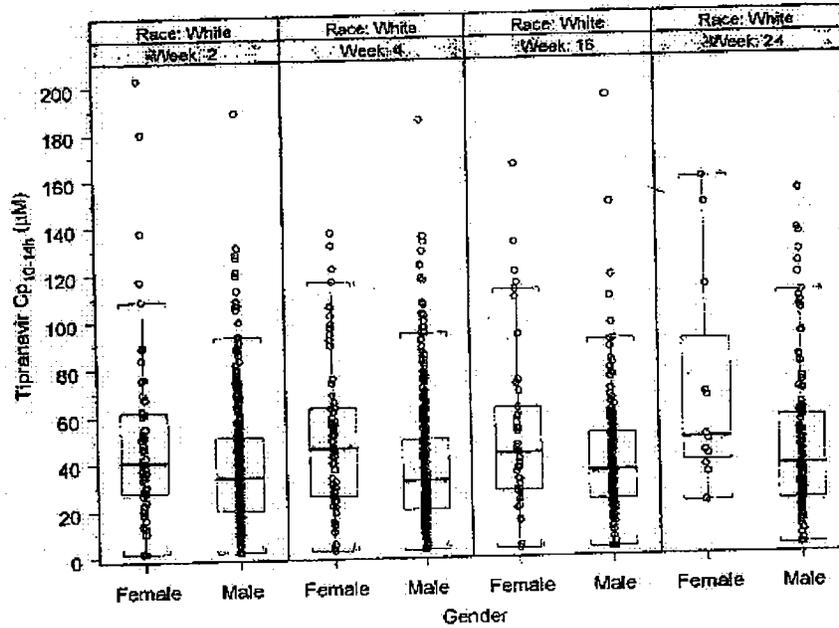
Trough TPV concentrations (10-14 h post-dose) from the 1182.12 and 1182.48 trials paneled gender and time



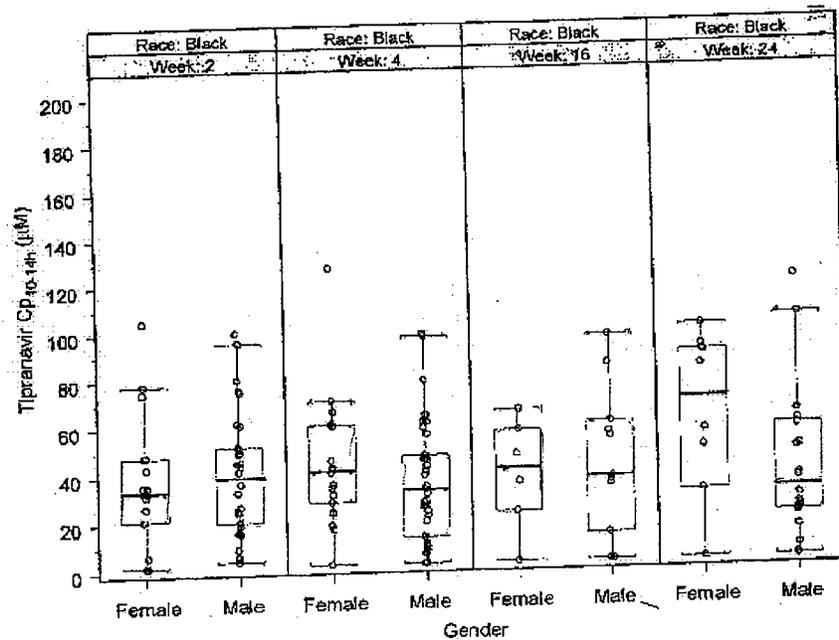
### 2.3.2.4. Race

Evaluation of steady-state plasma tipranavir trough concentrations from two pivotal phase III clinical trials indicated that white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races. Females of either race generally had higher trough tipranavir concentrations than males.

Trough TPV concentrations (10-14 h post-dose) from the 1182.12 and 1182.48 trials paneled gender and time for patients declaring "White" as their race



Trough TPV concentrations (10-14 h post-dose) from the 1182.12 and 1182.48 trials paneled gender and time for patients declaring "Black" as their race



#### 2.3.2.5. Renal Impairment

Tipranavir (co-administered with low dose ritonavir) pharmacokinetics have not been studied in patients with renal dysfunction. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

#### 2.3.2.6. Hepatic Impairment

Following a single dose of TPV/r 500mg/200mg in 9 subjects with mild hepatic insufficiency, the mean systemic exposure of tipranavir was comparable to that of 9 matched controls. After 7 days of bid dosing, the mean systemic exposure of tipranavir was higher for subjects with mild hepatic insufficiency compared to that of 9 matched controls and the ranges of 90% CI were quite large, e.g., geometric mean ratios with 90% CIs for AUC,  $C_{max}$  and  $C_{min}$  were 1.30 (0.88, 1.92), 1.14 (0.83, 1.56) and 1.84 (0.81, 4.20), respectively. A similar change in ritonavir exposure was also observed. Dosage adjustment may not be warranted for this group of patients based on the moderate change in tipranavir and ritonavir systemic exposure and safety profiles observed in this study. There were insufficient data (lack of data at the steady-state) from moderate hepatic insufficiency group to reach any conclusion. Since liver is the major organ that eliminates tipranavir from systemic circulation, for anticipated safety concerns, tipranavir/ritonavir should be contraindicated for patients with moderate or severe hepatic insufficiency.

### 2.4 Extrinsic Factors:

#### 2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The applicant evaluated the effects of drug-drug interactions and food on tipranavir exposure. Food effect is described in section 2.5.3. There are numerous significant drug-drug interactions described below.

#### 2.4.2. Drug-Drug Interactions

##### 2.4.2.1. Is there any *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, there is an *in vitro* basis to suspect *in vivo* drug-drug interactions.

TPV is a CYP3A substrate, a CYP 3A inhibitor, as well as a CYP3A inducer. TPV is also an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. The likelihood that TPV is an *in vivo* inhibitor of these enzymes is high.

TPV is a P-glycoprotein substrate, a weak P-gp inhibitor, and most likely a P-gp inducer as well. There are more details in the following sections.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

*In vitro* metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP isoform involved in tipranavir metabolism. Ketoconazole at concentrations of 1  $\mu\text{M}$  or 5  $\mu\text{M}$  inhibited the metabolism of tipranavir (50  $\mu\text{M}$ ) by 90% and 95%, respectively. Correlation analysis also strongly suggested the involvement of CYP3A4. CYP2D6 was confirmed to not be involved in the metabolism of tipranavir by incubating tipranavir with cDNA-expressed human CYP2D6.

2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes?

*In vitro* metabolism studies with human liver microsomes indicated that TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 and CYP3A4. The CYP activity markers used were phenacetin (CYP1A2), diclofenac (CYP2C9), (S)-mephenytoin (CYP2C19), bufuralol (CYP2D6), testosterone (CYP3A4) and midazolam (CYP3A4).

Tipranavir  $K_i$  and proposed  $[I]/K_i$  values for the major CYPs

CYP	$K_i$ ( $\mu\text{M}$ )	$[I]/K_i^*$
CYP1A2	24.2	3.9
CYP2C9	0.23	414.8
CYP2C19	5.3	18.0
CYP2D6	6.7	14.2
CYP3A4 (Midazolam)	0.88	108.4
CYP3A4 (Testosterone)	1.3	73.4

\*  $[I]$  is based on  $C_{\text{max}}$  of 95.4  $\mu\text{M}$  at steady-state of tipranavir/ritonavir 500 mg/200 mg bid.

For the calculation of  $[I]/K_i$ , *in vivo*  $C_{\text{max}}$  (bound plus unbound) was used to represent inhibitor concentrations  $[I]$ . As  $[I]/K_i$  ratios are greater than 1, drug interactions involving above-mentioned major human CYPs are considered likely.

TPV is also a CYP3A4 inducer. An *in vitro* metabolism study with human hepatocytes confirmed that TPV is a CYP3A4 inducer. The sponsor did not determine whether TPV is also an inducer to CYPs 1A2, 2C9 and 2C19.

Tipranavir, co-administered with low-dose ritonavir at the recommended dosage (500 mg/200 mg) is a net inhibitor of the P450 CYP3A. The Erythromycin Breath Test (ERMBT) results showed that the hepatic CYP3A activity was increased following 11 days repeated dosing of TPV alone and inhibited by co-administration of TPV/r. The ERMBT results suggest that TPV alone is a hepatic CYP3A inducer and the net effect of TPV/r combination is inhibition of hepatic CYP3A activity.

2.4.2.4. Is the drug a substrate, an inhibitor or inducer of P-glycoprotein transport processes?

Data from Caco-2 cells indicated that tipranavir's basolateral to apical permeability (secretory direction) was greater than its apical to basolateral permeability (absorptive

direction), suggesting that tipranavir is a substrate of apically located efflux pumps (e.g., P-gp). Data also demonstrated that P-gp inhibitors such as quinidine, verapamil and LY335979 could inhibit the efflux of tipranavir and thus increase tipranavir absorption from apical side of cells. Cremophor EL which is currently used in the SEDDS formulation markedly increased the tipranavir apical absorption, suggesting it may have a similar effect *in vivo*. Data from MDCK wild type and MDR1-transfected MDCK cell lines confirmed that tipranavir is a substrate for P-gp.

Permeability of tipranavir across wild-type MDCK and MDR1-transfected MDCK cell monolayers

Tipranavir with 0.25% (w/v) BSA	Perm. A to B $10^6$ (cm/sec)	Mass Balance (%)	Perm. B to A $10^6$ (cm/sec)	Mass Balance (%)	PDR
MDCK Wild Type	0.6 ± 0.0	97.2	0.8 ± 0.1	92.2	1.3
MDCK MDR-1	0.2 ± 0.0	96.2	3.0 ± 0.3	99.6	15.0

The applicant also mentioned that tipranavir is a weak P-gp inhibitor using digoxin as a P-gp marker substrate in Caco-2 cells, though data were not presented in the NDA. The information regarding whether tipranavir is an *in vitro* P-gp inducer is not available.

The following data suggest that the net combination of tipranavir and ritonavir at the proposed dose regimen (500 mg/200 mg) is potent P-gp induction:

1. Loperamide (LOP) is a known substrate of P-gp and P-gp plays a significant role in LOP's elimination. Co-administration of LOP with steady-state TPV or TPV/r resulted in 63% and 51% decrease in LOP AUC, respectively, and 58% and 61% decrease in LOP  $C_{max}$ , respectively. However, co-administration of LOP with steady-state RTV resulted in increases in LOP AUC (121%) and  $C_{max}$  (83%).
2. Clarithromycin (CLR) is a P-gp and CYP3A substrate. Steady-state TPV/r administration (500/200 mg bid) increased (CLR)  $AUC_{0-12h}$  and  $C_{p12h}$  by 19% and 68%, respectively, with no substantial change in the  $C_{max}$ . However, the formation of the major metabolite, 14-OH-CLR, was almost fully inhibited at the steady-state of TPV/r administration. The degree of CLR exposure increase is less than expected based on the degree of reduction of 14-OH-CLR formation. A possible explanation is that tipranavir is a P-gp inducer and the low dose of ritonavir can not compensate for the P-gp induction effect caused by tipranavir. Since CLR is a P-gp substrate, CLR is pumped back to intestinal lumen as unabsorbed drug by increased activity of intestinal P-gp. The net interplay between intestinal CYP3A and P-gp led to similar systemic exposure of CLR when co-administered with TPV/r at steady-state compared to that of CLR alone.
3. In the human mass balance study, daily trough level monitoring confirmed that the steady-state of TPV/r (500 mg/200 mg bid) is reached after about 7 days of dosing. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1. However, in plasma, unchanged TPV was predominant and accounted for 98.4% or greater of the total plasma radioactivity at the steady-state. If the lower TPV concentrations at steady-state were due to CYP3A induction, metabolites would

contribute to more of the plasma radioactivity. A possible explanation is that tipranavir is a potent P-gp inducer and the low dose of ritonavir cannot compensate the P-gp induction effect caused by tipranavir. Since tipranavir is a P-gp substrate, at steady-state, more tipranavir is pumped back to intestinal lumen as unabsorbed drug by increased activity of intestinal P-gp.

4. Co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased amprenavir, lopinavir and saquinavir steady-state trough plasma concentrations by 52%, 80% and 56%, respectively, when these protease inhibitors were administered with 200 mg ritonavir. A possible explanation is that tipranavir is a potent P-gp inducer and the low dose of ritonavir cannot compensate the P-gp induction effect caused by tipranavir. All the PIs studied in this trial are known dual substrates of CYP3A and P-gp and subject to high intestinal first-pass effect. Thus the net interplay between intestinal CYP3A and P-gp caused lower systemic exposure of these PIs when co-administered with tipranavir at the steady-state.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

No, current evidence does not indicate that other metabolic/transporter pathway may be important.

2.4.2.6. What other co-medications are likely to be administered to the target patient population?

In addition to other antiretroviral drugs, HIV-infected patients take drugs to treat opportunistic infections and side effects of antiretroviral agents, other common medications such as statins, antidepressants, antipsychotic agents, cardiac drugs, including Calcium channel blockers, antiarrhythmics, hormonal contraceptives, sedative/hypnotics, warfarin, anticonvulsants, antifungals, erectile dysfunction agents, methadone, anti-diabetic agents and macrolide antibiotics. The interaction potential is described in section 2.4.2.7.

2.4.2.7. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The applicant conducted numerous drug-drug interaction studies using the proposed to be marketed TPV SEDDS formulation in combination with low dose (100 or 200 mg) ritonavir, as described in this section. Also see Tables 1 and 2 below and Recommendations in the Executive Summary (Pages 2-3).

Antiretroviral agents: Nucleoside reverse transcriptase inhibitors (NRTIs): abacavir, didanosine (ddI), lamivudine (3TC), stavudine (d4T), tenofovir and zidovudine (ZDV)

Abacavir AUC values were reduced by 35% to 44% when abacavir was administered at three different TPV/r dose levels (TPV/r 250 mg/200 mg, 750 mg/100 mg and 1250 mg/100 mg). The extent of the interaction was not dose dependent. Appropriate doses for the combination of tipranavir/ritonavir with abacavir have not been established. The effect on the active moiety, intracellular carbovir triphosphate, is not known.

The interaction of TPV/r with enteric coated-ddI was initially studied in Study 1182.6 where ddI AUC values were reduced by 33% at the TPV/r 250 mg/200 mg dose level but there were no significant changes at the 1250 mg/100 mg and 750 mg/100 mg dose levels. In study 1182.42, the interaction of ddI with co-administered TPV and RTV could not be evaluated for the group of subjects that received TPV/r 750 mg/200 mg because early discontinuations provided only a single subject on Study Day 15. For the group of subjects that received ddI in the presence of TPV/r 500 mg/100 mg, early discontinuation reduced the number of subjects on Study Day 15 from 11 to 5. Results from the five completed subjects showed that AUC and  $C_{max}$  of ddI were not significantly changed with the co-administration of TPV/r, however the 90% confidence intervals were quite large, indicating a high degree of variability. While TPV AUC was not changed when co-administered with ddI,  $C_{max}$  did increase about 30% and  $C_{p12h}$  decreased about 30% with wide 90% CIs.

The results of studies 1182.6 and 1182.46 indicate there are no PK interactions between TPV/r and lamivudine, stavudine and tenofovir.

The interaction of tipranavir with zidovudine was initially studied in Study 1182.6 where TPV/r was found to decrease ZDV AUC and  $C_{max}$  by 47% and 68%, respectively. Study 1182.37 confirmed that co-administration of TPV/r with ZDV markedly decreased ZDV exposure, i.e., AUC decreased 43% at TPV 500 mg/RTV 100 mg dose and AUC decreased 33% at TPV 750 mg/RTV 200 mg dose. However, zidovudine glucuronide exposure ( $C_{max}$  and AUC) was not affected by the co-administration of TPV/r. Tipranavir exposure ( $C_{max}$ ,  $C_{p12h}$  and  $AUC_{0-12h}$ ) decreased about 13-23% when co-administered with ZDV at TPV/r 500 mg/100 mg dose, while tipranavir exposure was not significantly affected when ZDV was co-administered with TPV/r 750 mg/200 mg. At the proposed clinical dose, 500 mg TPV/200 mg RTV, when co-administered with 300 mg ZDV, ZDV plasma exposure is expected to decrease 30-40% based on the data from this study. The PK of either TPV or RTV is unlikely to change at the dose level of 500 mg/200 mg when co-administered with ZDV. Appropriate doses for the combination of tipranavir, co-administered with low-dose ritonavir, with zidovudine have not been established. Similar interaction observed between nelfinavir and zidovudine, ritonavir and zidovudine with no dose adjustment. The effect on the active moiety, intracellular ZDV-triphosphate, is not known.

Antiretroviral agents: Non-nucleoside reverse transcriptase inhibitors (NNRTIs):  
efavirenz (EFV) and nevirapine

In study 1182.41, steady-state efavirenz decreased steady-state TPV AUC 31%,  $C_{max}$  21% and  $C_{p12h}$  42% at the 500 mg/100 mg regimen, respectively, based on the cross study comparison (Studies 1182.5, 1182.22, 1182.37 and 1182.46). However, steady-state efavirenz had little effect on steady-state TPV AUC,  $C_{max}$  and  $C_{p12h}$  at the tipranavir/ritonavir 750 mg/200 mg regimen by the cross study comparison (Studies 1182.5, 1182.22, 1182.37, 1182.46 and 1182.55). The change of pharmacokinetic parameters of TPV was less pronounced in the RTV 200 mg group, suggesting that inhibition of CYP3A by the 200 mg RTV partially counteracted the effects of CYP3A induction by EFV. It is anticipated the effect of EFV on TPV/r 500/200 mg would be less than or similar to that of EFV on TPV/r 750/200 mg. A dose adjustment of TPV/r will not be needed in the presence of efavirenz. The effect of nevirapine on TPV SEDDS

formulation in combination with low dose ritonavir was not evaluated. However, similar degree of interaction should be expected as that of efavirenz.

Antiretroviral agents: Protease inhibitors (PIs): amprenavir/RTV, lopinavir/RTV (Kaletra) and saquinavir/RTV

Study 1182.51 was conducted in conjunction with two pivotal phase III trials, RESIST 1 and RESIST 2. Patient excluded from RESIST 1 and RESIST 2 because of having three or more mutations in protease codons 33, 82, 84 or 90 were eligible for screening for 1182.51. The working hypothesis was that the combination of TPV/r with a second PI might increase the chances of a clinical response in highly advanced HIV-1 infected patients. Study 1182.51 was a preliminary PK study to investigate the potential drug interactions between TPV/r and the other ritonavir boosted-PIs and to provide initial clinical data for this dual PI approach. All four arms received the same total dose of RTV after Week 4, i.e., 200 mg bid.

The dual RTV-boosted PI treatments were:

LPV/r (400/100 bid) plus OBR, with TPV/r (500/100) added at week 2  
APV/r (600/100 bid) plus OBR, with TPV/r (500/100) added at week 2  
SQV/r (1000/100 bid) plus OBR, with TPV/r (500/100) added at week 2

The co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased LPV, SQV, or APV steady-state trough plasma concentrations by 52%, 80% and 56%, respectively. These data were also consistent with the results of the intensive PK sub-study where co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased LPV, SQV, or APV steady-state trough plasma concentrations by 70%, 82% and 55%, respectively, AUC by 55%, 76% and 44%, respectively, and  $C_{max}$  by 47%, 70% and 39%, respectively. TPV exposure increased slightly in the APV/r and LPV/r groups, but decreased slightly when co-administered with SQV/r. RTV trough plasma concentrations were similar in APV/r and LPV/r groups with the addition of TPV/r. However RTV trough plasma concentrations in the SQV/r group decreased by 50% with the addition of TPV/r. This decrease in RTV concentration might account for the most dramatic reduction in SQV exposure with the addition of TPV/r. The decrease PI concentrations, when a second PI is administered with TPV/r, are an efficacy and resistance concern. Appropriate doses for the combination of tipranavir, co-administered with low-dose ritonavir, with other PIs have not been established.

Some other commonly co-administered drugs in HIV-infected patients: antacid, atorvastatin, clarithromycin, ethinyl estradiol/norethindrone, fluconazole, loperamide and rifabutin

Simultaneous ingestion of antacid and TPV/r reduced the plasma TPV concentrations by about 25-29%. The exact mechanism of the interaction between antacid and TPV/R is not known. Tipranavir/ritonavir dosing should be separated from antacid administration to prevent reduced absorption of tipranavir. The drug interactions between TPV/r and proton-pump inhibitors or H<sub>2</sub>-receptor antagonists are not expected based on the TPV's solubility-pH profile.

Atorvastatin (ATV) is extensively metabolized by CYP3A4. Co-administration of steady-state TPV/R (500 mg/200 mg) increased a single dose ATV's AUC by 9.4-fold,  $C_{max}$  by

8.6-fold and  $C_{p12}$  by 5.2-fold. No effect of single-dose ATV on the steady-state PK of TPV/r was observed. Similar findings have been reported for lopinavir/ritonavir 400/100 BID, which increased ATV AUC and  $C_{max}$  by 6- and 5-fold respectively. When co-administered with TPV/r, start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors not metabolized by CYP3A such as pravastatin, fluvastatin or rosuvastatin. Lovastatin and simvastatin should not be co-administered with TPV/r, because the concentrations of these low oral bioavailability CYP3A substrates are usually increased by CYP3A inhibitors to a great extent.

Clarithromycin (CLR) is used in HIV/AIDS patients to treat opportunistic infections. CLR is metabolized extensively in the liver by cytochrome P450 3A. One of two major metabolites, 14-hydroxy-R-clarithromycin (14-OH-CLR), is active against some bacteria. CLR is also an inhibitor of CYP3A enzyme and can increase the concentrations of drugs that primarily depend upon CYP3A metabolism. Study 1182.11 demonstrated that single-dose TPV/r (500/200 mg) did not affect the steady-state  $AUC_{0-12h}$  of CLR, but decreased the  $C_{max}$  by 12% and increased  $C_{p12h}$  by 50% and that steady-state TPV/r administration (500/200 mg bid) increased CLR  $AUC_{0-12h}$  and  $C_{p12h}$  by 19% and 68%, respectively, with no substantial change in the  $C_{max}$ . However, the formation of 14-OH-CLR was almost fully inhibited at the steady-state of TPV/r administration. No dosage reductions of tipranavir and clarithromycin for patients with normal renal function are necessary. The steady-state TPV  $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$  were increased by 112%, 43% and 59%, respectively, during co-administration of steady-state CLR.

The addition of TPV/r at doses of either 500/100 mg bid or 750/200 mg bid to norethindrone/ ethinyl estradiol (NET/EE) (1/0.035 mg) therapy reduced the total EE exposure ( $AUC_{0-24h}$ ) by 43-48%, and the maximal EE concentrations ( $C_{max}$ ) by approximately 50%. This reduction of > 40% in the exposure to EE may significantly compromise the efficacy of this oral contraceptive. Therefore oral contraceptives should not be the primary method of birth control in HIV-infected women of child-bearing potential using TPV/r. The 13-27% increase in the exposure ( $AUC_{0-24h}$ ) to NET after co-administration of TPV/r is not expected to be clinically relevant.

Fluconazole (FCZ) is routinely indicated for oropharyngeal and esophageal candidiasis, and for the treatment of other serious systemic fungal infections in HIV positive patients. FCZ was demonstrated to inhibit midazolam metabolism, a known substrate for CYP3A, administered both intravenously and orally. Co-administration of TPV/r 500/200 mg bid at steady-state caused small decreases in fluconazole exposures (-11% in  $C_{p24h}$ , -6% in  $C_{max}$  and -8% in  $AUC_{0-24h}$ ). In contrast, steady-state fluconazole appeared to have a significant effect on the steady-state PK of TPV, when compared to the results from a cross study comparison. The steady-state TPV  $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$  were increased by 104%, 56% and 46%, respectively, during co-administration of steady-state FCZ. This is likely due to the inhibition effect of FCZ on P-gp.

Co-administration of loperamide (LOP) with steady-state TPV or TPV/r resulted in 63% and 51% decrease in LOP AUC, respectively, and 58% and 61% decrease in LOP  $C_{max}$ , respectively. However, co-administration of LOP with steady-state RTV resulted in increases in LOP AUC (121%) and  $C_{max}$  (83%). The effect of single-dose LOP on the steady-state pharmacokinetics of TPV in combination with ritonavir was less substantial but the clinical relevance is unknown. For TPV, trough concentration was decreased 26% while  $C_{max}$  and  $AUC_{0-12h}$  remained unchanged. For RTV, trough concentration,  $C_{max}$  and  $AUC_{0-12h}$  were decreased by 30%, 28% and 22%, respectively.

A single 150 mg dose of rifabutin (RFB) increased the TPV (500 mg/200 mg TPV/r)  $C_{p12}$  at steady-state by 16% while there was no effect on AUC and  $C_{max}$ . However, steady-state TPV increased a single dose RFB's AUC,  $C_{max}$  and  $C_{p12}$  by 2.9-fold, 1.7-fold and 2.1-fold, respectively. This change may be due to inhibition of CYP3A4 mediated metabolism of RFB by ritonavir. However, the effect of multiple dose of RFB on the steady-state PK of TPV/r was not studied. The concern is that RFB is also a CYP3A and P-gp inducer and the multiple dose of RFB might shift the balance of induction and inhibition towards more induction side thus reducing the TPV exposure. Dosage reductions of rifabutin will be recommended.

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

Coadministered Drug	Coadministered Drug Dose	TPV/r Dose	n	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				$C_{max}$	AUC	$C_{min}$
Didanosine	400 mg (SD)	500/100 mg bid (MD)	5	1.32 (1.09, 1.60)	1.08 (0.82, 1.42)	0.66 (0.31, 1.43)
Efavirenz	600 mg qd (MD)	500/100 mg bid	21	0.79 (0.69, 0.89)	0.69 (0.57, 0.83)	0.58 (0.36, 0.86)
		750/200 mg bid (MD, cross study comparison)	25	0.97 (0.85, 1.09)	1.01 (0.85, 1.18)	0.97 (0.69, 1.28)
Tenofovir	300 mg (SD)	500/100 mg bid	22	0.83 (0.74, 0.94)	0.82 (0.75, 0.91)	0.79 (0.70, 0.90)
		750/200 mg bid (MD)	20	0.89 (0.84, 0.96)	0.91 (0.85, 0.97)	0.88 (0.78, 1.00)
Zidovudine	300 mg (SD)	500/100 mg bid	29	0.87 (0.80, 0.94)	0.82 (0.76, 0.89)	0.77 (0.68, 0.87)
		750/200 mg bid (MD)	25	1.02 (0.94, 1.10)	1.02 (0.92, 1.13)	1.07 (0.86, 1.34)
Atorvastatin	10 mg (1 dose)	500/200 mg bid (14 doses)	22	0.96 (0.86, 1.07)	1.08 (1.00, 1.15)	1.04 (0.89, 1.22)
Clarithromycin	500 mg bid (MD)	500/200 mg bid (MD, cross study comparison)	24	1.40 (1.24, 1.47)	1.66 (1.43, 1.73)	2.00 (1.58, 2.47)
Ethinyl estradiol / Norethindrone	0.035/1.0 mg (SD)	500/100 mg bid (MD)	21	1.10 (0.98, 1.24)	0.98 (0.88, 1.11)	0.73 (0.59, 0.90)
		750/200 mg bid (MD)	13	1.01 (0.96, 1.06)	0.98 (0.90, 1.07)	0.91 (0.69, 1.20)
Fluconazole	100 mg qd (MD)	500/200 mg bid (MD, cross study comparison)	19	1.32 (1.18, 1.47)	1.50 (1.29, 1.73)	1.69 (1.33, 2.09)
Loperamide	16 mg (SD)	750/200 mg bid (MD)	24	1.03 (0.92, 1.17)	0.98 (0.86, 1.12)	0.74 (0.62, 0.88)
Maalox	20 mL (SD)	500/200 mg (SD)	22	0.75 (0.63, 0.88)	0.73 (0.64, 0.84)	0.71 (0.59, 0.85)
Rifabutin	150 mg (SD)	500/200 mg bid (MD)	21	0.99 (0.93, 1.07)	1.00 (0.96, 1.04)	1.16 (1.07, 1.27)

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

Coadministered Drug	Coadministered Drug Dose	TPV/r Drug Dose	n	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without TPV/r; No Effect = 1.00		
				Cmax	AUC	Cmin
Abacavir†	300 mg bid (MD)	250/200 mg bid	28	0.56 (0.48, 0.66)	0.56 (0.49, 0.63)	-
		750/100 mg bid	14	0.54 (0.47, 0.63)	0.64 (0.55, 0.74)	-
		1250/100 mg bid (MD)	11	0.48 (0.42, 0.53)	0.65 (0.55, 0.76)	-
Didanosine††	200 mg bid, ≥60 Kg (MD) 125 mg bid, <60 Kg (MD)	250/200 mg bid	10	0.57 (0.42, 0.79)	0.67 (0.51, 0.88)	-
		750/100 mg bid	8	0.76 (0.49, 1.17)	0.97 (0.64, 1.47)	-
		1250/100 mg bid (MD)	9	0.77 (0.47, 1.26)	0.87 (0.47, 1.65)	-
	400 mg (SD)	500/100 mg bid 750/200 mg bid (MD)	5	0.80 (0.63, 1.02)	0.90 (0.72, 1.11)	1.17 (0.62, 2.20)
Lamivudine†	150 mg bid (MD)	250/200 mg bid	64	0.96 (0.89, 1.03)	0.95 (0.89, 1.02)	-
		750/100 mg bid	46	0.86 (0.78, 0.94)	0.96 (0.90, 1.03)	-
		1250/100 mg bid (MD)	35	0.71 (0.62, 0.81)	0.82 (0.66, 1.00)	-
Stavudine†	40 mg bid, ≥60 Kg (MD) 30 mg bid, <60 Kg (MD)	250/200 mg bid	26	0.90 (0.81, 1.02)	1.00 (0.91, 1.11)	-
		750/100 mg bid	22	0.76 (0.66, 0.89)	0.84 (0.74, 0.96)	-
		1250/100 mg bid (MD)	19	0.74 (0.69, 0.80)	0.93 (0.83, 1.05)	-
Tenofovir	300 mg (SD)	500/100 mg bid	22	0.77 (0.68, 0.87)	0.98 (0.91, 1.05)	1.07 (0.98, 1.17)
		750/200 mg bid (MD)	20	0.62 (0.54, 0.71)	1.02 (0.94, 1.10)	1.14 (1.01, 1.27)
Zidovudine††	300 mg bid (MD)	250/200 mg bid	48	0.54 (0.47, 0.62)	0.58 (0.51, 0.66)	-
		750/100 mg bid	31	0.51 (0.44, 0.60)	0.64 (0.55, 0.75)	-
		1250/100 mg bid (MD)	23	0.49 (0.40, 0.59)	0.69 (0.49, 0.97)	-

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Zidovudine glucuronide	300 mg (SD)	500/100 mg bid	29	0.82 (0.74, 0.90)	1.02 (0.97, 1.06)	1.52 (1.34, 1.71)
		750/200 mg bid (MD)	25	0.82 (0.73, 0.92)	1.09 (1.05, 1.14)	1.94 (1.62, 2.31)
Efavirenz††	600 mg qd (MD)	500/100 mg bid	24	1.09 (0.99, 1.19)	1.04 (0.97, 1.12)	1.02 (0.92, 1.12)
		750/200 mg bid (MD)	22	1.12 (0.98, 1.28)	1.00 (0.93, 1.09)	0.94 (0.84, 1.04)
Nevirapine†	200 mg bid (MD)	250/200 mg bid	26	0.97 (0.90, 1.04)	0.97 (0.91, 1.04)	0.96 (0.87, 1.05)
		750/100 mg bid	22	0.86 (0.76, 0.97)	0.89 (0.78, 1.01)	0.93 (0.80, 1.08)
		1250/100 mg bid (MD)	17	0.71 (0.62, 0.82)	0.76 (0.63, 0.91)	0.77 (0.64, 0.92)
Amprenavir/RTV†	600/100 mg bid (MD)	500/200 mg bid	16	0.61 (0.51, 0.73)*	0.56 (0.49, 0.64)*	0.45 (0.38, 0.53)*
		(MD)	74	-	-	0.44 (0.39, 0.49)**
Lopinavir/RTV†	400/100 mg bid (MD)	500/200 mg bid	21	0.53 (0.40, 0.69)*	0.45 (0.32, 0.63)*	0.30 (0.17, 0.51)*
		(MD)	69	-	-	0.48 (0.40, 0.58)**
Saquinavir/RTV†	600/100 mg bid (MD)	500/200 mg bid	20	0.30 (0.23, 0.40)*	0.24 (0.19, 0.32)*	0.18(0.13,0.26)*
		(MD)	68	-	-	0.20(0.16,0.25)**
Atorvastatin	10 mg (SD)	500/200 mg bid (MD)	22	8.61 (7.25, 10.21)	9.36 (8.02, 10.94)	5.19 (4.21, 6.40)
Clarithromycin 14-OH-clarithromycin	500 mg bid (MD)	500/200 mg bid (MD)	21	0.95 (0.83, 1.09)	1.19 (1.04, 1.37)	1.68 (1.42, 1.98)
			21	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
Ethinyl estradiol	0.035 mg (SD)	500/100 mg bid	21	0.52 (0.47, 0.57)	0.52 (0.48, 0.56)	-
		750/200 mg bid (MD)	13	0.48 (0.42, 0.57)	0.57 (0.54, 0.60)	-
Fluconazole	100 mg qd (MD)	500/200 mg bid (SD, MD)	19 19	0.97 (0.94, 1.01) 0.94 (0.91, 0.98)	0.99 (0.97, 1.02) 0.92 (0.88, 0.95)	0.98 (0.94, 1.02) 0.89 (0.85, 0.92)
Loperamide	16 mg (SD)	750/200 mg bid (MD)	24	0.39 (0.31, 0.48)	0.49 (0.40, 0.61)	-
N-Demethyl-Loperamide		24		0.21 (0.17, 0.25)	0.23 (0.19, 0.27)	
Norethindrone	1.0 mg (SD)	500/100 mg bid	21	1.03 (0.94, 1.13)	1.14 (1.06, 1.22)	-
		750/200 mg bid (MD)	13	1.08 (0.97, 1.20)	1.27 (1.13, 1.43)	-
Rifabutin	150 mg (SD)	500/200 mg bid (MD)	20	1.70 (1.49, 1.94)	2.90 (2.59, 3.26)	2.14 (1.90, 2.41)
25-O-desacetyl-rifabutin			20	3.20 (2.78, 3.68)	20.71 (17.66, 24.28)	7.83 (6.70, 9.14)
Rifabutin + 25-O-desacetyl-rifabutin <sup>a</sup>			20	1.86 (1.63, 2.12)	4.33 (3.86, 4.86)	2.76 (2.44, 3.12)
†HIV+ patients						
††HIV+ patients (TPV/r 250 mg/200 mg, 750mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/r 500 mg/100 mg and 750 mg/200 mg)						
<sup>a</sup> Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)						
*Intensive PK analysis						
**Therapeutic Drug Monitoring 8-16 hrs post-dose						

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2.4.2.8. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

2.4.2.9. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Follow-up in vivo evaluations using probe substrate drugs for these enzymes have not been conducted to rule out or confirm these potential interactions. Ritonavir is a moderate CYP2D6 inhibitor, and likely an inducer of CYP1A2, CYP2C9 and glucuronosyl transferases. The potential net effect when tipranavir is administered with ritonavir on CYP2D6 is inhibition. The net effect when tipranavir is administered with ritonavir on CYP1A2 and CYP2C9 is not known because of potential conflicting effects of tipranavir (inhibition) and ritonavir (induction) on these enzymes. Data are not available to indicate whether TPV inhibits or induces glucuronosyl transferases and whether TPV induces CYP1A2, CYP2C9 and CYP2C19.

2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Appropriate dosing with dual PIs, abacavir, ZDV has not been established.

## 2.5 General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Tipranavir is a low solubility drug. Its solubility is pH dependent with increasing solubility at basic pH due to ionization, consistent with the behavior of a weak acid. The solubility in pH 7.5 aqueous buffer is 17.1 µg/mL. The *in vitro* permeability data from Caco-2 cells indicated that tipranavir had a low  $P_c$  value, much lower than that of propranolol which is completely absorbed in humans after oral administration. The mass balance study using 500 mg tipranavir in combination of 200 mg ritonavir demonstrated low extent of oral absorption of tipranavir in humans. These data suggest that tipranavir is a low solubility and low permeability drug (BCS Class 4). However, the applicant classified tipranavir as a Class 2 compound (low solubility and high permeability).

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The proposed to-be-marketed SEDDS capsule formulation was used in the pivotal clinical trials.

2.5.3. What is the effect of food on the bioavailability (BA) of tipranavir from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

For SEDDS capsule formulation, the AUC<sub>0-12h</sub> and C<sub>max</sub> of TPV increased 31% (90% CI: 1.23, 1.36) and 16% (90% CI: 1.09, 1.24), respectively, with a high-fat meal compared to that with a light snack. However, the finding is inconclusive because the comparison was based on TPV steady-state PK (Day 7, light snack) to that obtained before steady-state TPV levels were reached (Day 4, high fat). The actual food effect could be less than that observed here.

The proposed label recommends the tipranavir capsules be taken with food.

2.5.4. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

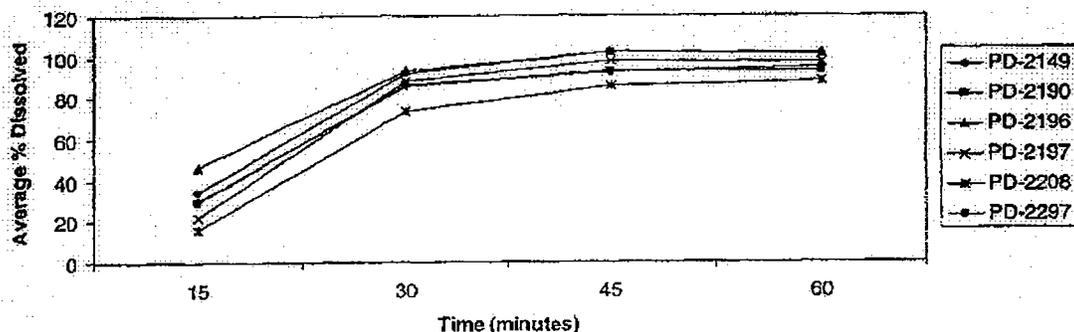
Tipranavir is formulated as an immediate release soft gelatin capsule containing a lipid-based self-emulsifying drug delivery system (SEDDS). When exposed to an aqueous environment, such as the GI tract, the SEDDS capsule-fill solution forms and maintains a highly dispersed colloidal system (fine emulsion). The dissolution test for tipranavir SEDDS 250 mg capsules is essentially a dispersion test that measures the rate and the extent of emulsification of the SEDDS formulation. The dissolution test procedure was developed and optimized with regards to apparatus, paddle speed, dissolution medium, pH of the medium, bath temperature, sample preparation and HPLC analysis. We agree to the selected method at the CMC end-of-phase II meeting.

The proposed dissolution method for tipranavir SEDDS 250 mg capsule is as follows:

Apparatus	USP II (paddles) with a volume of [ ]
Rotation Speed	[ ] rpm
Temperature	[ ]
Medium	[ ] phosphate buffer dissolution medium (pH [ ])
Sampling Times	60 minutes (single-point); 15, 30 45 and 60 minutes (dissolution profile)
Analytical Method	HPLC with UV detection at [ ]

The original proposed dissolution specification for tipranavir SEDDS 250 mg capsule was Q = [ ] dissolved in 60 minutes. The applicant agreed to change the specification to Q = [ ] in 60 minutes.

**Mean Dissolution Profiles for Six Pivotal Clinical Batches of tipranavir SEDDS 250 mg capsules**



2.5.5. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

**2.6. Analytical Section**

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Both tipranavir and ritonavir were measured using C  
J method.

2.6.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods measured total tipranavir and total ritonavir. Both moieties are highly protein bound, so free concentrations may be more appropriate. However, it is standard to measure only total concentrations of HIV protease inhibitors. The degree of protein binding is consistent across the relevant dose range of TPV. The effect of measuring total concentrations (tipranavir and other drugs) on drug interaction results is not known.

2.6.3. What bioanalytical methods are used to assess concentrations?

The following tables summarize the analytical methods used for tipranavir/ritonavir clinical development to support the registration of tipranavir/ritonavir:

3 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

### 3. Labeling Recommendations

The labeling recommendations to the clinical pharmacology section and other relevant sections of the label are highlighted below (Yellow highlights major changes made to the original version proposed by the sponsor):

#### CLINICAL PHARMACOLOGY

##### Pharmacodynamics

The median Inhibitory Quotient (IQ) determined from 301 highly treatment-experienced patients was about 75 (inter-quartile range: 29-189), from pivotal clinical trials 1182.12 and 1182.48. The IQ is defined as the tipranavir trough concentration divided by the viral IC<sub>50</sub> value, corrected for protein binding. There was a relationship between the proportion of patients with a  $\geq 1$  log<sub>10</sub> reduction of viral load from baseline at week 24 and their IQ value. Among the 206 patients receiving APTIVUS/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value < 75 and 55% in those with an IQ value  $\geq 75$ . Among the 95 patients receiving APTIVUS/ritonavir with enfuvirtide, the response rates in patients with an IQ value < 75 versus those with an IQ value  $\geq 75$  were 43% and 84%, respectively. These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.

[

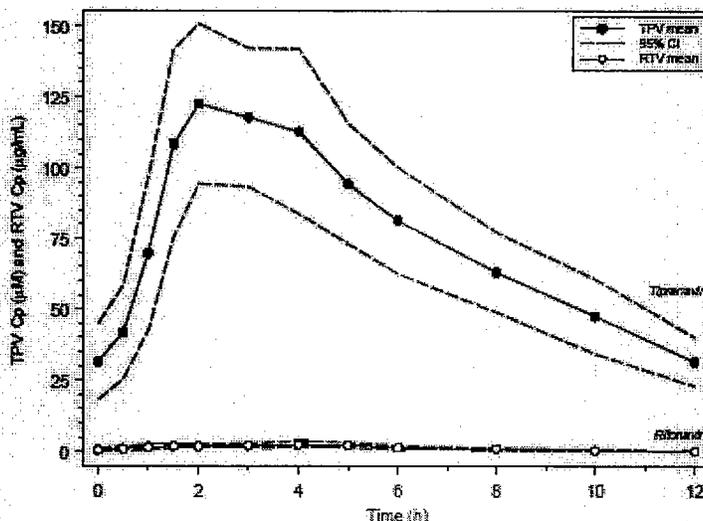
]

##### Pharmacokinetics in Adult Patients

In order to achieve effective tipranavir plasma concentrations and a twice-daily dosing regimen, co-administration of APTIVUS with 200 mg of ritonavir is essential (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Ritonavir inhibits hepatic cytochrome P450 3A (CYP 3A), the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal CYP 3A. In a dose-ranging evaluation in 113 HIV-negative male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following tipranavir co-administered with low-dose ritonavir (500/200 mg twice daily) compared to tipranavir 500 mg twice daily without ritonavir. Figure 1 displays mean plasma concentrations of tipranavir and ritonavir at steady state for the 500/200 mg tipranavir/ritonavir dose.

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**Figure 1 Mean Steady State Tipranavir Plasma Concentrations (95% CI) with Ritonavir Co-administration (tipranavir/ritonavir 500/200 mg BID)**



### Absorption and Bioavailability

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. *In vivo* data suggest that the net effect of tipranavir/ritonavir at the proposed dose regimen (500/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1, presumably due to intestinal P-gp induction. Steady state is attained in most subjects after 7-10 days of dosing. Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice-daily for greater than 2 weeks and without meal restriction produced the following pharmacokinetic parameters for female and male HIV-positive patients. See Table 3.

**Table 3 Pharmacokinetic Parameters of tipranavir/ritonavir 500/200 mg for HIV+ Patients by Gender**

	Females (n = 14)	Males (n = 106)
$C_{p\text{trough}}$ (µM)	41.6 ± 24.3	35.6 ± 16.7
$C_{\text{max}}$ (µM)	94.8 ± 22.8	77.6 ± 16.6
$T_{\text{max}}$ (h)	2.9	3.0
$AUC_{0-12h}$ (µM•h)	851 ± 309	710 ± 207
CL (L/h)	1.15	1.27
V (L)	7.7	10.2
$t_{1/2}$ (h)	5.5	6.0

Population pharmacokinetic parameters reported as mean ± standard deviation

## Effects of Food on Oral Absorption

APTIVUS capsules co-administered with ritonavir should be taken with food. Bioavailability is increased with a high fat meal. Tipranavir capsules, administered under high fat meal conditions or with a light snack of toast and skimmed milk, were tested in a multiple dose study. High-fat meals (868 kcal, 53% derived from fat, 31% derived from carbohydrates) enhanced the extent of bioavailability (AUC point estimate 1.31, confidence interval 1.23-1.39), but had minimal effect on peak tipranavir concentrations (C<sub>max</sub> point estimate 1.16, confidence interval 1.09-1.24).

When APTIVUS, co-administered with low-dose ritonavir, was co-administered with 20 mL of aluminum and magnesium-based liquid antacid, tipranavir AUC<sub>12h</sub>, C<sub>max</sub> and C<sub>12h</sub> were reduced by 25-29%. Consideration should be given to separating tipranavir/ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir.

## Distribution

Tipranavir is extensively bound to plasma proteins (> 99.9%). It binds to both human serum albumin and  $\alpha$ -1-acid glycoprotein. The mean fraction of APTIVUS (dosed without ritonavir) unbound in plasma was similar in clinical samples from healthy volunteers (0.015%  $\pm$  0.006%) and HIV-positive patients (0.019%  $\pm$  0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82  $\mu$ M. The unbound fraction of tipranavir appeared to be independent of total drug concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

## Metabolism

In vitro metabolism studies with human liver microsomes indicated that CYP 3A4 is the predominant CYP enzyme involved in tipranavir metabolism. The oral clearance of tipranavir decreased after the addition of ritonavir, which may represent diminished first-pass clearance of the drug at the gastrointestinal tract as well as the liver. The metabolism of tipranavir in the presence of 200 mg ritonavir is minimal. Administration of <sup>14</sup>C-tipranavir to subjects that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that unchanged tipranavir accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In feces, unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

## Elimination

Administration of <sup>14</sup>C-tipranavir to subjects (n=8) that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that most radioactivity (median 82.3%)

was excreted in feces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir/ritonavir in healthy volunteers (n=67) and HIV-infected adult patients (n=120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a dose of 500/200 mg twice daily with a light meal.

## **Pharmacokinetics in Special Populations**

### ***Renal Impairment***

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

### ***Hepatic Impairment***

In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose plasma concentrations of tipranavir and ritonavir were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of tipranavir administered with ritonavir has not been evaluated (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS**).

### ***Gender***

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of tipranavir/ritonavir 500/200 mg BID, the median plasma trough concentration of tipranavir was 43.9  $\mu$ M for females and 31.1  $\mu$ M for males. The difference in concentrations does not warrant a dose adjustment.

### ***Race***

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races.

### ***Geriatric Patients***

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There were an insufficient number of women greater than age 65 years in

the two trials to evaluate the elderly, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

### ***Pediatric Patients***

The pharmacokinetic profile of tipranavir in pediatric patients has not been established.

### **Drug Interactions**

See also **CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, Drug Interactions.**

APTIVUS co-administered with 200 mg of ritonavir can alter plasma exposure of other drugs and other drugs may alter plasma exposure of tipranavir.

#### ***Potential for tipranavir/ritonavir to Affect Other Drugs***

1. APTIVUS co-administered with 200 mg of ritonavir at the recommended dose, is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see **CONTRAINDICATIONS** and **PRECAUTIONS**).
2. Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir administered with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.
3. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. Data suggest that the net effect of tipranavir co-administered with 200 mg of ritonavir is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.
4. It is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

#### ***Potential for Other Drugs to Affect tipranavir***

1. Tipranavir is a CYP 3A substrate and a P-gp substrate. Co-administration of APTIVUS/ritonavir and drugs that induce CYP 3A and/or P-gp may decrease tipranavir plasma concentrations. Co-administration of APTIVUS/ritonavir and drugs that inhibit P-gp may increase tipranavir plasma concentrations.

2. Co-administration of APTIVUS/ritonavir with drugs that inhibit CYP 3A may not further increase tipranavir plasma concentrations, because the level of metabolites is low following steady-state administration of APTIVUS/ritonavir 500/200 mg twice daily.

Drug interaction studies were performed with APTIVUS, co-administered with 200 mg of ritonavir, and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of APTIVUS with 200 mg ritonavir, on the AUC, C<sub>max</sub> and C<sub>min</sub>, are summarized in Tables 4 and 5. For information regarding clinical recommendations (see **PRECAUTIONS, Drug Interactions, Tables 8 and 9**).

**Table 4 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs**

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

\* steady state comparison to historical data (n)

**Table 5 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of tipranavir/ritonavir**

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without TPV/ritonavir; No Effect = 1.00		
					C <sub>max</sub>	AUC	C <sub>min</sub>
Anprenavir/RTV <sup>a</sup>	600/100 mg BID (27 doses)	500/200 mg BID (28 doses)	16 74	↓ ↓	0.61 (0.51, 0.73) <sup>d</sup>	0.56 (0.49, 0.64) <sup>d</sup>	0.45 (0.38, 0.53) <sup>d</sup> 0.44 (0.39, 0.49) <sup>e</sup>
Abacavir	300 mg BID (43 doses)	250/200 mg BID	28	↓	0.56 (0.48, 0.66)	0.56 (0.49, 0.63)	-
		750/100 mg BID	14	↓	0.54 (0.47, 0.63)	0.64 (0.55, 0.74)	-
		1250/100 mg BID (42 doses)	11	↓	0.48 (0.42, 0.53)	0.65 (0.55, 0.76)	-
Atorvastatin	10 mg (1 dose)	500/200 mg BID (17 doses)	22	↑	8.61 (7.25, 10.21)	9.36 (8.02, 10.94)	5.19 (4.21, 6.40)
Orthohydroxy-atorvastatin			21, 12, 17	↓	0.02 (0.02, 0.03)	0.11 (0.08, 0.17)	0.07 (0.06, 0.08)
Parahydroxy-atorvastatin			13, 22, 1	↓	1.04 (0.87, 1.25)	0.18 (0.14, 0.24)	0.33 (NA)
Clarithromycin	500 mg BID (25 doses)	500/200 mg BID (15 doses)	21	↑	0.95 (0.83, 1.09)	1.19 (1.04, 1.37)	1.68 (1.42, 1.98)
14-OH-clarithromycin			21	↓	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
Didanosine	200 mg BID, ≥60 Kg 125 mg BID, <60 Kg (43 doses)	250/200 mg BID	10	↓	0.57 (0.42, 0.79)	0.67 (0.51, 0.88)	-
		750/100 mg BID	8	↔	0.76 (0.49, 1.17)	0.97 (0.64, 1.47)	-
		1250/100 mg BID (42 doses)	9	↔	0.77 (0.47, 1.26)	0.87 (0.47, 1.65)	-
	400 mg (1 dose)	500/100 mg BID (27 doses)	5	↔	0.80 (0.63, 1.02)	0.90 (0.72, 1.11)	1.17 (0.62, 2.20)
Efavirenz <sup>b</sup>	600 mg QD (15 doses)	500/100 mg BID	24	↔	1.09 (0.99, 1.19)	1.04 (0.97, 1.12)	1.02 (0.92, 1.12)
		750/200 mg BID (15 doses)	22	↔	1.12 (0.98, 1.28)	1.00 (0.93, 1.09)	0.94 (0.84, 1.04)
Ethinyl estradiol	0.035 mg (1 dose)	500/100 mg BID	21	↓	0.52 (0.47, 0.57)	0.52 (0.48, 0.56)	-
		750/200 mg BID (21 doses)	13	↓	0.48 (0.42, 0.57)	0.57 (0.54, 0.60)	-
Fluconazole	200 mg (Day 1) then 100 mg QD (6 or 12 doses)	500/200 mg BID (2 or 14 doses)	19	↔	0.97 (0.94, 1.01)	0.99 (0.97, 1.02)	0.98 (0.94, 1.02)
			19	↔	0.94 (0.91, 0.98)	0.92 (0.88, 0.95)	0.89 (0.85, 0.92)
Lopinavir/RTV <sup>a</sup>	400/100 mg BID (27 doses)	500/200 mg BID (28 doses)	21 69	↓ ↓	0.53 (0.40, 0.69) <sup>d</sup>	0.45 (0.32, 0.63) <sup>d</sup>	0.30 (0.17, 0.51) <sup>d</sup> 0.48 (0.40, 0.58) <sup>e</sup>
Loperamide	16 mg (1 dose)	750/200 mg BID (21 doses)	24	↓	0.39 (0.31, 0.48)	0.49 (0.40, 0.61)	-
N-Demethyl-Loperamide			24	↓	0.21 (0.17, 0.25)	0.23 (0.19, 0.27)	-

<sup>a</sup>HIV+ patients

<sup>b</sup>HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/ritonavir 500 mg/100 mg and 750

mg/200 mg)

<sup>c</sup>Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)

<sup>d</sup>Intensive PK analysis

<sup>e</sup>Drug levels obtained at 8-16 hrs post-dose

**Table 5 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of tipranavir/ritonavir (continued)**

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

<sup>a</sup>HIV+ patients

<sup>b</sup>HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/ritonavir 500 mg/100 mg and 750 mg/200 mg)

<sup>c</sup>Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)

<sup>d</sup>Intensive PK analysis

<sup>e</sup>Drug levels obtained at 8-16 hrs post-dose

## INDICATIONS AND USAGE

APTIVUS® (tipranavir), co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of APTIVUS/ritonavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response (see **CLINICAL PHARMACOLOGY, Microbiology** and **INDICATIONS AND USAGE, Description of Clinical Studies**).
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**). The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**).
- Liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment (see **WARNINGS**).
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment (see **WARNINGS**).
- The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use (see **CLINICAL PHARMACOLOGY** and **CONTRAINDICATIONS**).
- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

## CONTRAINDICATIONS

APTIVUS (tipranavir) is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

APTIVUS is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency (see **WARNINGS**).

Co-administration of APTIVUS with 200 mg of ritonavir, with drugs that are highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in Table 7 below. For information regarding clinical recommendations (see **PRECAUTIONS, Drug Interactions, Tables 8 and 9**).

**Table 7 Drugs that are Contraindicated with Tipranavir, Co-Administered with 200 mg of Ritonavir**

<b>Drug Class</b>	<b>Drugs within Class that are Contraindicated with APTIVUS, Co-administered with 200 mg of ritonavir</b>
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

Due to the need for co-administration of APTIVUS with 200 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

## WARNINGS

**ALERT: Find out about medicines that should NOT be taken with APTIVUS.** This statement is included on the product's bottle label.

APTIVUS (tipranavir) must be co-administered with 200 mg of ritonavir to exert its therapeutic effect (see **DOSAGE AND ADMINISTRATION**). Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions (effect of tipranavir and ritonavir on other drugs).

Please refer to ritonavir prescribing information for additional information on precautionary measures.

## Drug Interactions

Tipranavir administered with ritonavir can alter plasma exposure of other drugs and other drugs can alter plasma exposure of tipranavir and ritonavir. Tipranavir co-administered with 200 mg of ritonavir at the recommended dosage is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of tipranavir/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

The mechanisms of the potential interactions are described in the **CLINICAL PHARMACOLOGY, Drug Interactions** section.

Drugs that are contraindicated or not recommended for co-administration with APTIVUS are included in Table 8 below. These recommendations are based on either drug interaction studies or they are predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

**Table 8 Drugs that Should Not be Co-administered with APTIVUS  
Co-administered with 200 mg of Ritonavir**

<b>Drug Class/Drug Name</b>	<b>Clinical Comment</b>
<b>Antiarrhythmics</b> Amiodarone, bepridil, flecainide, propafenone, quinidine	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
<b>Antihistamines</b> Astemizole, terfenadine	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Antimycobacterials</b> Rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>Ergot derivatives</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	<b>CONTRAINDICATED</b> 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.
<b>GI motility agents</b> Cisapride	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal products</b> St. John's wort	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
<b>HMG CoA reductase inhibitors</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptics</b> Pimozide	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Sedatives/hypnotics</b> Midazolam, triazolam	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Clinically significant drug-drug interactions of APTIVUS co-administered with 200 mg of ritonavir are summarized in the Table 9 below.

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Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
<b>Nucleoside reverse transcriptase inhibitors:</b>		
Abacavir	↓ Abacavir AUC by approximately 40%	Clinical relevance of reduction in abacavir levels not established. Dose adjustment of abacavir cannot be recommended at this time.
Didanosine (EC)	↓ Didanosine	Clinical relevance of reduction in didanosine levels not established. For optimal absorption, didanosine should be separated from TPV/ritonavir dosing by at least 2 hours.
Zidovudine	↓ Zidovudine AUC by approximately 35%. ZDV glucuronide concentrations were unaltered.	Clinical relevance of reduction in zidovudine levels not established. Dose adjustment of zidovudine cannot be recommended at this time.
<b>Protease inhibitors (co-administered with 200 mg of ritonavir):</b>		
Amprenavir Lopinavir Saquinavir	↓ Amprenavir, ↓ Lopinavir, ↓ Saquinavir	Combining amprenavir, lopinavir or saquinavir with APTIVUS/ritonavir is not recommended. No formal drug interaction data are currently available for the concomitant use of APTIVUS, co-administered with 200 mg of ritonavir, with protease inhibitors other than those listed above.
Other Agents for Opportunistic Infections		
<b>Antifungals:</b>		
Fluconazole	↑ Tipranavir, ↔ Fluconazole	Fluconazole increases TPV concentrations but dose adjustments are not needed.
Itraconazole	↑ Itraconazole (not studied)	Fluconazole doses > 200 mg/day are not recommended.
Ketoconazole	↑ Ketoconazole (not studied)	
Voriconazole	↓ Voriconazole (not studied)	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.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
Other Agents for Opportunistic Infections		
<b>Antimycobacterials:</b>		
Clarithromycin	↑ Tipranavir, ↑ Clarithromycin, ↓ 14-hydroxy-clarithromycin metabolite	No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary.  For patients with renal impairment the following dosage adjustments should be considered: <ul style="list-style-type: none"> <li>• For patients with CL<sub>CR</sub> 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.</li> </ul> For patients with CL <sub>CR</sub> < 30 mL/min the dose of clarithromycin should be decreased by 75%.
Rifabutin	Tipranavir not changed, ↑ Rifabutin ↑ Desacetyl-rifabutin	Single dose study. Dosage reductions of rifabutin by 75% are recommended (e.g. 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.
Other Agents Commonly used		
<b>Calcium Channel Blockers:</b> Diltiazem Felodipine Nifedipine Nisoldipine Verapamil	Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on calcium channel blockers that are dual substrates of CYP 3A and P-gp due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ↑ Diltiazem ↑ Felodipine (CYP 3A)	Caution is warranted and clinical monitoring of patients is recommended.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

	<p>substrate but not P-gp substrate)            ↓ Nifedipine            ↓ Nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate)            ↓ Verapamil</p>	
Despiramine	<p>Combination with TPV/ritonavir not studied            ↑ Despiramine</p>	<p>Dosage reduction and concentration monitoring of despiramine is recommended.</p>
Disulfiram/Metronidazole	<p>Combination with TPV/ritonavir not studied</p>	<p>APTIVUS capsules contain alcohol that can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).</p>
<b>HMG-CoA reductase inhibitors:</b>		<p>Start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors. Concomitant use of APTIVUS, co-administered with 200 mg of ritonavir, with lovastatin or simvastatin is not recommended.</p>
Atorvastatin	<p>↑ Tipranavir, ↑ Atorvastatin            ↓ Hydroxy-atorvastatin metabolites</p>	
<b>Hypoglycemics:</b>	<p>Combination with TPV/ritonavir not studied.</p>	<p>Careful glucose monitoring is warranted.</p>
<p>Glimepiride            Glipizide            Glyburide            Pioglitazone            Repaglinide            Tolbutamide</p>	<p>↓ Glimepiride (CYP 2C9)            ↓ Glipizide (CYP 2C9)            ↓ Glyburide (CYP 2C9)            ↓ Pioglitazone (CYP 2C8 and CYP 3A4)            ↓ Repaglinide (CYP 2C8 and CYP 3A4)            ↓ Tolbutamide (CYP 2C9)</p>	
	<p>The effect of TPV/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.</p>	
<b>Immunosuppressants:</b>	<p>Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp.</p>	<p>More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilized.</p>
<p>Cyclosporine            Sirolimus            Tacrolimus</p>	<p>↓ Cyclosporine            ↓ Sirolimus            ↓ Tacrolimus</p>	
<b>Narcotic analgesics:</b>		

**Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)**

Meperidine	Combinations with TPV/ritonavir not studied ↓ Meperidine, ↑ Normeperidine	Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Methadone	↓ Methadone by 50%	Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.
<b>Oral contraceptives/Estrogens:</b>		Alternative methods of nonhormonal contraception should be used when estrogen based oral contraceptives are co-administered with tipranavir and 200 mg of ritonavir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency. Women using estrogens may have an increased risk of non serious rash.
Ethinyl estradiol	↓ Ethinyl estradiol concentrations by 50%	
<b>PDE5 inhibitors:</b>		Concomitant use of PDE5 inhibitors with tipranavir and ritonavir should be used with caution and in no case should the starting dose of:
Sildenafil	Combinations with TPV/ritonavir not studied. ↑ Sildenafil	<ul style="list-style-type: none"> <li>• sildenafil exceed 25 mg within 48 hours</li> <li>• tadalafil exceed 10 mg every 72 hours</li> <li>• vardenafil exceed 2.5 mg every 72 hours</li> </ul>
Tadalafil	↑ Tadalafil	
Vardenafil	↑ Vardenafil	
<b>Selective Serotonin-Reuptake Inhibitors:</b>		Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of APTIVUS/ritonavir therapy.
Fluoxetine	Combination with TPV/ritonavir not studied.	
Paroxetine	↑ Fluoxetine	
Sertraline	↑ Paroxetine	
	↑ Sertraline	
Warfarin	Combination with TPV/ritonavir not studied. Cannot predict the effect of TPV/ritonavir on S-Warfarin due to conflicting effect of TPV and	Frequent INR (international normalized ratio) monitoring upon initiation of tipranavir/ritonavir therapy.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

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RTV on CYP 2C9

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**INDICATIONS AND USAGE**

**CONTRAINDICATIONS**

**PRECAUTIONS**

**DOSAGE AND ADMINISTRATION**

**General**

The recommended dose of APTIVUS (tipranavir) Capsules is 500 mg (two 250 mg capsules), co-administered with 200 mg of ritonavir [ ] twice daily. APTIVUS Capsules, co-administered with [ ] 200 mg of ritonavir should be taken with food. Bioavailability is increased with a high fat meal.

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## 4. Appendices

### 4.1 Individual Study Review

#### 1182.2

**TITLE:** An open-label exploratory study of tipranavir and ritonavir in combination with one nucleoside reverse transcriptase inhibitor and one non-nucleoside transcriptase inhibitor in multiple protease inhibitor-experienced HIV patients

**OBJECTIVES:** To determine an effective and safe dose of tipranavir in combination with ritonavir on a background of one NRTI and one NNRTI in multiple protease-inhibitor-experienced HIV-1-positive patients.

**SUBJECTS AND STUDY DESIGN:** This was a phase II, randomized, open-label study in HIV-1-positive patients who had failed multiple PI-containing regimens. In the original protocol, the planned study duration was 24 weeks, which was extended to 48 and then to 96 weeks. Eligible patients were given the option of entering Trial 1182.17 and were allowed to continue in the Trial 1182.2 up to Week 112. Patients originally received the hard filled capsule (HFC) formulation of tipranavir and were subsequently switched to the SEDDS formulation in the form of soft elastic capsule (SEC). The HFC dosage regimens of TPV/RTV selected for this study were 1200 mg TPV/100 mg ritonavir BID and 2400 mg TPV/200 mg RTV BID. Dose selection was based on the previous clinical trials of TPV conducted by P&U. When switched to SEDDS formulation, the regimens were 500 mg TPV/100 mg RTV BID and 1000 mg TPV/100 mg RTV BID. The relative bioavailability of SEDDS formulation of tipranavir was about 2- to 3-fold of that of the HFC formulation (Study report U00-3267). The dose of ritonavir was reduced in the high-dose group based on safety concerns. All patients were switched to the SEDDS formulation by their Week 32 visit. Shortly after initiation of the trial, the background regimen was changed from 1 NNRTI plus 1 NRTI to efavirenz plus 1NRTI. The mean duration of exposure to the HFC formulation was 2.5 to 3 months, and to the SEDDS formulation was 15 to 18 months.

The primary efficacy endpoints were change from baseline in HIV-1 RNA concentrations at Weeks 16, 24, 48 and 80, and occurrence of HIV-1 RNA levels below the limit of quantitation. The safety was evaluated by treatment emergent and drug related adverse events, Grade 3 and 4 laboratory abnormalities and serious adverse events.

Total of 41 patients entered the study with 19 in low-dose group of tipranavir and 22 in high-dose group tipranavir. The overall demographic characteristics of 41 subjects were as following: Male (78%) and female (22%); White (68.3%), Black (26.8%) and mixed (4.9%).

**INVESTIGATOR AND STUDY LOCATION:** Multicenter

**FORMULATION:** Tipranavir: 300 mg HFC, 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules.

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples for tipranavir, ritonavir and efavirenz plasma concentrations were collected on Day1 (pre-dose) and at Week 2, 4, 8, 12, 24, and at early discontinuation. The actual sample collection windows were from just after drug administration to 26 hours and 3 to 30 hours after the last administration for TPV/RTV and efavirenz, respectively. For trough concentrations, only TPV/RTV levels that were taken between 8 and 16 hours after last administration were used.

**ASSAY:** Plasma samples were analyzed for TPV, RTV and efavirenz by  $\square$  using respective HPLC/  $\square$  methods. The calibration curve ranged from  $\square$  ng/mL to  $\square$  ng/mL for TPV and  $\square$   $\mu$ g/mL to  $\square$   $\mu$ g/mL for efavirenz.

**PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP ANALYSIS:** The correlation between drug trough levels from Week 2 and 24 and HIV-1 RNA change from baseline to Week 24 was analyzed using log-linear regression method.

**PHARMACOKINETIC RESULTS:**

Table 1. Tipranavir Steady-State Plasma Concentrations from 8 to 16 Hours after Drug Administration for Patients Switched from the HFC Formulation to the SEDDS Formulation

	Study Treatment/Tipranavir Formulation/Tipranavir Plasma Concentration (µM)			
	TPV 2400 mg (HFC)/RTV 200 mg BID to TPV 1000 mg (SEDDS)/RTV 100 mg BID		TPV 1200 mg (HFC)/RTV 100 mg BID to TPV 500 mg (SEDDS)/RTV 100 mg BID	
	HFC	SEDDS	HFC	SEDDS
n	26	15	12	16
Mean	80.20	26.11	31.14	33.24
Std Dev.	66.04	29.38	42.22	32.07
Minimum				
1st Quartile	20.72	10.96	5.36	16.38
Median	73.71	17.27	10.01	21.43
3rd Quartile	124.53	19.83	41.83	34.47
Maximum				

This reflects the total number of samples. An individual patient may contribute more than a single steady-state sample over the 24-week study period for each treatment group and respective formulation.

Figure 1. Tipranavir Steady-State Plasma Concentrations after Drug Administration for Patients Switched from the HFC Formulation to the SEDDS Formulation (The broken line at 20 µM represents 10 times the tipranavir protein-adjusted IC<sub>90</sub> for wild-type HIV.)

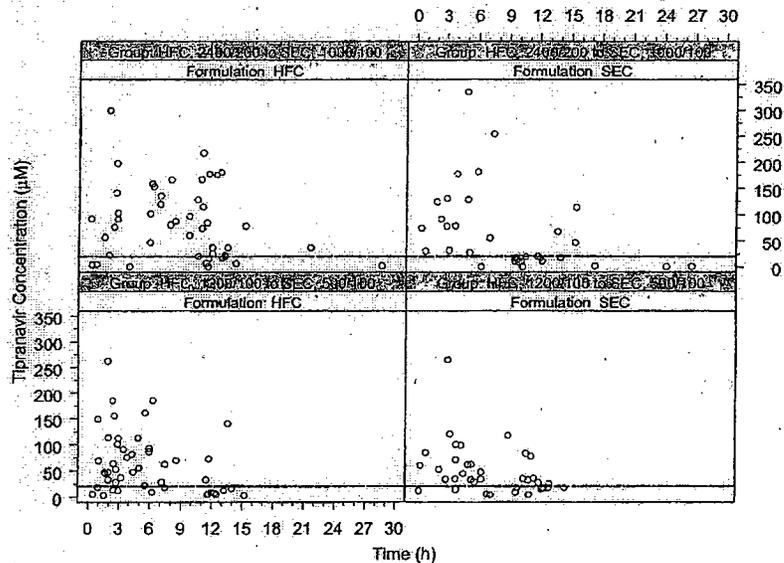
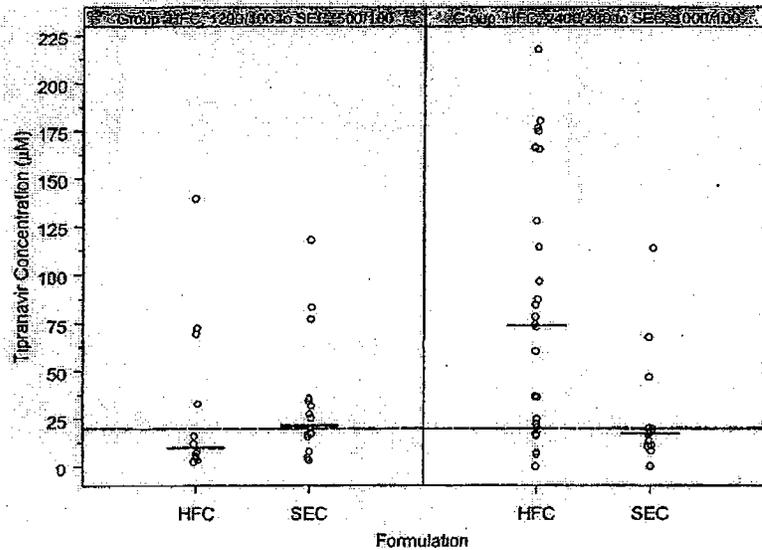
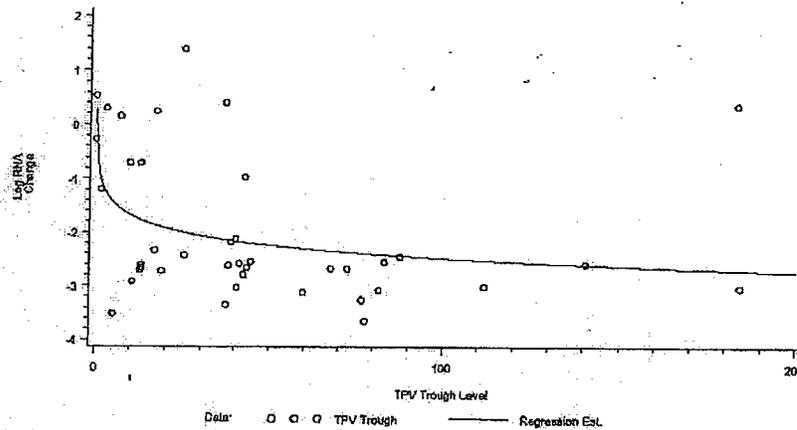


Figure 2. Tipranavir Steady-State Median (Solid Line) and Individual Plasma Concentrations from 8 to 16 Hours after Drug Administration for Patients Switched from the HFC Formulation to the SEDDS Formulation (The broken line at 20  $\mu\text{M}$  represents 10 times the tipranavir protein-adjusted  $\text{IC}_{90}$  for wild-type HIV.)



**PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP ANALYSIS:**

Figure 3. Viral Load Reduction (log<sub>10</sub> copies/mL) at Week 24 (LOCF) Compared with Intra-Individual Geometric Mean Tipranavir Trough Concentration (µM) up to Week 24



**EFFICACY RESULTS:** Tipranavir showed sustained median viral load reduction in both treatment groups over more than 80 weeks. Initial analysis indicated the superiority of the low-dose group at Weeks 16 and 48. However, when adjusted for overall adherence and occurrence of diarrhea  $\geq$  Grade 2, the differences were not maintained, indicating that the difference between treated groups may have been due to a low adherence and a higher incidence of diarrhea  $\geq$  Grade 2 in the high-dose group (See details in Medical Officer's review).

Figure 4. Median Change from Baseline in HIV-1 RNA Values (log10 copies/mL) for the FAS as Treated (LOCF Analysis)

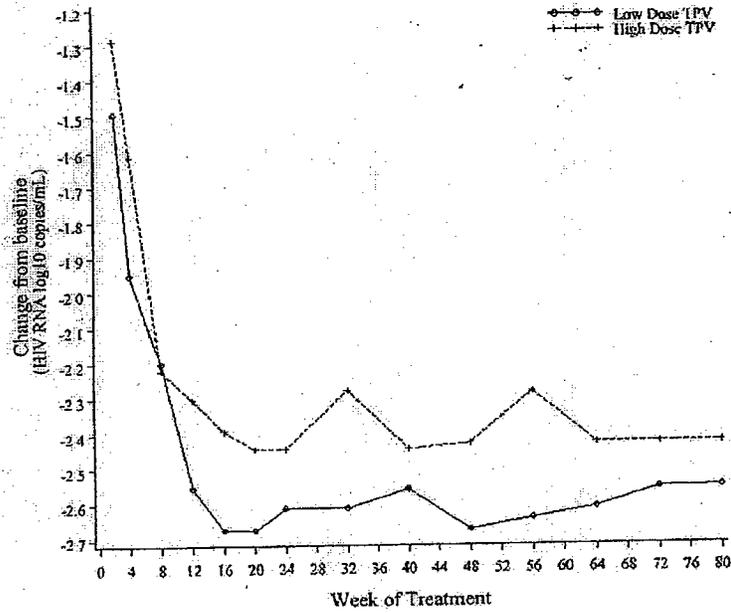
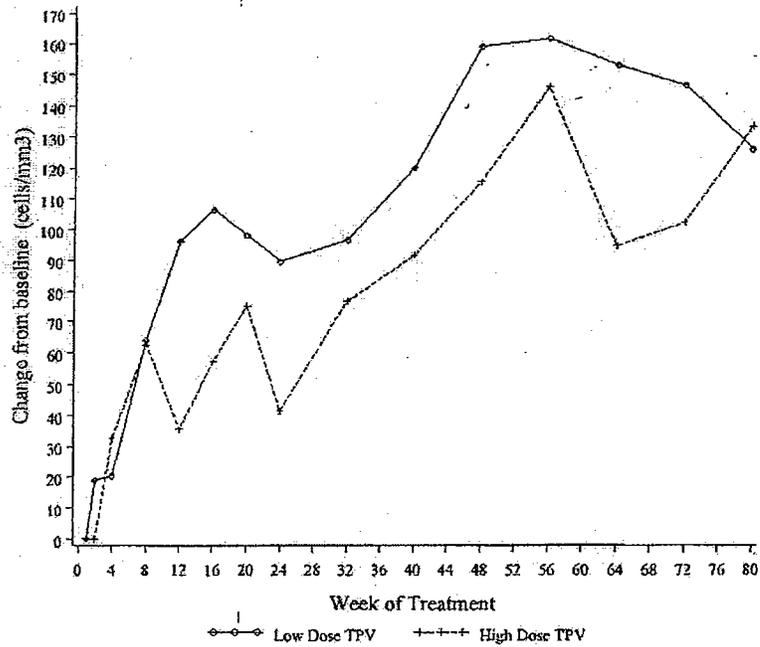


Figure 5. Median Change from Baseline in Absolute CD4+ Counts for the FAS as Treated (LOCF Analysis)



**SAFETY RESULTS:** The majority of the AEs observed during the trial were mild to moderate intensity. No new or unexpected safety concerns were observed compared to previous data. There was no discernable dose-response effect of tipranavir changes observed though higher incidence of diarrhea, nausea and vomiting in the high-dose group (See details in Medical Officer's review).

**CONCLUSIONS AND DISCUSSION:**

Only about 50% of the plasma samples for trough level determination were taken within the acceptable 8- and 16-hour time window after tipranavir administration. No definitive conclusions regarding the relationships tipranavir trough levels and pharmacodynamic parameters, such as changes in HIV-1 RNA values can be made. Based on the quality of the pharmacokinetic data and limited number of doses tested in the current study, further dose-finding studies were needed to select dose(s) for the phase III trial(s).

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#### 1182.4

**TITLE:** An open-label, randomized study comparing therapy (tipranavir and ritonavir vs. saquinavir and ritonavir) used with two nucleoside reverse transcriptase inhibitors in single protease inhibitor-experienced HIV patients

**OBJECTIVES:** To evaluate the efficacy and safety of two different doses of tipranavir in combination with ritonavir compared with a standard dual PI combination of saquinavir and ritonavir and to evaluate the dose response of two different doses of tipranavir in combination with ritonavir for efficacy and safety

**SUBJECTS AND STUDY DESIGN:** This was a phase II, randomized, open-label study in adult HIV-1-positive patients who had failed a single PI-containing regimen. Patients were randomly assigned to receive TPV 500 mg/RTV 100 mg BID, TPV 1250 mg/RTV 100 mg BID, or SQV 400 mg/RTV 400 mg BID used with two nucleoside reverse transcriptase inhibitors. Patients were treated for 24 weeks followed by a 24-week extension phase. Then eligible patients rolled over to Trial 1182.17.

The primary efficacy endpoints were change from baseline in HIV-1 RNA concentrations at the specified study visits through Week 24, and occurrence of HIV-1 RNA levels below the limit of quantitation. The safety was evaluated by treatment emergent and drug related adverse events, Grade 3 and 4 laboratory abnormalities and serious adverse events.

Total of 79 patients entered the study with 25 in low-dose group of tipranavir, 25 in high-dose group tipranavir and 29 in saquinavir group. The overall demographic characteristics of 79 subjects were as following: Male (78.5%) and female (21.5%); White (49.4%), Black (40.5%) and mixed and unknown (10.1%).

**INVESTIGATOR AND STUDY LOCATION:** Multicenter

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Ritonavir: 100 mg soft elastic capsules. Saquinavir SGCs, 200 mg

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples for tipranavir and ritonavir plasma concentrations were collected on Day 1 (pre-dose) and at Week 2, 4, 8, 12, 24. For trough concentrations, only TPV/RTV levels that were taken between 8 and 16 hours after last administration were used for PK or PK/PD analysis.

**ASSAY:** Plasma samples were analyzed for TPV and RTV by LC-MS/MS using respective HPLC-MS/MS methods. The calibration curve ranged from 1 ng/mL to 100 ng/mL for TPV.

Figure 3. Ritonavir Steady-State Plasma Concentrations for Patients Receiving TPV 500 mg/RTV 100 mg and TPV 1250 mg/RTV 100 mg

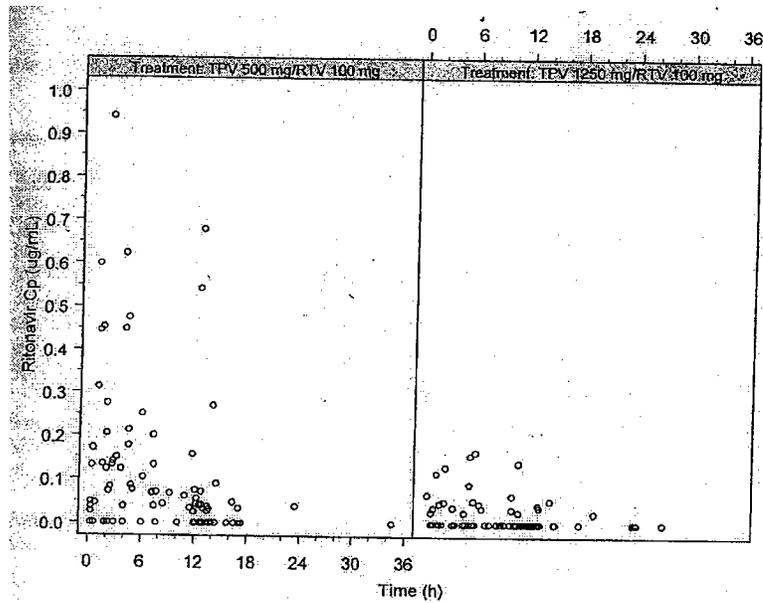


Table 1. Summary of Tipranavir Steady-State Trough Plasma Concentrations Collected between 8 and 16 Hours Postdose for Patients Receiving TPV 500 mg/RTV 100 mg and TPV 1250 mg/RTV 100 mg

Summary Statistic	Tipranavir Cp (uM)	
	TPV 500 mg/RTV 100 mg	TPV 1250 mg/RTV 100 mg
Minimum	BLQ	BLQ
1st Quartile	4.14	2.64
Mean	17.58	32.92
Median	6.67	13.11
3rd Quartile	20.49	52.31
Maximum	[	]
n <sup>1</sup>	40	43
Std. Dev.	26.25	43.05
Sample Geometric Mean	8.72	11.32
n <sup>1</sup>	38	40
Patient Geometric Mean	10.43	9.65
n <sup>2</sup>	15	17

<sup>1</sup> Represents all samples in the dose group.

<sup>2</sup> Represents the geometric mean of the patient geometric means.

Table 2. Summary of Ritonavir Steady-State Trough Plasma Concentrations Collected between 8 and 16 Hours Postdose for Patients Receiving TPV 500 mg/RTV 100 mg and TPV 1250 mg/RTV 100 mg

Summary Statistic	Ritonavir C <sub>p</sub> (ug/mL)	
	TPV 500 mg/RTV 100 mg	TPV 1250 mg/RTV 100 mg
Minimum	BLQ	BLQ
1st Quartile	BLQ	BLQ
Mean	0.064	0.010
Median	0.026	BLQ
3rd Quartile	0.052	BLQ
Maximum	0.141	0.026
n <sup>1</sup>	38	41
Std Dev.	0.141	0.026
Sample Geometric Mean	0.065	0.050
n <sup>1</sup>	21	7
Patient Geometric Mean	0.073	0.054
n <sup>2</sup>	10	5

<sup>1</sup>Represents all samples in the dose group.

<sup>2</sup>Represents the geometric mean of the patient geometric means.

**EFFICACY RESULTS:** All three treatments in this trial, TPV 500 mg/RTV 100 mg BID, TPV 1250 mg/RTV 100 mg BID, and SQV 400 mg/RTV 400 mg BID were effective in producing a decline in plasma HIV-1 RNA concentrations and rates of response were similar (See detail analysis in Medical Officer's review).

**SAFETY RESULTS:** The overall safety profile was similar to that observed in previous tipranavir trials (See details in Medical Officer's review).

**CONCLUSIONS AND DISCUSSION:** Overall, the tipranavir and ritonavir plasma concentrations over the 12-hour dosing interval were consistent with the concentration range observed in other TPV/RTV studies. However, ritonavir concentrations in TPV/RTV 1250mg/100 mg group were much lower than those in TPV/RTV 500 mg/100 mg group. This could be attributed to CYP3A induction by the higher dose of TPV, which resulted in increased metabolism of RTV, ultimately resulted in decreased RTV concentrations.

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## 1182.5

**TITLE:** An open-label, parallel group, multiple-dose investigation of the pharmacokinetics of tipranavir soft elastic capsules SEDDS and ritonavir soft gel capsules and their effects on cytochrome P-450 3A4 activity in normal healthy volunteers

**OBJECTIVES:** To establish the tipranavir-ritonavir steady-state dose-exposure relationships when administered on a twice a day (bid) dosing regimen, to determine the effects of tipranavir and ritonavir on cytochrome P-450 3A4 activity, and to establish the dependency of the TPV M1 metabolite on RTV co-administration

**SUBJECTS AND STUDY DESIGN:** This was an open-label, parallel group and multiple-dose design study. 113 subjects entered the study and 95 subjects completed the study (93 subjects in the PK analysis). Briefly, equal number of subjects were randomly allocated to one of eight TPV/RTV dose arms (250 mg, 500 mg, 750 mg, 1000 mg and 1250 mg TPV; 100 or 200 mg RTV). The subjects were to take TPV alone for the first 10 days and then RTV was added at either 100 mg or 200 mg for additional 21 days.

Group #	Days 1-10	Days 11-32
	TPV alone (mg, bid)	TPV/RTV (mg/mg, bid)
1	250	250/200
2	500	500/100
3	500	500/200
4	750	750/100
5	750	750/200
6	1000	1000/100
7	1000	1000/200
8	1250	1250/100

The overall demographic characteristics of subjects were as following: Male (39.8%) and female (60.2%); White (83.2%) and Black (16.8%).

During non-confined treatment periods, subjects were instructed to take medication no less than 1 hour after a light snack; otherwise, medication was taken at least 1 hour before or 2.5 hours after regular meals.

### INVESTIGATOR AND STUDY LOCATION: [

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. The ERMBT was provided by [ ] form of a kit which contained all the materials required to conduct the test including pharmaceutical grade [ ] erythromycin for intravenous administration.

**PHARMACOKINETIC SAMPLE COLLECTION:** Intensive PK sampling was collected on Study Days 11, 18, 25 and 32 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post dose. Trough level samples were taken on Days 8 and 9. ERMBT was conducted on Day 0 (baseline) and on Days 11, 18, 25 and 32.

**ASSAY:** Plasma samples were analyzed for TPV/RTV by [ ] using a validated high performance liquid chromatography [ ] method. The calibration curve ranged from — ng/mL to — ng/mL. There was no synthetic analytical standard for TPV M1 metabolite. Therefore TPV M1 metabolite concentrations were reported as "pseudo-concentrations" and assumed that a 1:1 relationship existed between the [ ] measurement of TPV and TPV M1 metabolite.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental PK analysis was conducted using WinNonlin (v.3.1, Pharsight). Steady-state pharmacokinetic parameters including  $C_{max\ ss}$ ,  $T_{max\ ss}$ ,  $C_{min\ ss}$ ,  $AUC_{0-12h}$  were calculated for TPV at Study Day 11 and for both TPV and RTV at Study Days 8, 25 and 32. Regression analyses were used to predict the TPV exposure ( $C_{max\ ss}$ ,  $C_{min\ ss}$  and  $AUC_{0-12h}$ ) as functions of the TPV dose in combination with either 100 mg or 200 mg ritonavir. For the ERMBT, the primary variable of interest was the measurement of expired  $^{14}CO_2$ . TPV M1 plasma concentrations were also determined.

**PHARMACOKINETIC RESULTS:**

Table 1. Geometric mean maximum plasma tipranavir concentrations ( $\mu M$ ) on Days 11, 18, 25 and 32

Treatment (mg bid)		Tipranavir Geometric Mean $C_{max}$ ( $\mu M$ ) for Subjects by Study Day			
Ritonavir	Tipranavir	11*	18	25	32
100	500	28.21	147.40	111.07	130.09
	750	36.97	63.52	71.05	110.07
	1000	62.52	214.26	246.02	232.71
	1250	69.22	174.32	217.02	175.39
200	250	13.73	75.48	73.13	58.47
	500	33.18	153.51	123.39	129.20
	750	52.24	164.41	151.57	168.82
	1000	56.09	216.21	189.90	135.78

\*Prior to administration of RTV bid

Table 2. Geometric mean time to maximum plasma tipranavir concentrations (hr) on Days 11, 18, 25 and 32

Treatment (mg bid)		Tipranavir Median $T_{max}$ (hr) for Subjects by Study Day			
Ritonavir	Tipranavir	11*	18	25	32
100	500	2.00	2.00	2.00	2.00
	750	1.50	2.00	2.00	2.00
	1000	2.00	2.00	2.50	2.50
	1250	2.00	2.00	3.00	2.50
200	250	1.25	2.00	2.00	2.00
	500	1.75	2.00	2.00	3.00
	750	2.00	2.00	2.50	2.00
	1000	2.00	2.50	3.00	2.50

\*Prior to administration of RTV bid

Table 3. Geometric mean morning and evening plasma tipranavir trough concentrations ( $\mu M$ ) on Days 11, 18, 25 and 32

Treatment (mg bid)		Tipranavir Geometric Mean Morning (AM) $C_{min}$ ( $\mu M$ ) for Subjects by Study Day					
Ritonavir	Tipranavir	8*	9*	11*	18	25	32
100	500	0.99	0.58	0.54	34.25	26.69	25.30
	750	1.49	0.57	0.74	19.37	13.48	38.10
	1000	1.40	0.84	1.23	57.77	38.31	57.24
	1250	4.47	1.43	1.70	32.65	44.62	33.57
200	250	0.44	0.25	0.24	21.89	18.72	11.73
	500	0.68	0.60	0.71	27.90	21.55	20.47
	750	0.87	0.46	0.54	60.53	43.11	51.93
	1000	1.22	0.89	0.77	70.20	57.82	42.36

\*Prior to administration of RTV bid

Treatment (mg bid)		Tipranavir Geometric Mean Evening (PM) C <sub>min</sub> (µM) for Subjects by Study Day			
Ritonavir	Tipranavir	11*	18	25	32
100	500	0.47	25.95	12.54	17.96
	750	0.63	19.34	11.91	14.01
	1000	1.42	39.09	42.88	58.22
	1250	1.51	34.46	47.96	25.23
200	250	0.22	16.61	14.66	12.88
	500	0.60	37.27	29.09	33.74
	750	0.70	37.50	33.02	46.32
	1000	0.97	78.03	49.68	30.26

\*Prior to administration of RTV bid

Table 4. Geometric mean tipranavir area under the plasma concentration-time curves (hr·µM) on Days 11, 18, 25 and 32

Treatment (mg bid)		Tipranavir Geometric Mean AUC (hr·µM) for Subjects by Study Day			
Ritonavir	Tipranavir	11*	18	25	32
100	500	71.2	939.3	656.0	755.4
	750	105.6	352.3	425.9	635.9
	1000	218.5	1333.7	1662.5	1583.7
	1250	238.1	1192.1	1483.0	1083.3
200	250	28.3	481.7	468.9	375.7
	500	97.0	1012.0	855.5	933.5
	750	139.1	1123.4	998.6	1235.3
	1000	173.1	1727.5	1370.5	963.0

\*Prior to administration of RTV bid

Table 5. Tipranavir harmonic mean half-lives (hr) on Days 11, 18, 25 and 32

Treatment (mg bid)		Tipranavir Harmonic Mean Half-lives (hours) for Subjects by Study Day			
Ritonavir	Tipranavir	11*	18	25	32
100	500	2.9	3.4	2.9	3.4
	750	2.2	4.2	3.6	3.2
	1000	2.2	3.7	2.8	4.1
	1250	2.1	3.3	3.9	3.3
200	250	2.9	4.4	4.2	4.9
	500	2.2	4.6	4.1	4.8
	750	2.5	4.5	4.3	4.6
	1000	2.6	5.2	4.2	3.7

\*Prior to administration of RTV bid

Table 6. Geometric mean maximum plasma ritonavir concentrations (µg/mL) on Days 18, 25 and 32

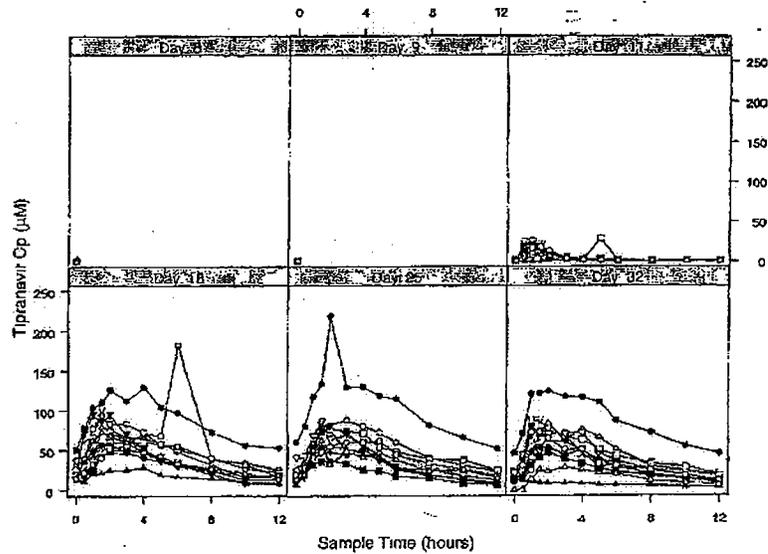
Treatment (mg bid)		Ritonavir Geometric Mean C <sub>max</sub> (µg/mL)		
Ritonavir	Tipranavir	18	25	32
100	500	1.19	0.91	0.78
	750	0.70	0.50	0.66
	1000	0.71	0.71	0.98
	1250	0.45	0.79	0.60
200	250	3.19	3.69	2.64
	500	2.19	2.55	2.36
	750	2.43	2.05	3.03
	1000	2.53	2.12	1.39

Table 7. Erythromycin breath test: geometric mean % <sup>14</sup>CO<sub>2</sub> metabolized per hour on Days 0, 11, 18, 25 and 32

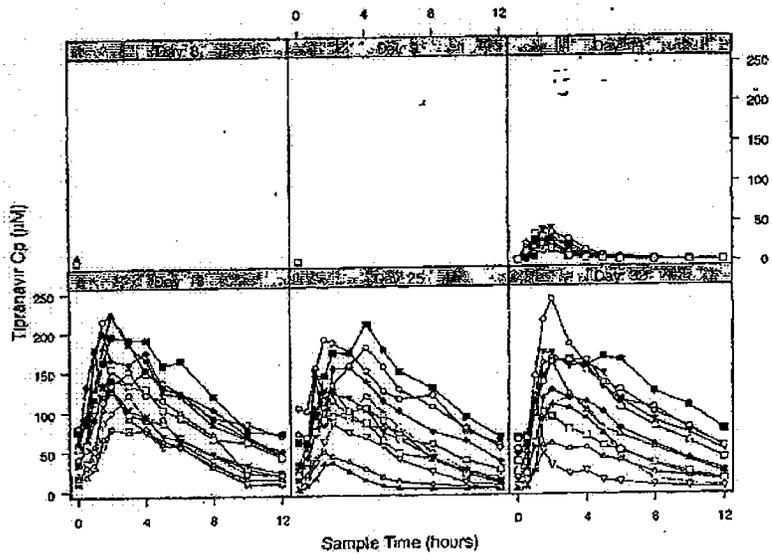
Treatment (mg bid)		Study Days				
Ritonavir	Tipranavir	0	11	18	25	32
100	500	2.02	3.46	0.20	0.27	0.21
	750	2.68	3.07	0.59	0.62	0.41
	1000	2.29	3.14	0.38	0.23	0.25
	1250	2.08	2.49	0.27	0.28	0.26
200	250	2.45	2.95	0.11	0.13	0.12
	500	2.68	3.13	0.15	0.12	0.13
	750	2.41	3.08	0.20	0.18	0.16
	1000	1.90	3.03	0.15	0.15	0.18

Figure 1. Plasma tipranavir concentration-time curves over the course of the study for all TPV/RTV combinations (bid) studied (Ritonavir was added to the dose regimen on Day 11)

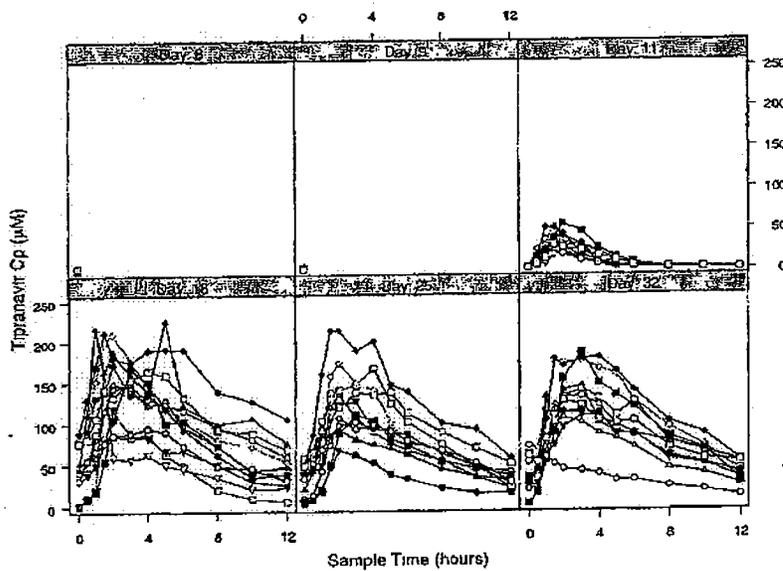
TPV/RTV dose (mg bid): 250/200



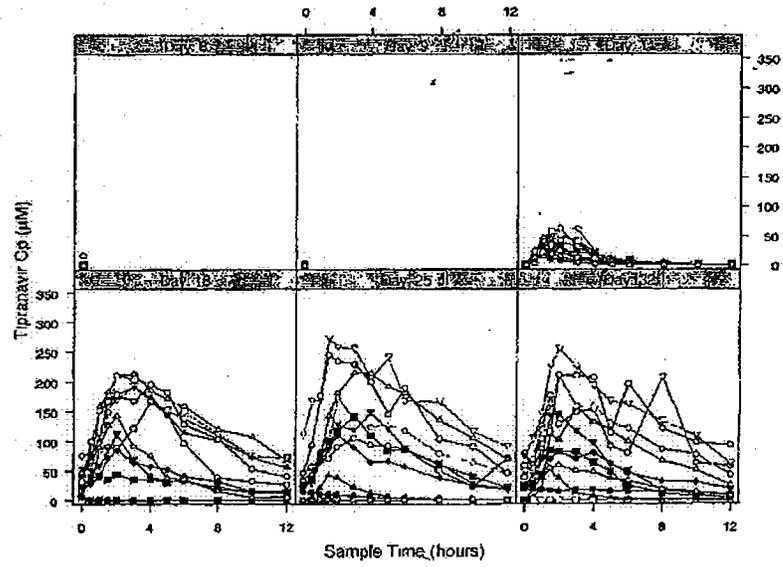
TPV/RTV dose (mg bid): 500/100



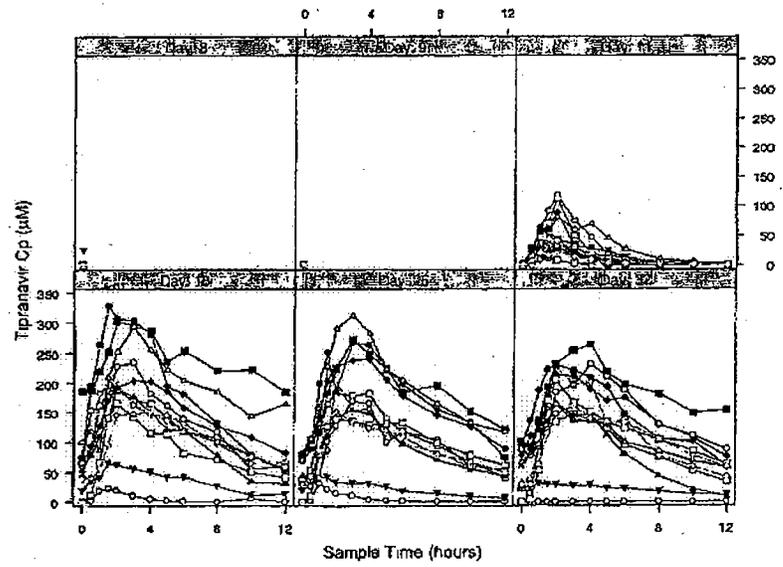
TPV/RTV dose (mg bid): 500/200



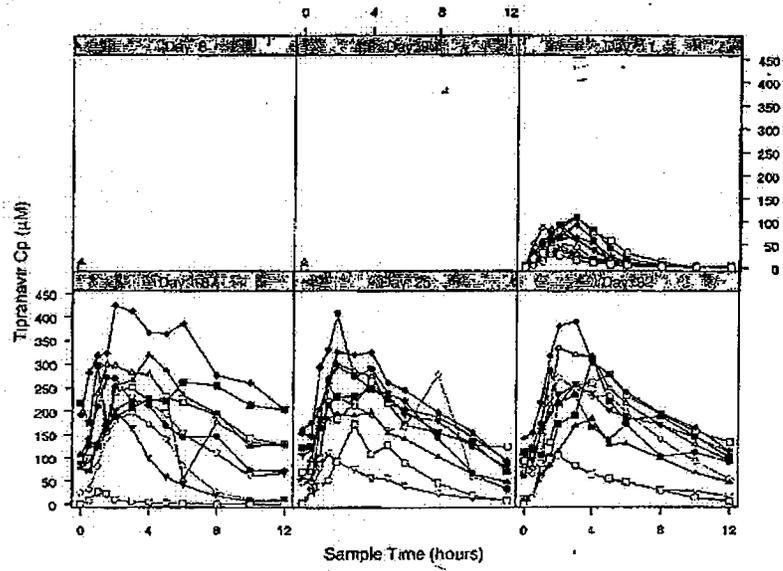
TPV/RTV dose (mg bid): 750/100



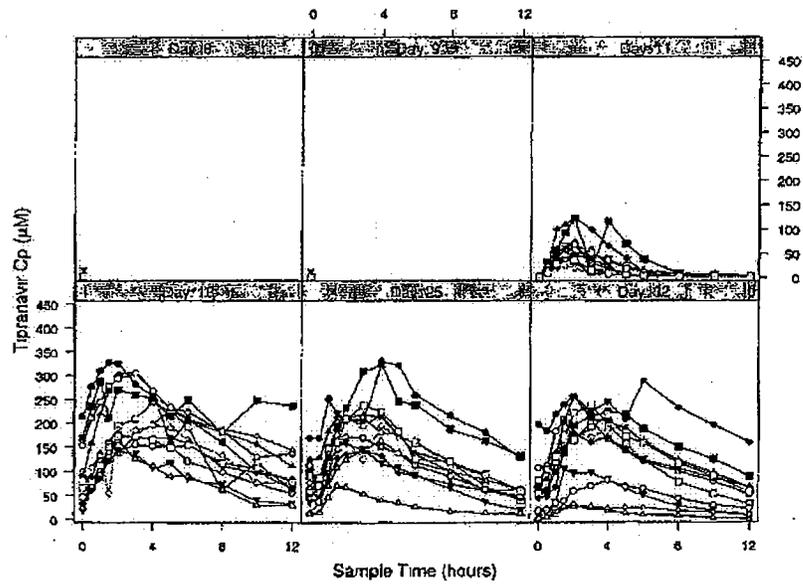
TPV/RTV dose (mg bid): 750/200



TPV/RTV dose (mg bid): 1000/100



TPV/RTV dose (mg bid): 1000/200



TPV/RTV dose (mg bid): 1250/100

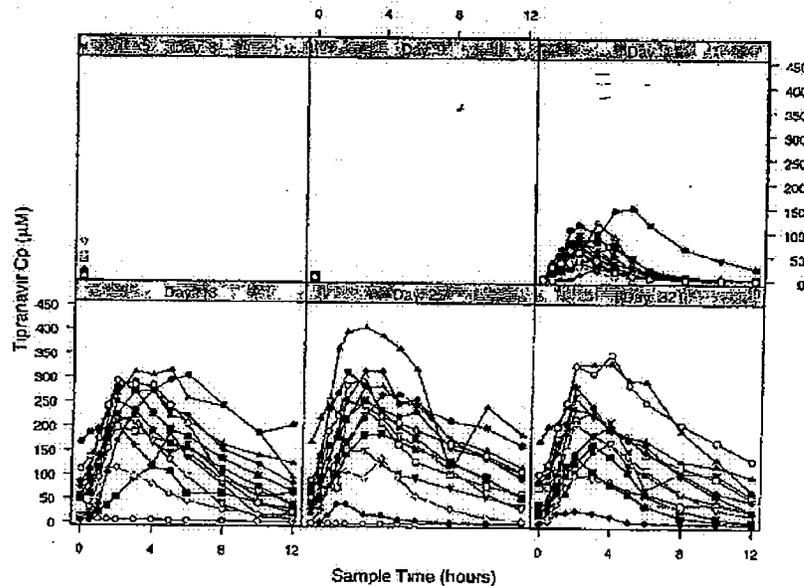
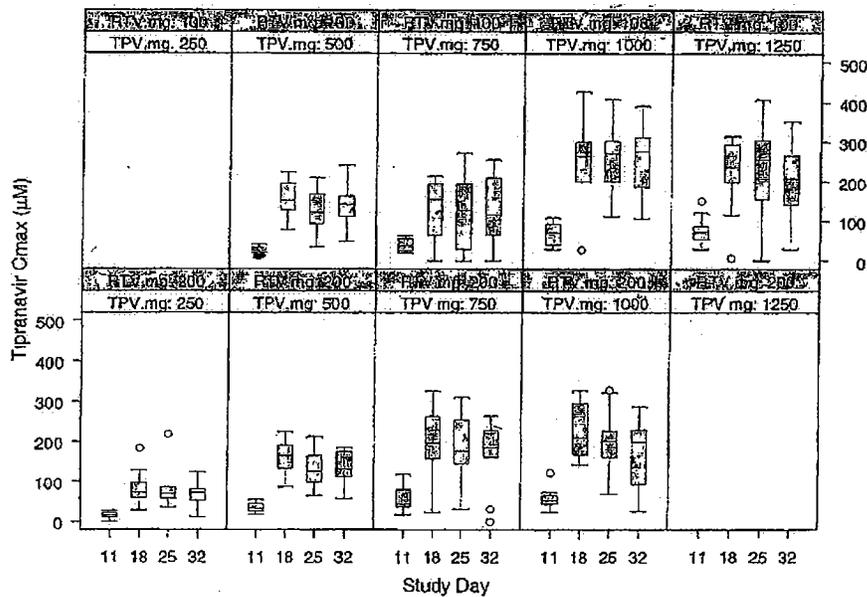


Figure 2. Maximum plasma tipranavir concentrations ( $\mu\text{M}$ ) over the course of the study for the dose combination of TPV/RTV



Box plot representation of the data where the box represents the 25<sup>th</sup> through 75<sup>th</sup> percentile, the bar inside the box is the median, and the whiskers extend to 1.5 interquartile ranges

Figure 3. Area under the plasma tipranavir concentration-time curves (hr- $\mu$ M) over the course of the study for the dose combination of TPV/RTV

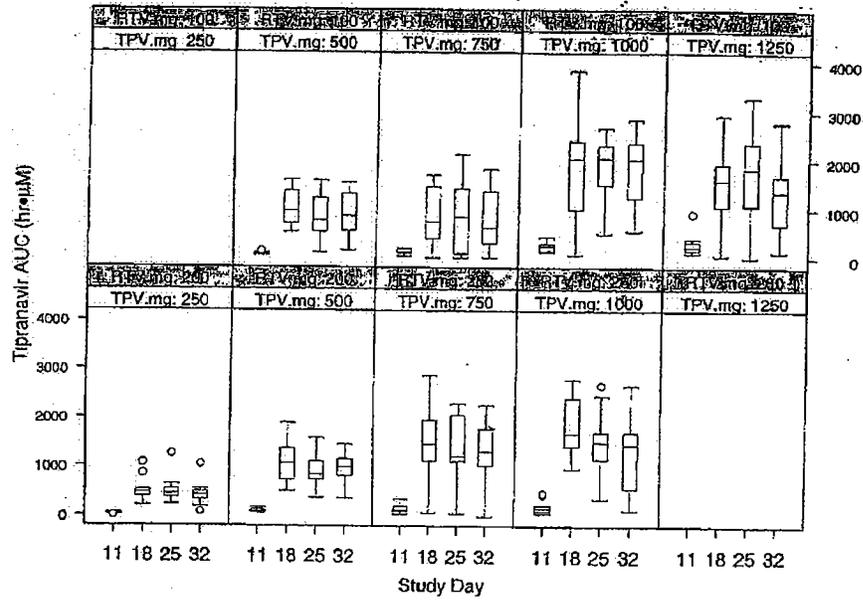


Figure 4. Morning trough plasma tipranavir concentrations ( $\mu$ M) over the course of the study for the dose combination of TPV/RTV

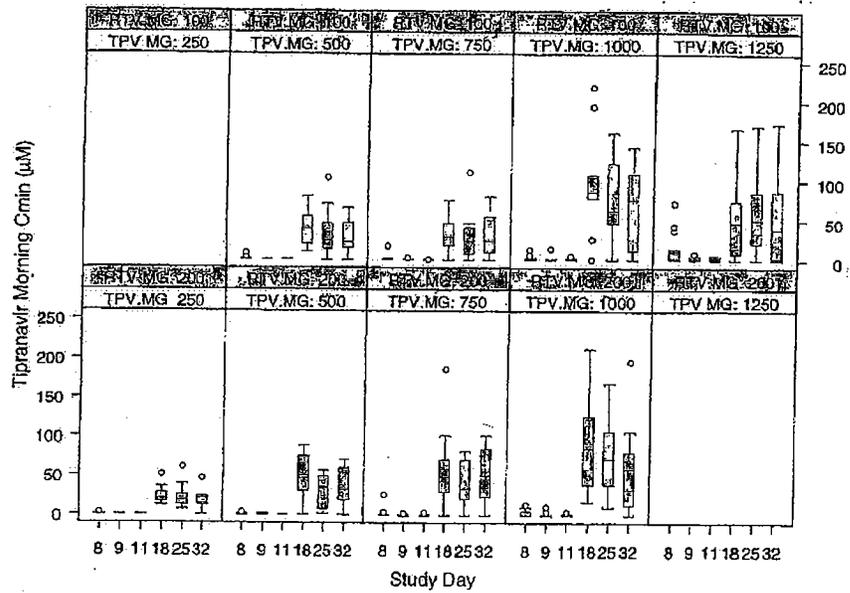


Figure 5. Maximum plasma ritonavir concentrations ( $\mu\text{g/mL}$ ) over the course of the study for the dose combination of TPV/RTV

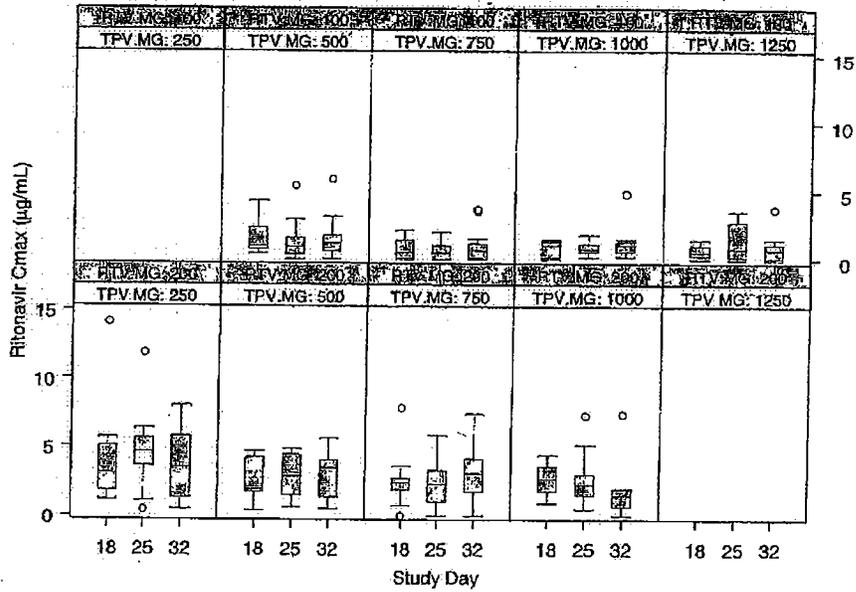


Figure 6. Erythromycin breath test results over the course of the study for the dose combination of TPV/RTV

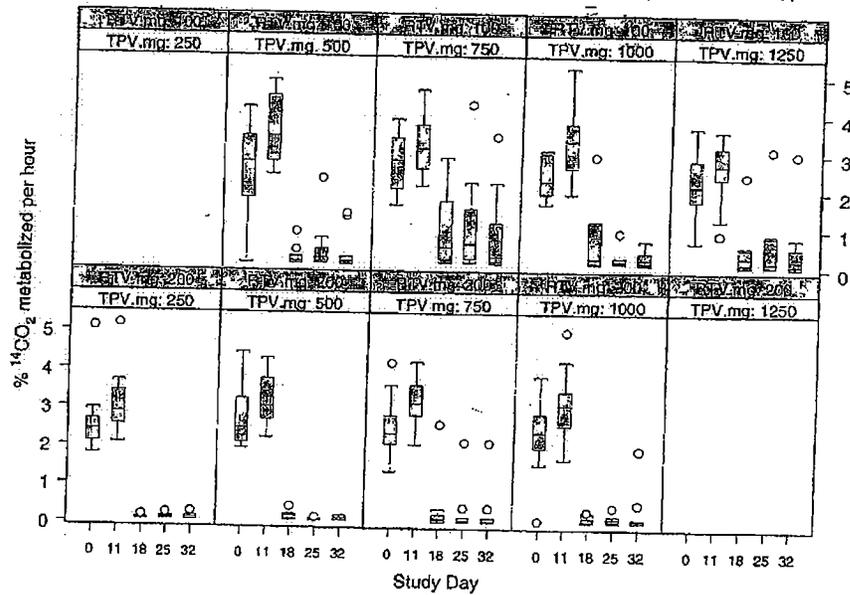
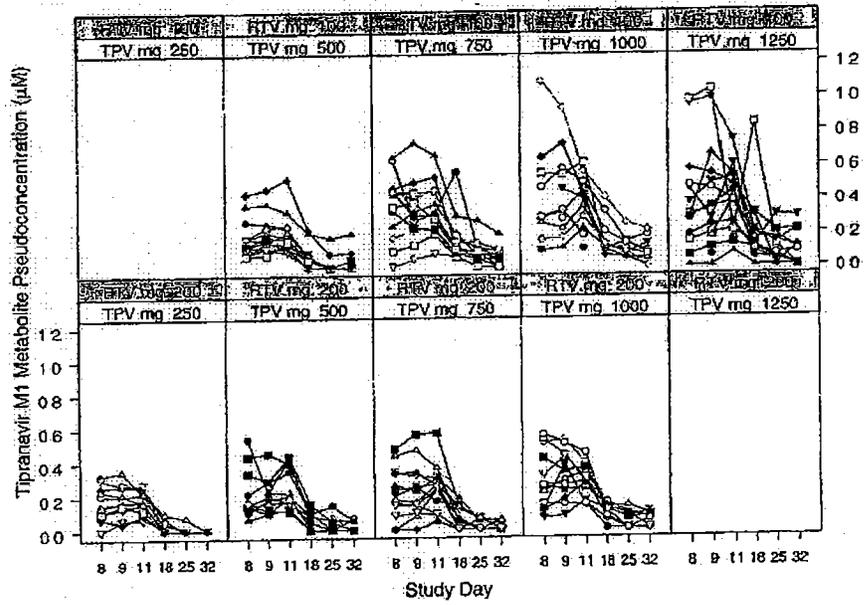


Figure 7. Mean morning trough plasma tipranavir M1 metabolite concentrations ( $\mu\text{M}$ ) over the course of the study for the dose combination of TPV/RTV



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Figure 8. Regression analysis of plasma tipranavir  $C_{min}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)

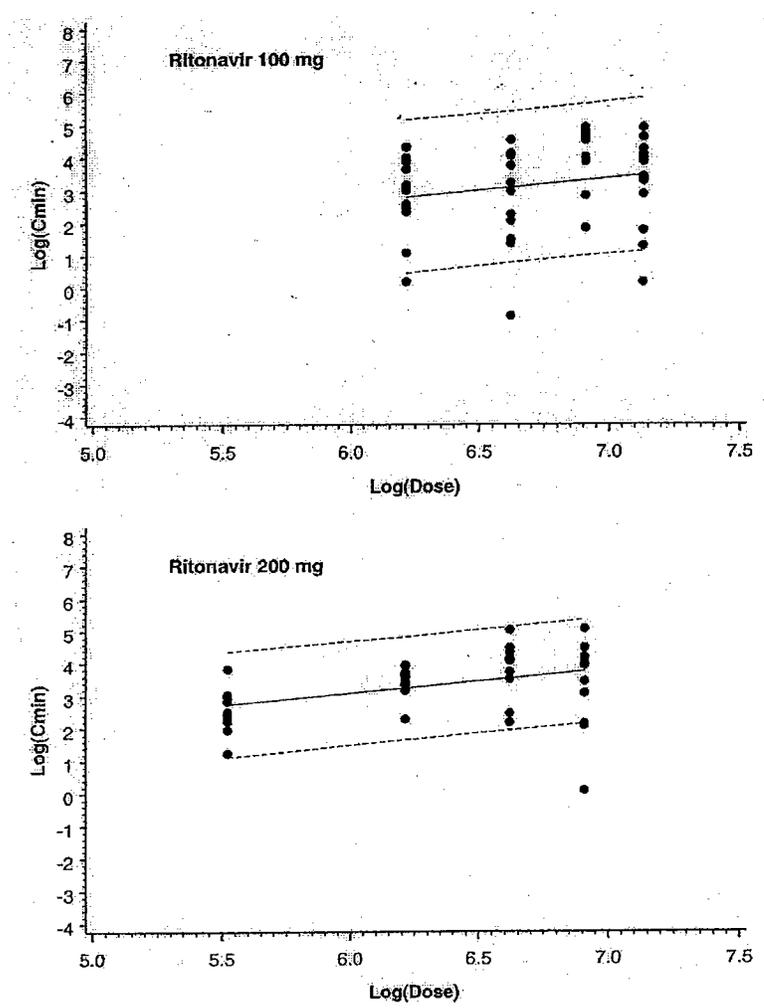


Figure 9. Regression analysis of plasma tipranavir  $C_{max}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)

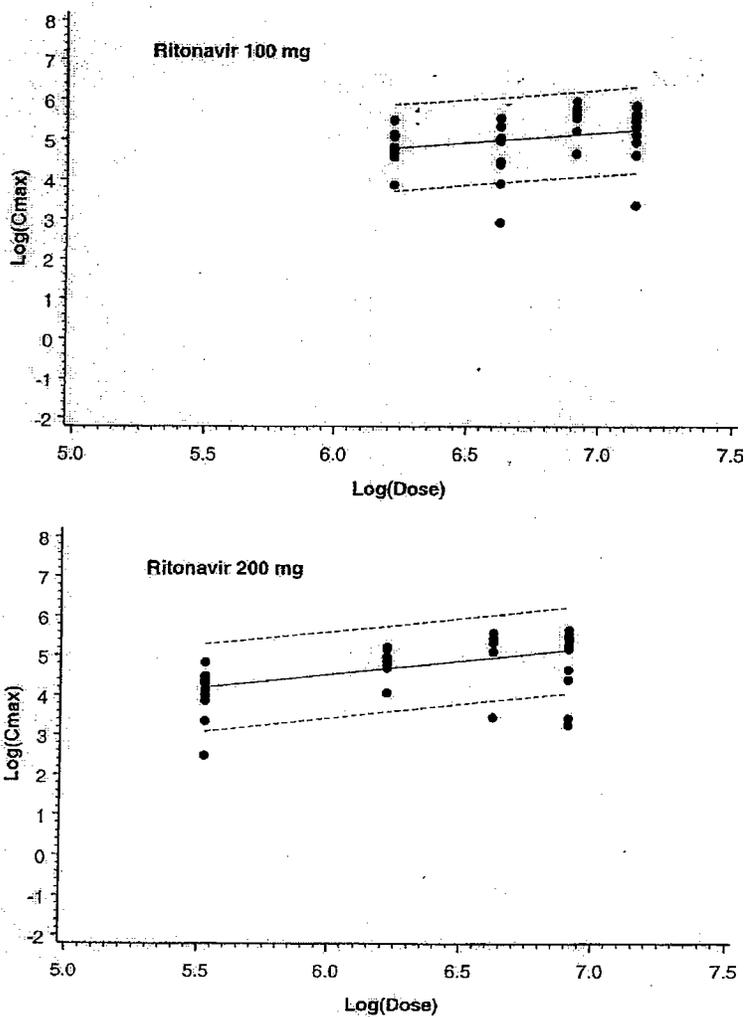
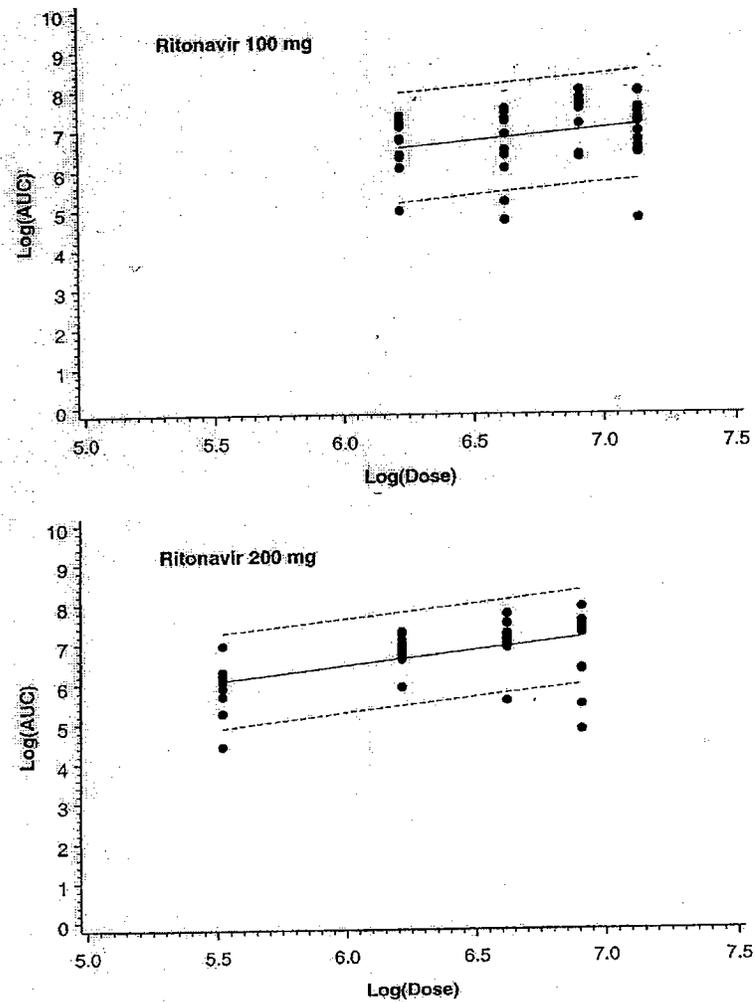


Figure 10. Regression analysis of plasma tipranavir  $AUC_{12h}$  vs. tipranavir dose after 3 weeks of ritonavir co-administration (Solid line: geometric mean; broken lines: 90% CI)



#### SAFETY RESULTS:

There was no difference in the toxicity profiles associated with TPV alone or TPV plus RTV in the study. Major adverse events were GI disturbances (91%), headache (30%) and dizziness (17%). Of the GI adverse events diarrhea (75%), nausea (53%), and vomiting (41%) were the most often reported. There were no dose limiting toxicities and no serious adverse events during this 32-day trial (See details in Medical Officer's review).

#### CONCLUSIONS AND DISCUSSION:

This study demonstrated that co-administration of TPV with low doses of RTV (100 mg or 200 mg) bid at steady-state resulted in the increase of the mean plasma TPV  $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$  by 19- to 99-fold, 3- to 4-fold, and 4- to 13-fold, respectively, at TPV/RTV doses studied compared to TPV given alone. TPV steady-state was reached in about 7 to 10 days. TPV mean half-lives ranged from 2.6 hours for the TPV alone subjects, 3.6 to 3.9 hours for the 100 mg RTV subjects and 4.5 to 5.2 hours for the 200 mg RTV subjects.

For example,  $C_{min}$  levels of were about 0.6  $\mu$ M following administration of 500 mg TPV alone. However, the dose combination of 500 mg TPV/200 mg RTV achieved  $C_{min}$  levels of about 20  $\mu$ M, 10 times the protein-adjusted  $IC_{90}$  for HIV PI resistant strains. The regression analysis also suggested that linear relationships in TPV exposure ( $C_{min}$ ,  $C_{max}$  and  $AUC_{0-12h}$ ) verses doses administered in combination with either 100 mg or 200 mg ritonavir. The variability of TPV exposure was high even in the presence of ritonavir co-administration. However, the variability of TPV exposure in combination with 200 mg ritonavir appeared less than that of tipranavir with 100 mg ritonavir.

The ERMBT results showed that the hepatic CYP3A activity was increased following 11 days repeated dosing of TPV and inhibited by co-administration of TPV/RTV. It suggested that TPV alone was a hepatic CYP3A inducer and the net effect of TPV/RTV combinations was inhibition of hepatic CYP3A activity. It was further supported by the levels of M1 metabolite formation with and without ritonavir.

This study suggested that targeted TPV plasma levels could be achieved with bid dosing regimens co-administered with low doses of ritonavir 100 mg or 200 mg, bid.

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**TITLE:** An open-label multinational study of the effects of three dose pairs of tipranavir/ritonavir (b.i.d.) on the pharmacokinetic characteristics of protocol-defined, baseline, triple drug nucleoside and non-nucleoside reverse transcriptase inhibitor therapy in HIV-1 infected subjects

**OBJECTIVES:** The primary objective was to determine the effects of three tipranavir and ritonavir dose combinations (TPV/r 1250/100 mg, 750/100 mg and 250/200 mg, b.i.d.) on the steady-state pharmacokinetics of abacavir, didanosine, efavirenz, lamivudine, nevirapine, stavudine and zidovudine at approved doses. The secondary objective was to assess the safety of three TPV/RTV combinations when used with protocol-defined antiretroviral agents.

**SUBJECTS AND STUDY DESIGN:** This was an open-label study conducted in HIV-positive adult males and females who had low, stable HIV-1 RNA viral levels ( $\leq 20,000$  copies/mL) and were on a three-drug combination of NRTIs and NNRTIs for at least 12 weeks. 208 patients who entered the study were sequentially allocated to one of three TPV/r dose-pair treatment groups. The three combinations of TPV/r were investigated consecutively in the following order: TPV/r 1250mg/100mg b.i.d., TPV/r 750mg/100 mg b.i.d. and TPV/r 250mg/200mg b.i.d. Enrolment was stratified according to baseline NRTIs and NNRTIs that patients were taking. Numbers of treated patients by TPV/r treatment and baseline ARV medication were listed below.

Baseline Therapy	Number of Patients			Total
	TPV 1250 mg/ RTV 100 mg	TPV 750 mg/ RTV 100 mg	TPV 250 mg/ RTV 200 mg	
<b>Number treated</b>	<b>58</b>	<b>63<sup>1</sup></b>	<b>87</b>	<b>208</b>
ZDV/3TC/EFV	8	10	11	29
ZDV/3TC/NVP	7	7	12	26
d4T/3TC/EFV	5	5	6	16
d4T/3TC/NVP	9	13	13	35
d4T/ddI/EFV	7	5	8	20
d4T/ddI/NVP	5	6	6	17
ZDV/3TC/ABC	17	16	31	64

<sup>1</sup> Patient #634 received a baseline ARV therapy (3TC/EFV/ABC) not in the approved list (see Section 9.4.1) and was therefore not included in this table.

The first part of the study was a 22-day pharmacokinetic study and second part was an optional safety extension. Patients who achieved viral load levels of  $<400$  copies/mL or a viral reduction of  $>0.5$  log from baseline at Day 28 were permitted to continue treatment for an additional 140 days.

The overall demographic characteristics of subjects were as following: Male (84.1%) and female (15.9%); White (78.8%), Black (20.7%) and Asian (0.5%).

On pharmacokinetic sample collections days, a light snack was consumed if needed to avoid nausea. On other days, medication could have been taken with or without food. Didanosine had to be taken on an empty stomach. Patients taking didanosine received a meal no less than two hours before and after didanosine dosing.

The doses for NNRTIs and NRTIs used in the study were abacavir (300 mg b.i.d.), didanosine (EC formulation, 400 mg q.d. for subjects with body weight  $\geq 60$  kg, 250 mg q.d. for subjects with body weight  $< 60$  kg), efavirenz (600 mg q.d.), lamivudine (150 mg b.i.d.), nevirapine (200 mg b.i.d.), stavudine (40 mg b.i.d. for subjects with body weight  $\geq 60$  kg, 30 mg b.i.d. for subjects with body weight  $< 60$  kg) and zidovudine (300 mg b.i.d.) and Combivir (ZDV 300 mg +3TC 150 mg b.i.d.).

**INVESTIGATOR AND STUDY LOCATION:** A total of 33 centers from six countries entered patients in this trial

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDSS) formulation. Norvir: 100 mg soft elastic capsules.

**PHARMACOKINETIC SAMPLE COLLECTION:** Intensive PK sampling for NRTIs and NNRTIs was collected on the mornings of Study Days 1 and 22 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post dose with additional 14, 16 and 24 hour sampling for efavirenz. In addition, a morning trough sample was collected on Day 14.

**ASSAY:** Plasma samples were analyzed for TPV/RTV by [ ] using a validated high performance liquid chromatography [ ] method. The calibration curve ranged from [ ] ng/mL to [ ] ng/mL. Plasma samples were analyzed for abacavir, didanosine, efavirenz, lamivudine, nevirapine, stavudine and zidovudine by [ ] using a validated [ ] method. The calibration curve ranged from [ ] µg/mL for abacavir, didanosine, efavirenz, lamivudine, nevirapine, stavudine and zidovudine.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental PK analysis was conducted using WinNonlin (v.3.1, Pharsight). The primary endpoints were  $C_{min ss}$  for NNRTIs at baseline and Day 22 (Day 23 for subjects on efavirenz) and  $AUC_{0-r}$  for NRTIs at baseline and Day 22.

**PHARMACOKINETIC RESULTS:**

Table 1. Descriptive statistics for abacavir  $AUC_{0-12}$  values

TPV/RTV Dose	Without or With TPV/RTV	N	AUC (h·µg/mL)					
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio
TPV 1250 mg/ RTV 100 mg	Without	11	5.64			5.19	46.59	
	With	11	3.78			3.38	52.56	0.65
TPV 750 mg/ RTV 100 mg	Without	14	4.83			4.61	34.76	
	With	14	3.04			2.93	29.43	0.64
TPV 250 mg/ RTV 200 mg	Without	28	6.15			5.91	30.30	
	With	28	3.71			3.29	45.58	0.56

Table 2. Descriptive statistics for didanosine  $AUC_{0-12}$  values

TPV/RTV Dose	Without or With TPV/RTV	N	AUC (h·µg/mL)					
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio
TPV 1250 mg/ RTV 100 mg	Without	9	1.51			1.13	124.58	
	With	9	1.08			1.00	46.94	0.88
TPV 750 mg/ RTV 100 mg	Without	8	1.85			1.71	48.71	
	With	8	1.71			1.66	24.65	0.97
TPV 250 mg/ RTV 200 mg	Without	10	2.47			2.08	71.23	
	With	10	1.59			1.39	56.99	0.67

Table 3. Descriptive statistics for efavirenz  $C_{min,ss}$  values

TPV/RTV Dose	Without or With TPV/RTV	N	C24h ( $\mu\text{M}$ )							
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio		
TPV 1250 mg/RTV 100 mg	Without	15	4.90	/	/	3.96	68.13			
	With	15	4.95			4.03	71.98	1.02		
TPV 750 mg/RTV 100 mg	Without	19	4.29					3.63	66.88	
	With	19	3.89					3.35	60.42	0.92
TPV 250 mg/RTV 200 mg	Without	23	3.95					3.42	58.86	
	With	23	4.53					3.44	91.18	1.01

Table 4. Descriptive statistics for lamivudine  $\text{AUC}_{0-12}$  values

TPV/RTV Dose	Without or With TPV/RTV	N	$\text{AUC}_{0-12}$ ( $\text{h}\cdot\mu\text{g}/\text{mL}$ )							
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio		
TPV 1250 mg/RTV 100 mg	Without	35	6.45	/	/	5.98	40.54			
	With	35	5.52			4.88	66.21	0.82		
TPV 750 mg/RTV 100 mg	Without	46	6.03					5.77	31.49	
	With	46	5.80					5.56	30.19	0.96
TPV 250 mg/RTV 200 mg	Without	64	6.95					6.58	33.69	
	With	64	6.61					6.28	32.33	0.95

Table 5. Descriptive statistics for nevirapine  $C_{min,ss}$  values

TPV/RTV Dose	Without or With TPV/RTV	N	C12h ( $\mu\text{g}/\text{mL}$ )							
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio		
TPV 1250 mg/RTV 100 mg	Without	17	4.60	/	/	4.29	39.93			
	With	17	3.83			3.30	64.34	0.77		
TPV 750 mg/RTV 100 mg	Without	22	4.31					4.08	35.75	
	With	22	4.07					3.79	40.14	0.93
TPV 250 mg/RTV 200 mg	Without	26	3.97					3.76	33.67	
	With	26	4.09					3.60	51.30	0.96

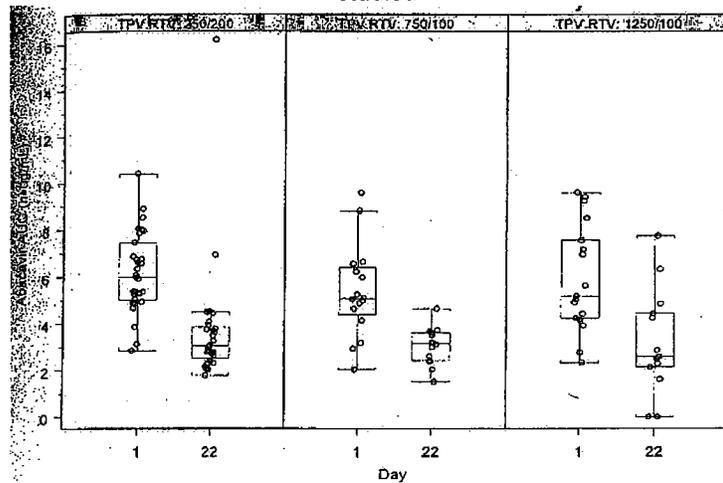
Table 6. Descriptive statistics for stavudine AUC<sub>0-12</sub> values

TPV/RTV Dose	Without or With TPV/RTV	N	AUC (h·µg/mL)					
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio
TPV 1250 mg/RTV 100 mg	Without	19	1.65			1.56	33.50	
	With	19	1.54			1.46	35.98	0.93
TPV 750 mg/RTV 100 mg	Without	22	1.61			1.54	33.52	
	With	22	1.36			1.30	34.59	0.84
TPV 250 mg/RTV 200 mg	Without	26	1.51			1.46	26.50	
	With	26	1.54			1.47	32.04	1.00

Table 7. Descriptive statistics for zidovudine AUC<sub>0-12</sub> values

TPV/RTV Dose	Without or With TPV/RTV	N	AUC (h·µg/mL)					
			Mean	Min	Max	Geometric Mean	Geometric CV	Geometric Mean Ratio
TPV 1250 mg/RTV 100 mg	Without	23	1.40			1.21	68.73	
	With	23	1.01			0.84	84.97	0.69
TPV 750 mg/RTV 100 mg	Without	31	1.53			1.42	42.12	
	With	31	1.00			0.91	48.44	0.64
TPV 250 mg/RTV 200 mg	Without	48	1.69			1.53	51.51	
	With	48	1.03			0.89	55.90	0.58

Figure 1. Abacavir AUC<sub>0-12</sub> (hr·µg/mL) and C<sub>max</sub> (µg/mL) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied



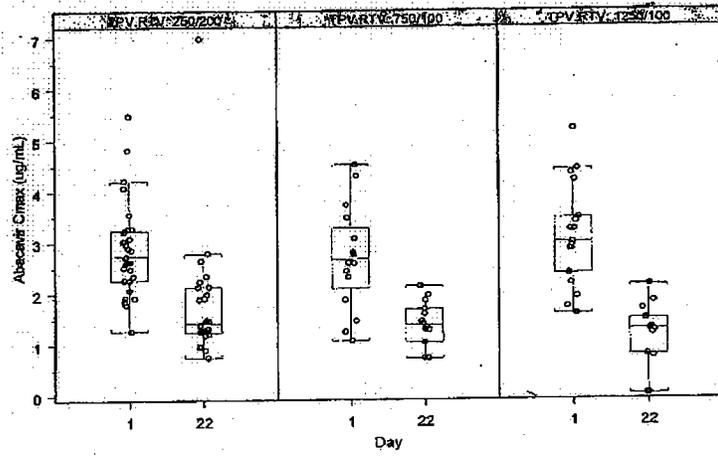


Figure 2. DDI AUC<sub>0-12</sub> (hr-ug/mL) and C<sub>max</sub> (ug/mL) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied

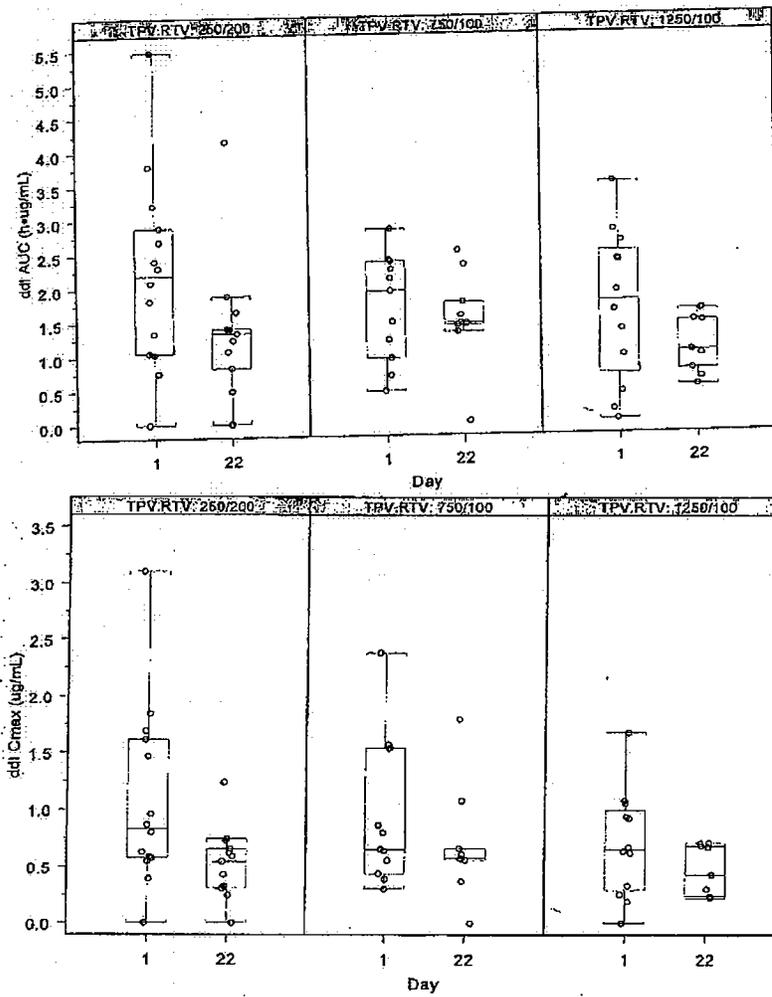
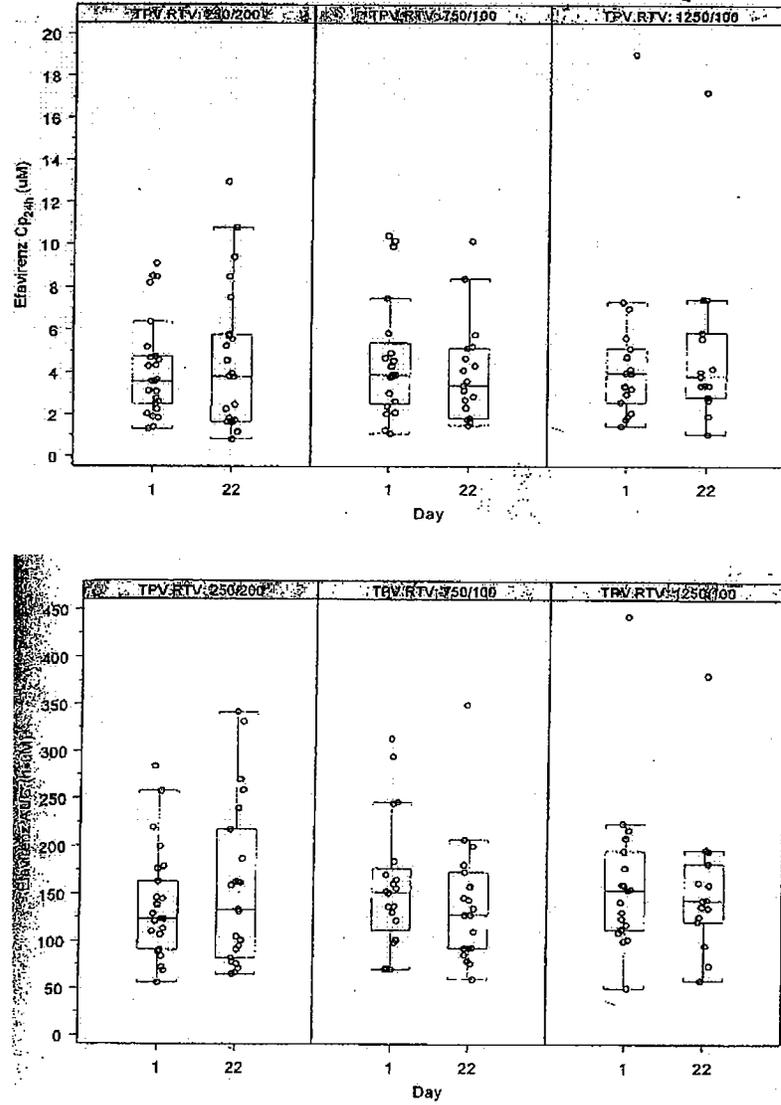


Figure 3. Efavirenz  $C_{24h}$  ( $\mu\text{M}$ ),  $\text{AUC}_{0-24}$  ( $\text{hr}\cdot\mu\text{M}$ ) and  $C_{\text{max}}$  ( $\mu\text{M}$ ) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied



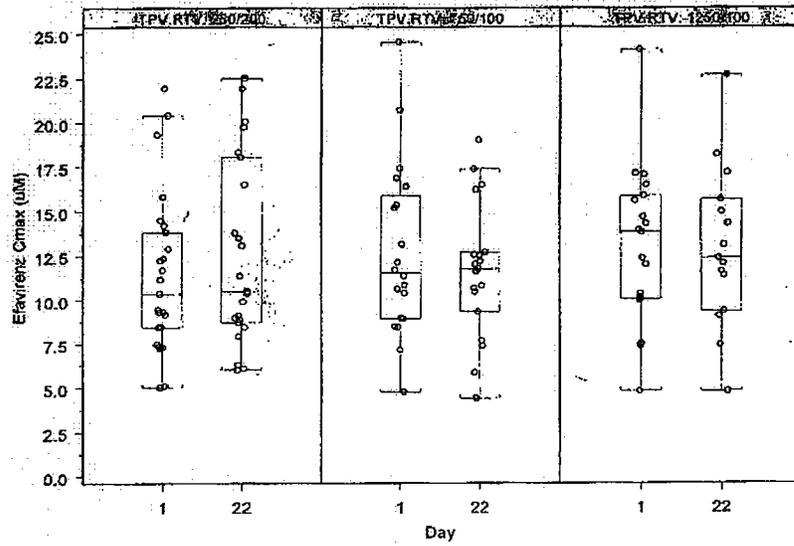
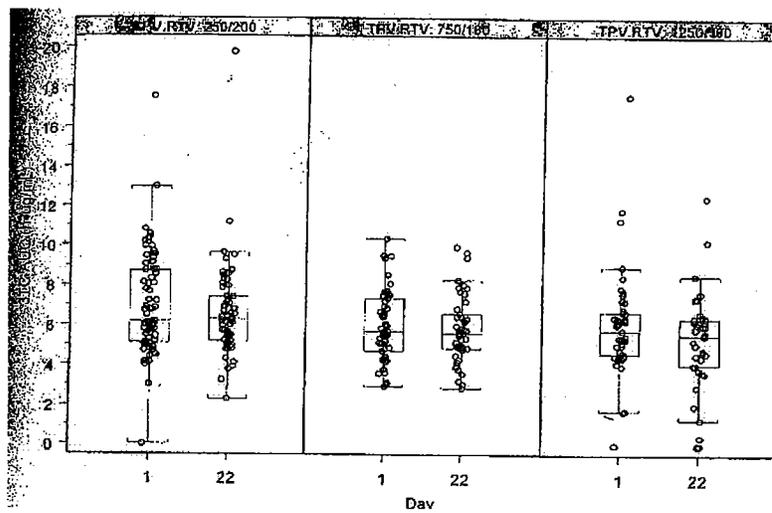


Figure 4. 3TC AUC<sub>0-12</sub> (hr-µg/mL) and C<sub>max</sub> (µg/mL) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied



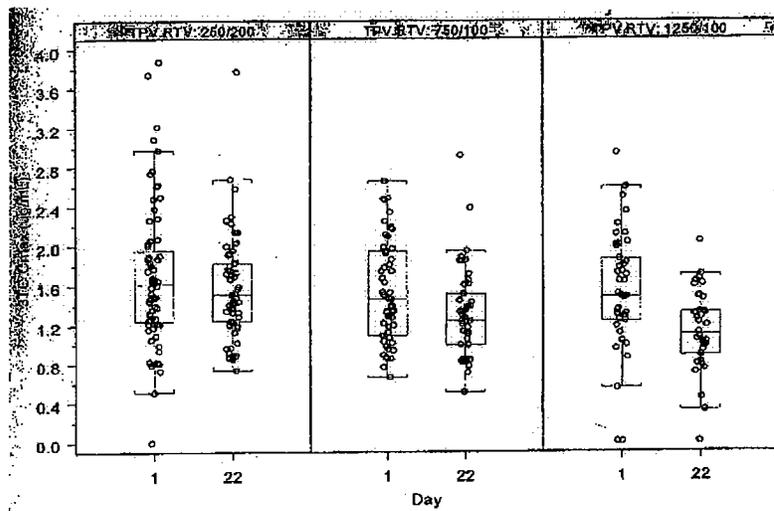
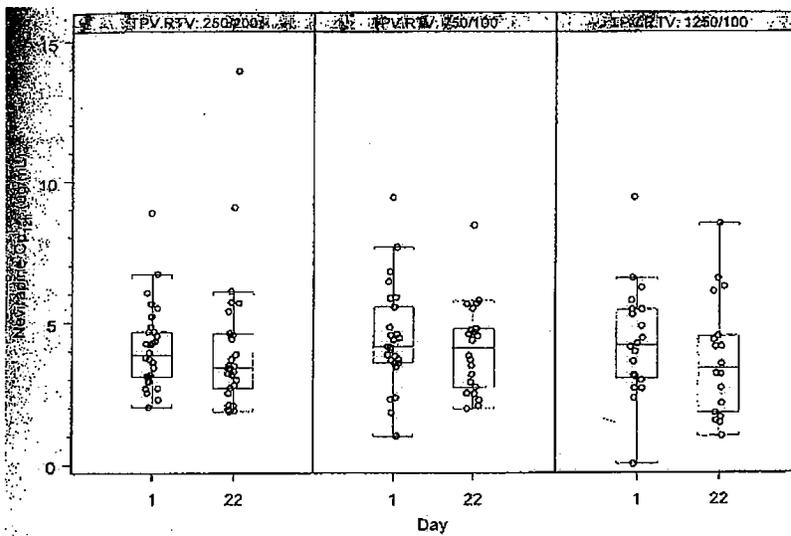
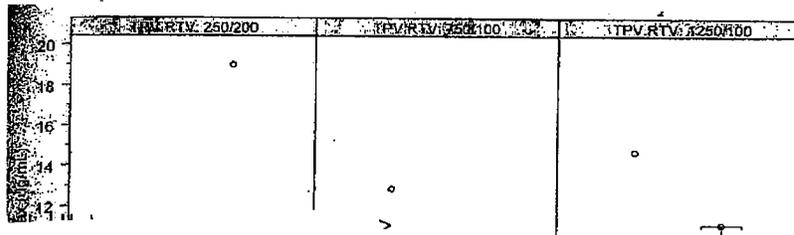
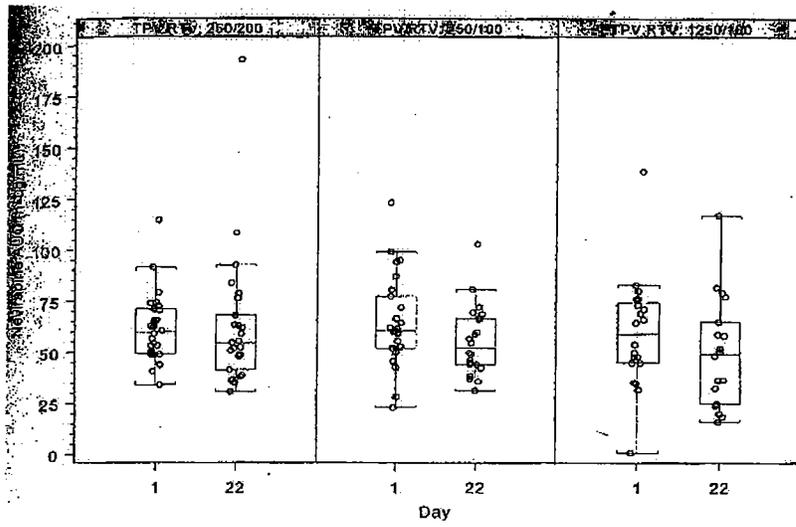


Figure 5. Nevirapine  $C_{12h}$  ( $\mu\text{g/mL}$ ),  $AUC_{0-12}$  ( $\text{hr}\cdot\mu\text{g/mL}$ ) and  $C_{\text{max}}$  ( $\mu\text{g/mL}$ ) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied





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Figure 6. d4T AUC<sub>0-12</sub> (hr·µg/mL) and C<sub>max</sub> (µg/mL) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied

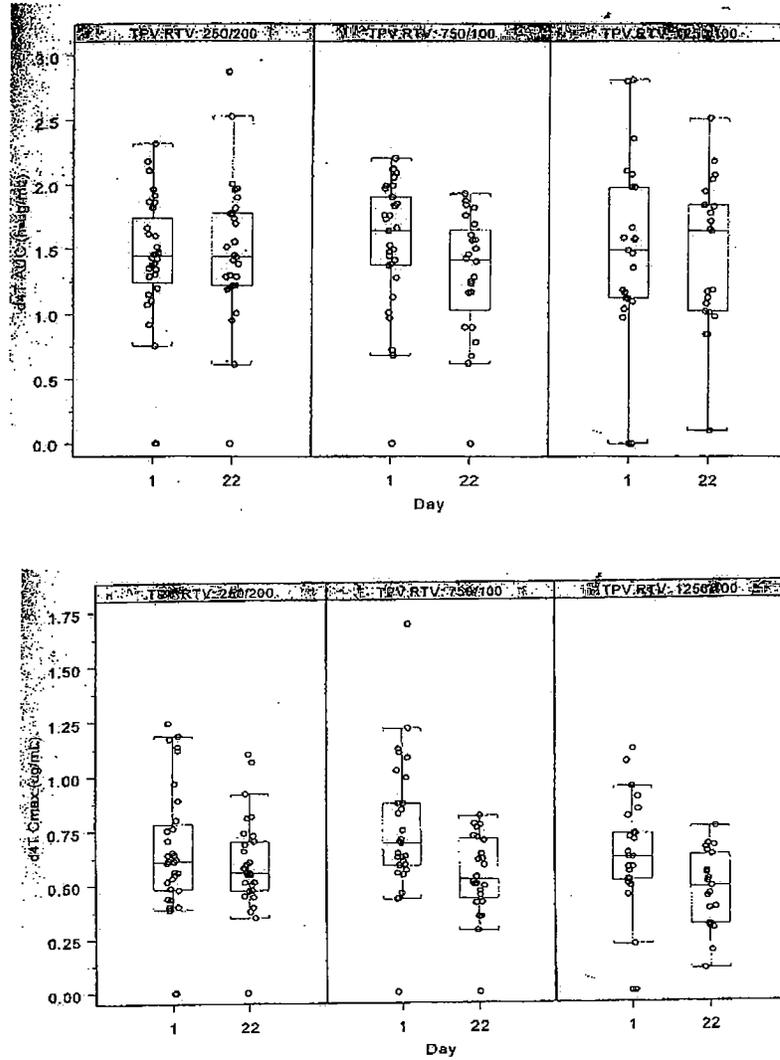
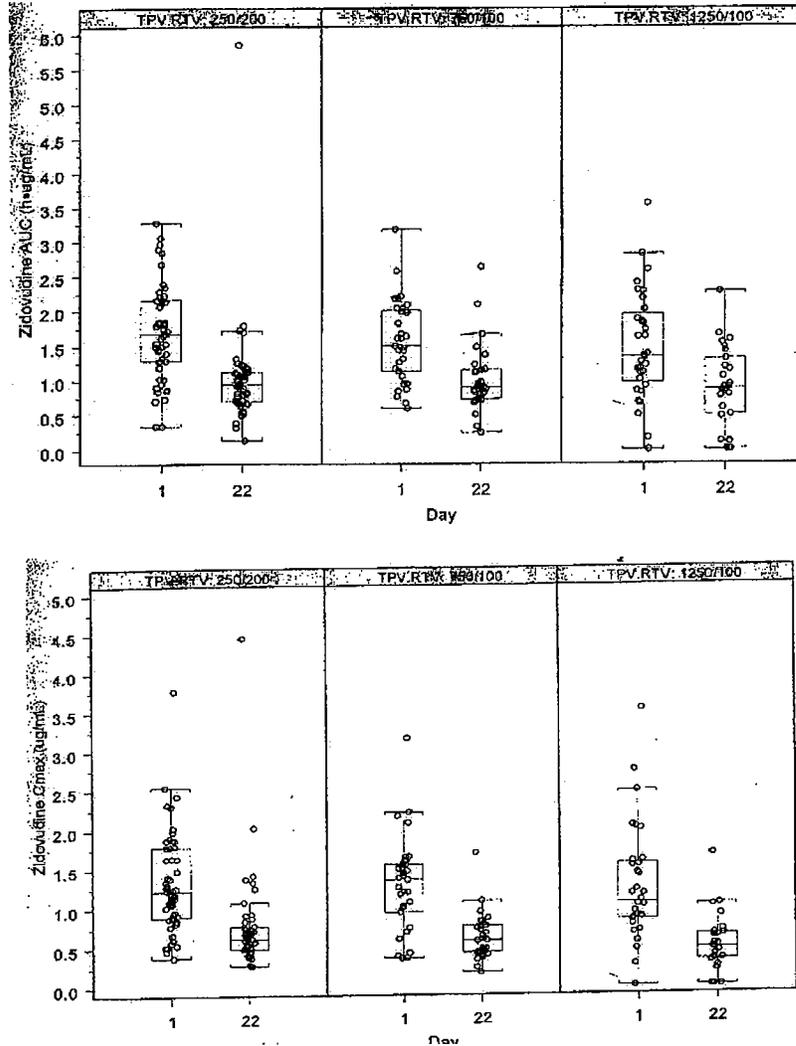


Figure 7. Zidovudine AUC<sub>0-12</sub> (hr-μg/mL) and C<sub>max</sub> (μg/mL) values at steady-state in the absence of TPV/r (Day 1) and in the presence of TPV/r (Day 22) after three weeks of TPV/r b.i.d. administration at doses studied



**SAFETY RESULTS:**

Please see Medical Office's review.

**CONCLUSIONS AND DISCUSSION:**

This study served as a screening study to determine potential pharmacokinetic interactions between three dose pairs of TPV/r and commonly used three-drug combinations of NRTIs and NNRTIs (only looking at TPV/r effect on other drugs). At three dose levels used in the study (i.e., TPV/r 1250 mg/100 mg, 750mg/100 mg and 250 mg/200 mg), the steady-state plasma concentrations of TPV were at or above 20 μM, 10 times the protein adjusted IC<sub>90</sub> for PI-resistant strains of HIV-1, based on previous PK studies.

TPV/r at the three dose pairs studied did not affect the PK of lamivudine, stavudine, efavirenz or nevirapine at their respective approved doses. Enteric-coated didanosine AUC values were reduced by

33% in the TPV/r 250 mg/200 mg dose level but no changes in the 1250 mg/100 mg and 750 mg/100 mg dose levels. However, the AUC values of both abacavir and zidovudine were reduced by 35% to 44% and 31% to 42%, respectively, in three TPV/r dose levels. The extent of the interaction did not appear dose dependent. The clinical significance of these findings has not been identified.

Ritonavir is reported to have interaction with zidovudine likely due to interaction with the glucuronyl transferase. Ritonavir is an UGT inducer and UGT is involved in the metabolism of zidovudine. The apparent mechanisms for the TPV/r-abacavir interaction and TPV/r-didanosine interaction are not clear.

The sponsor reported a large proportion (62.5%) of protocol deviations in the study. However, the majority of them were considered minor to PK evaluation.

The effects of studied NNRTIs and NTRIs on the PK of TPV/RTV were not presented in the report. Further definitive drug interaction studies, e.g. TPV/r with individual NNRTIs or NTRIs is needed to define the preliminary observations in the current study.

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1182.10

**TITLE:** A single-center, open-label study in healthy adult volunteers, to determine the effects of single-dose and steady-state TPV/RTV 500/200 mg on the steady-state pharmacokinetics of fluconazole 100 mg qd (200 mg loading dose)

**OBJECTIVES:** To determine the effects of single-dose and steady-state TPV/RTV 500/200 mg on the steady-state pharmacokinetics of fluconazole

**SUBJECTS AND STUDY DESIGN:** This was an open-label study conducted in healthy adult subjects. Seventy-seven subjects were screened for the study and twenty subjects entered the study. Briefly, all 20 subjects received a loading dose (200 mg) of fluconazole (FCZ) on Day 1 followed by a daily 100 mg FCZ dose for 13 days. Fluconazole PK profile at steady-state was obtained on Day 6. On Day 7 the subjects were started on a twice daily dosing regimen with TPV/RTV (500 mg/200 mg). TPV/RTV treatment was continued until the last dose on the evening of Day 13. The effect of single-dose TPV/RTV on the steady-state PK of fluconazole was determined by comparing the fluconazole PK profile on Day 7 to that on Day 6. The effect of steady-state TPV/RTV on the steady-state PK of fluconazole was determined by comparing PK profile of FCZ on Day 13 to that on Day 6. The effect of steady-state FCZ on steady-state TPV/RTV was determined by comparing the TPV PK profile on Day 13 to historical data (from Studies U03-3236 and U01-3295).

Study drugs could be taken with a light snack, except on PK Days, 6, 7 and 13. Subjects were required to fast overnight before administration of the morning dose of study drug on the serial PK sampling days (Days 6, 7 and 13). Subjects fasted for at least 1 hour after dosing on these days.

The overall demographic characteristics of 20 subjects were as following: Male (90 %) and female (10%); White (95%) and Black (5%).

**INVESTIGATOR AND STUDY LOCATION:** [

]

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Diflucan: 100 mg tablets.

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples were collected for assay of FCZ concentrations on Days 6, 7 and 13 and of TPV concentrations on Days 7 and 13 prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 post dose.

**ASSAY:** Plasma samples were analyzed for TPV by [ using a validated high performance liquid chromatography [ method. The calibration curve ranged from [ ] ng/mL to [ ] ng/mL. FCZ concentrations were performed also by [ using a validated high performance liquid chromatography [ method. The calibration curve ranged from — µg/mL to — µg/mL.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for  $C_{max}$ ,  $C_{p24h}$  and  $AUC_{0-24h}$  were provided for FCZ (with and without TPV/RTV) and geometric means and coefficients of variation for  $C_{max}$ ,  $C_{12h}$  and  $AUC_{0-12h}$  were provided for tipranavir co-administered with RTV and FCZ. The geometric mean ratios with 90% confidence intervals were calculated between treatments.

**PHARMACOKINETIC RESULTS:**

Table 1. Summary of the steady-state pharmacokinetic parameters of FCZ, alone and in combination with single-dose and steady-state TPV/r (n=19)

FCZ PK parameter <sup>§</sup>	FCZ alone (Day 6)	FCZ + two doses TPV/r (Day 7)	FCZ + steady-state TPV/r (Day 13)
T <sub>max</sub> (h)	2.1	2.8	2.4
C <sub>max</sub> (µg/mL)	5.3	5.1	4.9
AUC <sub>0-24h</sub> (h*µg/mL)	99.0	98.2	90.6
C <sub>p24h</sub> (µg/mL)	3.6	3.5	3.2
Cl/F (L/h)	1.0	1.0	1.1
V (L)	74.0	68.9	73.2
Lambda z (h <sup>-1</sup> )	0.014	0.015	0.015
t <sub>1/2</sub> (h)	50.8	46.9	46.0

\*Results for Subject 107 are omitted because of potential anomalous Cp FCZ at 24 h post dose on Study Day 6 (see 11.4.3).

§ Geometric Mean

Table 2. Summary of geometric mean ratios and 90% confidence intervals for steady-state pharmacokinetic parameters of FCZ in combination with single-dose and steady-state TPV/r

Comparison	n	AUC <sub>0-24h</sub>			C <sub>max</sub>			C <sub>p24h</sub>		
		% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 6 versus Day 7	19 <sup>1</sup>	-1	0.99	0.97-1.02	-3	0.97	0.94-1.01	-2	0.98	0.94-1.02
Day 6 versus Day 13	19	-8	0.92	0.88-0.95	-6	0.94	0.91-0.98	-11	0.89	0.85-0.92

<sup>1</sup> Results for Subject 107 are omitted because of potential anomalous Cp FCZ at 24h post dose on Study Day 6 (see 11.4.3).  
Source data: Appendix Listing 16.3.3.1: 1 and Appendix Listing 16.3.3.1: 2

Figure 1. Effect of single-dose TPV/r 500/200 mg on the steady-state FCZ pharmacokinetic parameters ( $C_{p24h}$ ,  $C_{max}$  and  $AUC_{0-24h}$ )

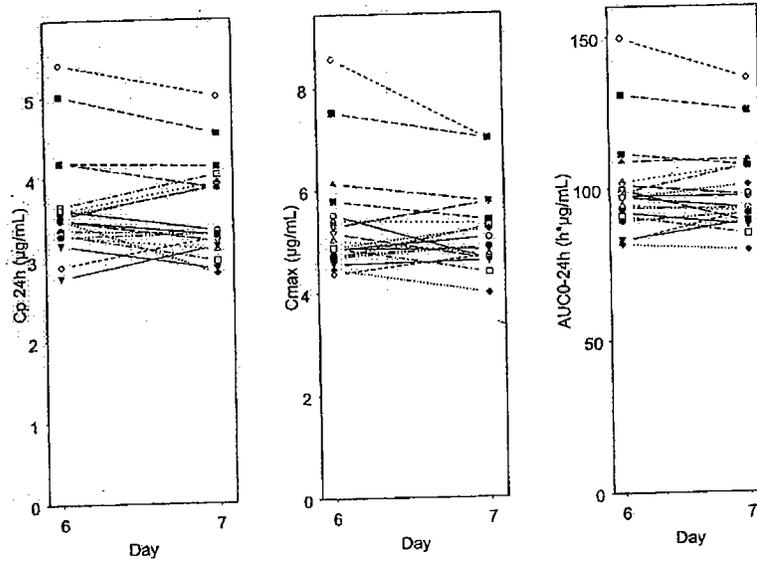


Figure 2. Effect of steady-state TPV/r 500/200 mg BID on the steady-state FCZ pharmacokinetic parameters ( $C_{p24h}$ ,  $C_{max}$  and  $AUC_{0-24h}$ )

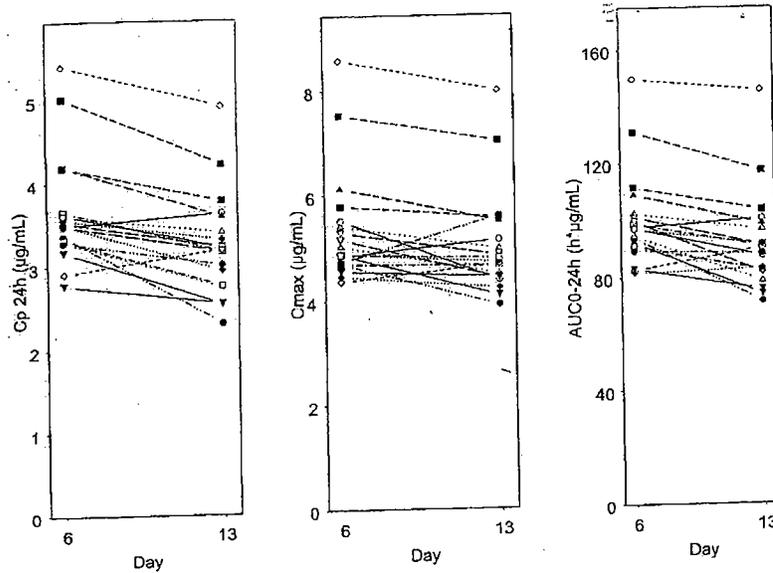


Table 3. Summary of the steady-state pharmacokinetic parameters of TPV when used as TPV/r 500/200 mg BID

TPV PK parameter <sup>§</sup>	TPV/r 500/200 mg + FCZ (Day 13) <sup>a</sup>	TPV/r 500/200 mg alone (BI Protocol 1182.5) <sup>b</sup>	% difference (current study versus 1182.5)
T <sub>max</sub> (h)	2.3	2.6	- 12%
C <sub>max</sub> (μM)	179.9	123.4	+ 46%
AUC <sub>0-12h</sub> (h*μM)	1332.8	855.6	+ 56%
C <sub>p12h</sub> (μM)	59.5	29.1	+ 104%
Cl/F (L/h)	0.62	0.97	-36%
V (L)	5.6	6.0	-6.7%
Lambda z (h <sup>-1</sup> )	0.11	0.16	- 31%
t <sub>1/2</sub> (h)	6.3	4.3	+ 47%

<sup>a</sup> n=20

<sup>b</sup> n=11

<sup>§</sup> Geometric Mean

**SAFETY RESULTS:** In general, treatment with TPV/r 500/200 mg in the presence of steady-state FCZ was well tolerated with the majority of observed AEs being mild in intensity. No unexpected safety issues arose in the study nor were there any discontinuations due to AEs (See details in Medical Office's review).

**CONCLUSIONS AND DISCUSSION:** FCZ is routinely indicated for oropharyngeal and esophageal candidiasis, and for the treatment of other serious systemic fungal infections in HIV positive patients. The likelihood that the co-prescription of TPV/RTV and FCZ in the HIV positive patient population is high. TPV and RTV are extensively metabolized by the CYP3A enzyme. TPV has been shown to be a moderate inducer of CYP3A enzyme, while RTV is a potent inhibitor of this enzyme system. FCZ was demonstrated to inhibit midazolam metabolism, a known substrate for CYP3A, administered both intravenously and orally. FCZ was also shown to increase plasma exposure of other HIV protease inhibitors. TPV 500 mg/RTV 200 mg BID dose is the proposed dose for HIV infection and FCZ dose used in this study was the most frequently used dose in the HIV patients.

In this study, co-administration of two doses of TPV/RTV 500/200 mg had little effect on the steady-state pharmacokinetics of fluconazole (Changes in C<sub>p24h</sub>, C<sub>max</sub> and AUC<sub>0-24h</sub> were ≤ 3%). Co-administration steady-state levels of TPV/RTV 500/200 mg BID caused small decreases in fluconazole exposures (-11% in C<sub>p24h</sub>, -6% in C<sub>max</sub> and -8% in AUC<sub>0-24h</sub>). In contrast, steady-state levels of fluconazole appeared to have a significant effect on the steady-state PK of TPV, when compared to the results from a previous study of TPV/RTV 500/200 mg BID alone. The steady-state TPV C<sub>p12h</sub>, C<sub>max</sub> and AUC<sub>0-12h</sub> were increased by 104%, 56% and 46%, respectively, during co-administration of steady-state FCZ. This is likely due to the inhibitory effect of FCZ on P-gp. The clinical significance of TPV exposure increase is not known.

## 1182.11

**TITLE:** A single-center, open-label study in healthy adult volunteers to determine the effects of single-dose and steady-state TPV/RTV (500/200 mg) on the steady-state pharmacokinetics of clarithromycin (BIAXIN) 500 mg bid and a preliminary assessment of the effects of a standard high-fat meal on the steady-state pharmacokinetics of tipranavir

**OBJECTIVES:** To determine the effects of single-dose and steady-state TPV/RTV 500/200 mg on the steady-state pharmacokinetics of clarithromycin and to determine the effects of a standard high-fat meal on the steady-state pharmacokinetics of tipranavir

**SUBJECTS AND STUDY DESIGN:** This was an open-label study conducted in healthy adult subjects. 158 subjects were screened for the study and 24 subjects entered the study. Briefly, subjects received:

Days 1-12: Morning dose of CLR at 8 AM and evening dose of CLR at 8 PM

Day 6-12: Morning dose of TPV/r at 8 AM and evening dose of TPV/r at 8 PM (in concert with CLR doses)

Day 10: Morning dose was to be taken within 5 minutes of completing the high-fat meal (868 Kcal with 51% from fat)

Day 13: Morning dose of TPV/r and morning dose of CLR at 8 AM

Study drugs could be taken with a light snack, except on PK Days 5, 6 and 13. Subjects fasted for at least 1 hour after dosing on these days. On Day 10, however, the morning dose was taken within 5 minutes of high-fat breakfast.

The overall demographic characteristics of 20 subjects were as following: Male (70.8%) and female (29.2%); White (91.7%) and Black (8.3%).

### **INVESTIGATOR AND STUDY LOCATION:** [

]

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Biaxin: 500 mg tablets

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples were collected for assay of CLR and 14-OH-CLR concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose on Days 5, 6 and 13. Blood samples were collected for assay of TPV concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose on Days 6, 10 and 13.

**ASSAY:** Plasma samples were analyzed for TPV by [ using a validated high performance liquid chromatography [ method. The calibration curve ranged from — ng/mL to — ng/mL. CLR and 14-OH-CLR concentrations were performed by [ method.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for  $C_{max}$ ,  $C_{p12}$  and  $AUC_{0-12h}$  were provided for CLR and 14-OH-CLR and (with and without TPV/RTV), and for tipranavir co-administered with RTV and CLR with and without a high-fat meal. The geometric mean ratios with 90% confidence intervals were calculated between treatments.

## PHARMACOKINETIC RESULTS:

Table 1. Summary of the steady-state pharmacokinetic parameters of CLR 500 mg BID, alone and in combination with single-dose and steady-state TPV/r 500/200 mg BID

CLR PK parameter <sup>§</sup>	CLR alone (Day 5) <sup>1</sup>	CLR + single-dose TPV/r (Day 6) <sup>1</sup>	CLR + steady-state TPV/r (Day 13) <sup>2</sup>
T <sub>max</sub> (h)	1.5*	2.1	2.0
C <sub>max</sub> (µg/mL)	2.80	2.47	2.49
AUC <sub>0-12h</sub> (h*µg/mL)	21.87	22.02	24.41
C <sub>p 12h</sub> (µg/mL)	0.97	1.46	1.53
Cl/F (L/h)	22.86	22.70	20.48
V (L)	201.04	335.15	334.05
Lambda z (h <sup>-1</sup> )	0.114	0.068	0.061
t <sub>1/2</sub> (h)	6.10	10.23	11.31

<sup>§</sup> Geometric Mean

<sup>1</sup> n=24

<sup>2</sup> n=21 (excluding subjects 1004, 1022, and 1023)

\*For subject 1021 T<sub>max</sub> was at 0.0 h, as a result the geometric mean cannot be calculated. Median value is presented.

Table 2. Summary of geometric mean ratios and 90% confidence intervals for steady-state pharmacokinetic parameters of CLR 500 mg BID in combination with single-dose and steady-state TPV/r 500/200 mg BID

Comparison	n	AUC <sub>0-12h</sub>			C <sub>max</sub>			C <sub>p12h</sub>		
		% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 6 versus Day 5	24	0.0	1.00	0.91-1.11	-12	0.88	0.78-1.00	+50	1.50	1.31-1.71
Day 13 versus Day 5	21 <sup>1</sup>	+19	1.19	1.04-1.37	-5	0.95	0.83-1.09	+68	1.68	1.42-1.98

<sup>1</sup> Excluding subjects 1004, 1022, and 1023.

Table 3. Summary of the steady-state pharmacokinetic parameters of 14-OH-CLR after administration of CLR 500 mg BID, alone and in combination with single-dose and steady-state TPV/r 500/200 mg BID

14-OH-CLR PK parameter <sup>§</sup>	CLR alone (Day 5) <sup>1</sup>	CLR + single-dose TPV/r (Day 6) <sup>1</sup>	CLR + steady-state TPV/r (Day 13) <sup>2</sup>
T <sub>max</sub> (h)	2.2	0.5*	2.0*
C <sub>max</sub> (µg/mL)	0.76	0.57	0.02
AUC <sub>0-12h</sub> (h*µg/mL)	6.86	3.67	0.20
C <sub>p 12h</sub> (µg/mL)	0.43	0.17	0.02
Lambda z (h <sup>-1</sup> )	0.054	0.102	0.019
t <sub>1/2</sub> (h)	12.75	6.80	36.65

<sup>§</sup> Geometric Mean

<sup>1</sup> n=24

<sup>2</sup> n=21 (excluding subjects 1004, 1022, and 1023)

\*For several subjects T<sub>max</sub> was at 0.0 h, as a result the geometric mean cannot be calculated. Median value is presented.

Table 4. Summary of geometric mean ratios and 90% confidence intervals for steady-state pharmacokinetic parameters of 14-OH-CLR after administration of CLR 500 mg BID in combination with single-dose and steady-state TPV/r 500/200 mg BID

Comparison	n	AUC <sub>0-12h</sub>			C <sub>max</sub>			C <sub>p12h</sub>		
		% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 6 versus Day 5	24	-46	0.54	0.48-0.59	-25	0.75	0.68-0.83	-61	0.39	0.35-0.44
Day 13 versus Day 5	21 <sup>1</sup>	-97	0.03	0.02-0.04	-97	0.03	0.02-0.04	-95	0.05	0.04-0.07

<sup>1</sup> Excluding subjects 1004, 1022, and 1023.

Figure 1. Effect of single-dose TPV/r 500/200 mg on the steady-state CLR 500 mg BID pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$ )

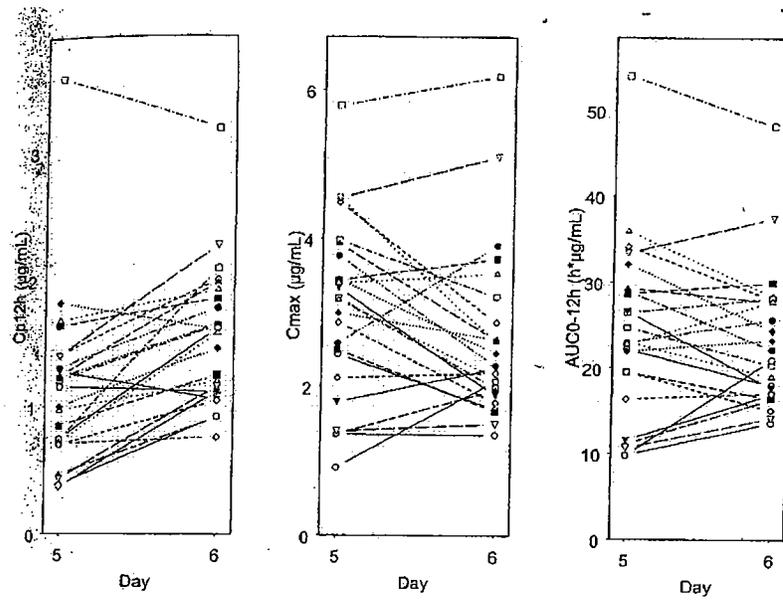


Figure 2. Effect of steady-state TPV/r 500/200 mg BID on the steady-state CLR 500 mg BID pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$ )

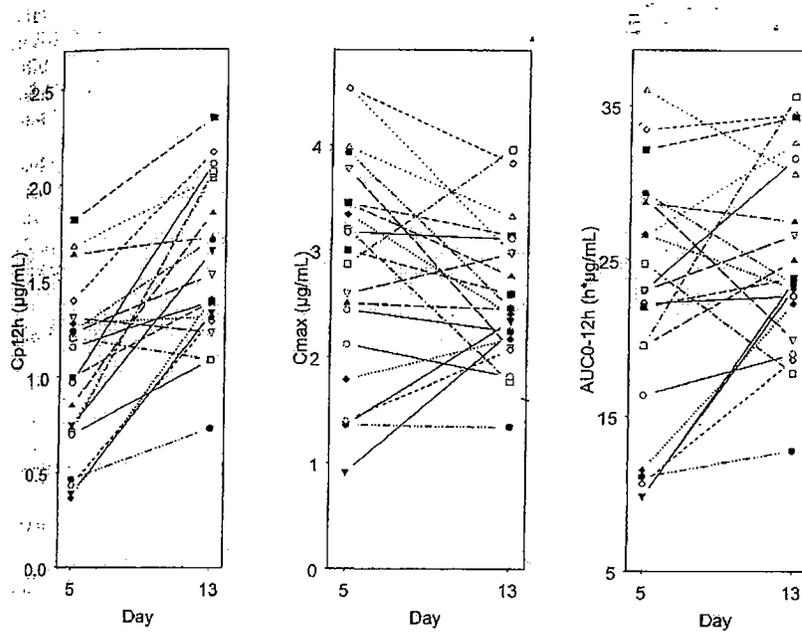


Figure 3. Effect of single-dose TPV/r 500/200 mg on the steady-state 14-OH-CLR pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$ )

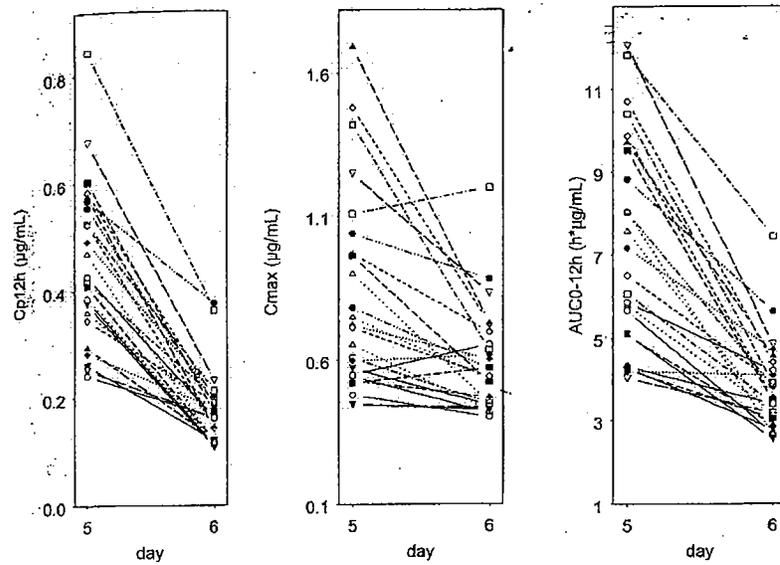


Figure 4. Effect of steady-state TPV/r 500/200 mg BID on the steady-state 14-OH-CLR pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and  $AUC_{0-12h}$ )

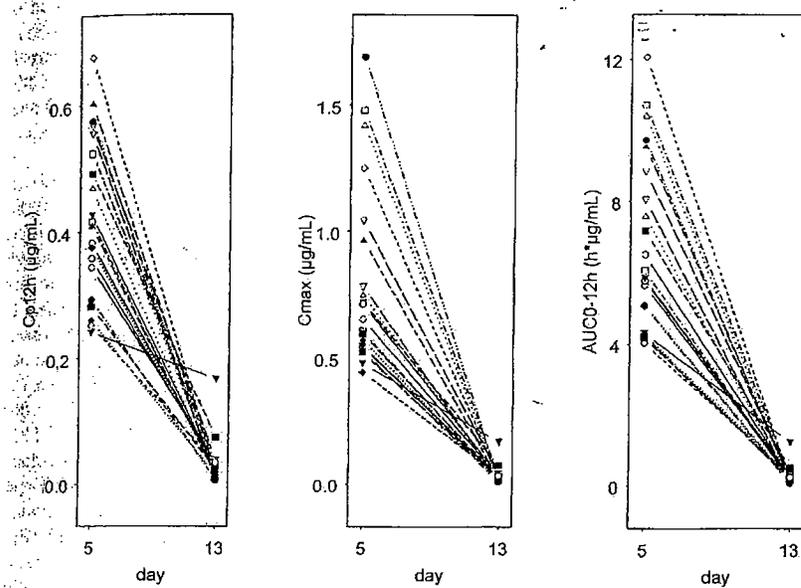


Table 5. Summary of the steady-state pharmacokinetic parameters of TPV 500 mg BID co-administered with ritonavir 200 mg BID on Day 13 vs. historical data

TPV PK parameter <sup>§</sup>	TPV/r 500/200 mg + CLR (Day 13) <sup>§</sup>	TPV/r 500/200 mg alone (BI Protocol 1182.5) <sup>b</sup>	% difference (current study versus 1182.5)
T <sub>max</sub> (h)	2.2	2.6	-15%
C <sub>max</sub> (μM)	176.9	123.4	+43
AUC <sub>0-12h</sub> (h*μM)	1359.9	855.6	+59
Cp <sub>12h</sub> (μM)	61.7	29.1	+112%
Cl/F (L/h)	0.61	0.97	-37%
V (L)	5.63	6.0	-6%
Lambda z (h <sup>-1</sup> )	0.11	0.16	-31%
t <sub>1/2</sub> (h)	6.4	4.3	+49%

<sup>a</sup>n=21 (excluding subjects 1004, 1022, and 1023)

<sup>b</sup>n=11

<sup>§</sup> Geometric Mean

Table 6. Summary of the steady-state pharmacokinetic parameters of TPV 500 mg BID co-administered with ritonavir 200 mg BID on Day 10 vs. on Day 13

TPV PK parameter <sup>§</sup>	TPV/r 500/200 mg + high-fat meal (Day 10) <sup>1</sup>	TPV/r 500/200 mg + regular meal (Day 13) <sup>1</sup>
T <sub>max</sub> (h)	2.5	2.2
C <sub>max</sub> (μM)	205.6	176.9
AUC <sub>0-12h</sub> (h*μM)	1781.9	1359.9
Cp <sub>12h</sub> (μM)	107.95	61.7
Cl/F (L/h)	0.47	0.61
V (L)	7.03	5.63
Lambda z (h <sup>-1</sup> )	0.07	0.11
t <sub>1/2</sub> (h)	10.5	6.4

<sup>1</sup>n=21 (excluding subjects 1004, 1022, and 1023)

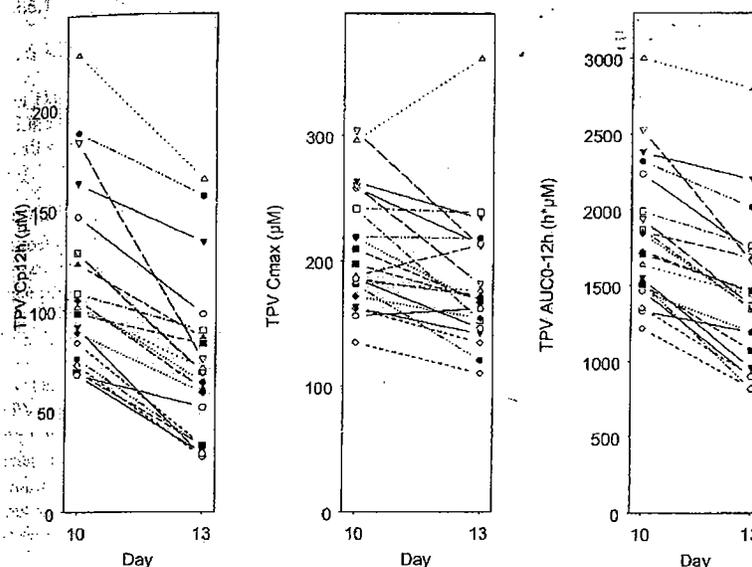
<sup>§</sup> Geometric Mean

Table 7. Summary of geometric mean ratios and 90% confidence intervals for steady-state pharmacokinetic parameters of TPV with a high-fat meal (on Day 10) vs. in fasted condition (on day 13)

Comparison	n	AUC <sub>0-12h</sub>			C <sub>max</sub>			C <sub>p12h</sub>		
		% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 10 versus Day 13	21 <sup>1</sup>	+31	1.31	1.23-1.39	+16	1.16	1.09-1.24	+75	1.75	1.55-1.97

<sup>1</sup> Excluding subjects 1004, 1022, and 1023.

Figure 5. Effect of a high-fat meal on the steady-state TPV pharmacokinetic parameters (C<sub>p12h</sub>, C<sub>max</sub> and AUC<sub>0-12h</sub>) when co-administered with ritonavir and CLR



**SAFETY RESULTS:** In general, treatment with TPV/r 500/200 mg in the presence of steady-state CLR was well tolerated with the majority of observed AEs being mild in intensity. No unexpected safety issues were reported in the study (See details in Medical Officer's review).

**CONCLUSIONS AND DISCUSSION:** Clarithromycin is used extensively in HIV/AIDS patients. CLR is metabolized extensively in the liver by cytochrome P450 3A. One of two major metabolites, 14-hydroxy-R-clarithromycin (14-OH-CLR), is active in antibacterial function. CLR is also a P-gp substrate and inhibitor. The net effect of TPV/r on CYP3A is inhibition. This study demonstrated that the steady-state TPV/r administration (500/200 mg BID) increased CLR AUC<sub>0-12h</sub> and C<sub>p12h</sub> by 19% and 68%, respectively, with no substantial change in the C<sub>max</sub>. The formation of 14-OH-CLR was almost fully inhibited at the steady-state of TPV/r administration. This confirmed that the net effect of steady-state effect of TPV/r 500/200 mg BID is inhibition of CYP3A mediated CLR metabolism. However, the degree of CLR exposure increase is less than expected based on the degree of reduction of 14-OH-CLR formation. A possible explanation is that tipranavir is a P-gp inducer and the low dose of ritonavir can not compensate the P-gp induction effect caused by tipranavir.

On the other hand, the steady-state  $AUC_{0-12h}$ ,  $C_{max}$  and  $C_{p12h}$  of TPV were substantially increased (>43%) by co-administration of CLR, compared to the results from a previous study 1182.5. This could be explained by the inhibitory effect of CLR on P-gp.

The  $AUC_{0-12h}$ ,  $C_{max}$  and  $C_{p12h}$  of TPV increased 31%, 16% and 75%, respectively, with a high-fat meal. However, the finding is inconclusive because the comparison was based on TPV steady-state PK (day 13, fasted) to that obtained before steady-state TPV levels were reached (Day 10, fed). The actual food effect could be less than what observed here.

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1182.21

**TITLE:** A two-way pharmacokinetic interaction study of single-dose atorvastatin (LIPITOR) with tipranavir/ritonavir (500 mg/200 mg) at steady-state and the effect of antacid (MAALOX) on the pharmacokinetics of single-dose tipranavir/ritonavir (500 mg/200 mg) in healthy volunteers

**OBJECTIVES:** To determine the effects of steady-state TPV/RTV 500/200 mg on the single-dose pharmacokinetics of atorvastatin (ATV), the effects of single-dose atorvastatin on the steady-state pharmacokinetics of tipranavir, effect of single dose of TPV/RTV on CYP3A4 activity as assessed by ERMBT, and the effects of antacid on the pharmacokinetics of tipranavir

**SUBJECTS AND STUDY DESIGN:** This was an open-label study conducted in healthy adult subjects. 36 subjects were screened for the study and 23 subjects entered the study. Briefly, subjects received:

Days 1:            ATV (40 mg) at 8 AM  
Day 8:            A single dose of TPV/r (500 mg/200 mg) at 8 AM  
Day 13:           A single dose of TPV/r (500 mg/200 mg) at 8 AM, followed immediately by a single dose of antacid (Maalox, (20 mL)  
Days 14-21:       TPV/r (500 mg/200 mg) BID  
Days 20:           ATV (10 mg) at 8 AM

Subjects were fasted overnight for pharmacokinetic sampling days. Breakfast was consumed at least 1 hour after morning dose.

The erythromycin breath test (ERMBT) for CYP3A4 activity was administered on Day 7, 8, 9 and 10 as a sub-pharmacologic, one-minute intravenous 3 µCi infusion in 5% dextrose of (<sup>14</sup>C-Nmethyl) erythromycin. Duplicate breath collections at 20 minutes after infusion estimated the percentage of radio-labeled erythromycin converted to (<sup>14</sup>C) carbon dioxide. The radioactivity was measured by [ ]

The overall demographic characteristics of 23 subjects were as following: Male (47.8%) and female (52.2%); White (95.7%) and Black (4.3%).

**INVESTIGATOR AND STUDY LOCATION:** [ ]

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Lipitor: 10 mg tablets, Maalox suspension: 350 mL liquid bottle.

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples were collected for assay of ATV and its metabolite, ortho-hydroxy-ATV (O-OH-ATV) concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 post dose on Days 1-3 and 20-22. Blood samples were collected for assay of TPV concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose on Days 8, 13, 19 and 20. Additional trough blood samples for TPV were taken on Days 16, 17 and 18.

**ASSAY:** Plasma samples were analyzed for TPV by [ ] using a validated high performance liquid chromatography [ ] method. The calibration curve ranged from — ng/mL to — ng/mL. ATV and O-OH-ATV concentrations were evaluated by [ ] using [ ] method. The lower limit of quantitation was — ng/ml for ATV and — ng/mL for O-OH-ATV.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation

for  $C_{max}$ ,  $C_{p12}$  and  $AUC_{0-\infty}$  (or  $AUC_{0-12h}$ ) were provided for ATV and its metabolite, O-OH-ATV (with and without TPV/RTV), and for tipranavir co-administered with RTV with ATV or antacid. The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

#### PHARMACOKINETIC RESULTS:

Table 1. Summary of the single-dose pharmacokinetic parameters of ATV, alone and in combination with steady-state TPV/r 500/200 mg BID

PK parameter <sup>§</sup>	ATV 40 mg alone (Day 1)	ATV 10 mg + TPV/r (Day 20)	
		observed	normalized <sup>§§</sup>
$T_{max}$ (h)	0.9	2.6	-
$C_{max}$ (ng/mL)	17.6	37.8	151
$AUC_{0-\infty}$ (h•ng/mL)	89.3	209	836
$C_{p12h}$ (ng/mL)	2.25	2.91	11.7
Cl/F (L/h)	448	47.8	-
V (L)	4,540	432	-
$\lambda_z$ (h <sup>-1</sup> )	0.099	0.111	-
$t_{1/2}$ (h)	7.02	6.27	-

§ Geometric Mean

§§ Dose-normalized pharmacokinetic parameters (observed parameter value x (40 mg/10 mg)).

Table 2. Summary of the single-dose pharmacokinetic parameters of O-OH-ATV, after administration of ATV alone and in combination with steady-state TPV/r 500/200 mg BID

PK parameter <sup>§</sup>	ATV 40 mg alone (Day 1)	ATV 10 mg + TPV/r (Day 20)
$T_{max}$ (h)	1.6	5.0
$C_{max}$ (ng/mL)	12.4	0.275 <sup>§§</sup>
$AUC_{0-\infty}$ (h•ng/mL)	117	13.6
$C_{p12h}$ (ng/mL)	3.49	0.236 <sup>§§</sup>
$\lambda_z$ (h <sup>-1</sup> )	0.081	0.025
$t_{1/2}$ (h)	8.60	27.72

§ Geometric Mean

§§ One or more values are BLQ, therefore median value is presented.

Table 3. Summary of geometric mean ratios and 90% confidence intervals for ATV and O-OH-ATV pharmacokinetic parameters after administration of single-dose ATV alone and in combination with steady-state TPV/r 500/200 mg BID (Day 20 versus Day 1)

	AUC <sub>0-∞</sub>			C <sub>max</sub>			C <sub>p12h</sub>		
	% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
ATV <sup>b</sup>	+836	9.36	8.02-10.94	+761	8.61	7.25-10.21	+419	5.19	4.21-6.40
O-OH-ATV	-89%	0.11 <sup>c</sup>	0.08-0.17	-98%	0.02 <sup>d</sup>	0.02-0.03	-93%	0.07 <sup>a</sup>	0.06-0.08

Figure 1. Effect of steady-state TPV/r 500/200 mg BID on the single-dose, dose-normalized ATV pharmacokinetic parameters (C<sub>p12h</sub>, C<sub>max</sub> and AUC)

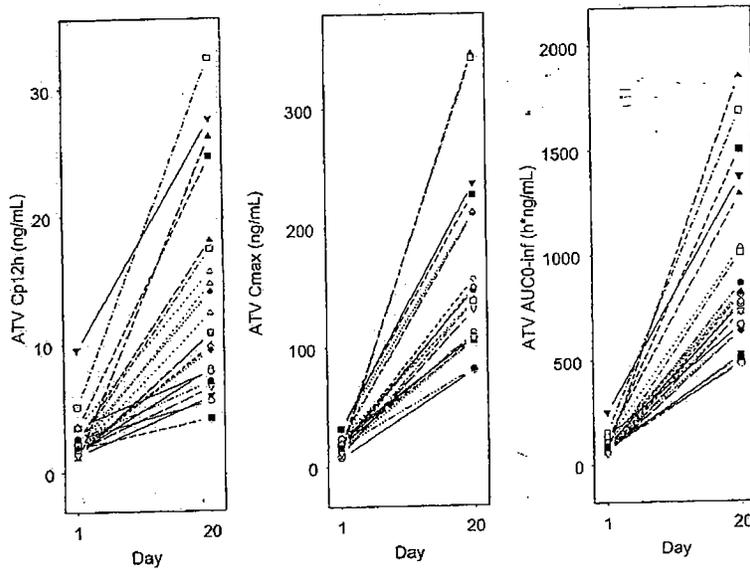


Figure 2. Effect of steady-state TPV/r 500/200 mg BID on O-OH-ATV pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and AUC) after a single-dose of ATV

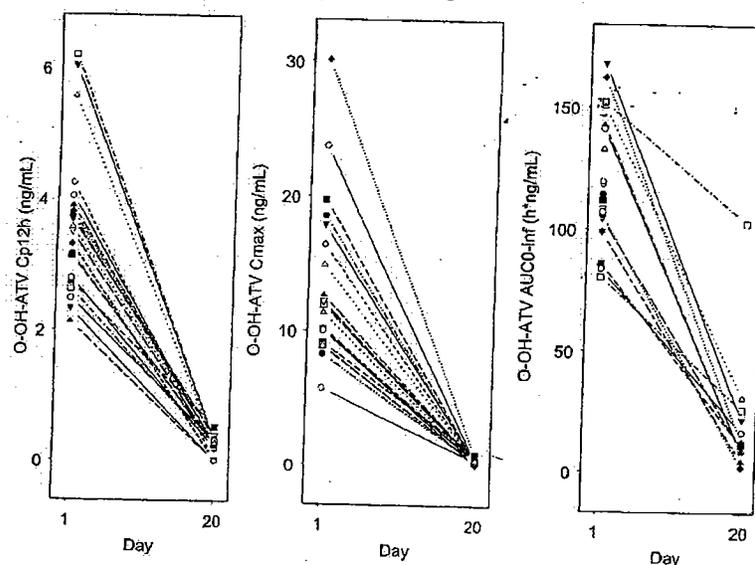


Table 4. Summary of the steady-state pharmacokinetic parameters of TPV, alone and in combination with 10 mg ATV

TPV PK parameter <sup>§</sup>	TPV/r alone (Day 19)	TPV/r + ATV (Day 20)
$T_{max}$ (h)	2.8	2.6
$C_{max}$ ( $\mu$ M)	122.417	117.635
AUC <sub>0-12h</sub> (h* $\mu$ M)	768.883	826.781
$C_{p12h}$ ( $\mu$ M)	30.139	31.482
Cl/F (L/h)	1.079	1.003
V (L)	8.618	7.345
$\lambda_z$ (h <sup>-1</sup> )	0.125	0.137
$t_{1/2}$ (h)	5.54	5.07

<sup>§</sup> Geometric Mean

Table 5. Summary of geometric mean ratios and 90% confidence intervals for TPV pharmacokinetic parameters alone and in combination with a single-dose 10 mg ATV (Day 20 versus Day 19)

Comparison	AUC <sub>0-12h</sub>			C <sub>max</sub>			C <sub>p12h</sub>		
	% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 20 versus Day 19	+8%	1.08	1.00-1.15	-4%	0.96	0.86-1.07	+4%	1.04	0.89-1.22

Figure 3. Effect of single-dose ATV 10 mg on the steady-state TPV pharmacokinetic parameters (C<sub>p12h</sub>, C<sub>max</sub> and AUC)

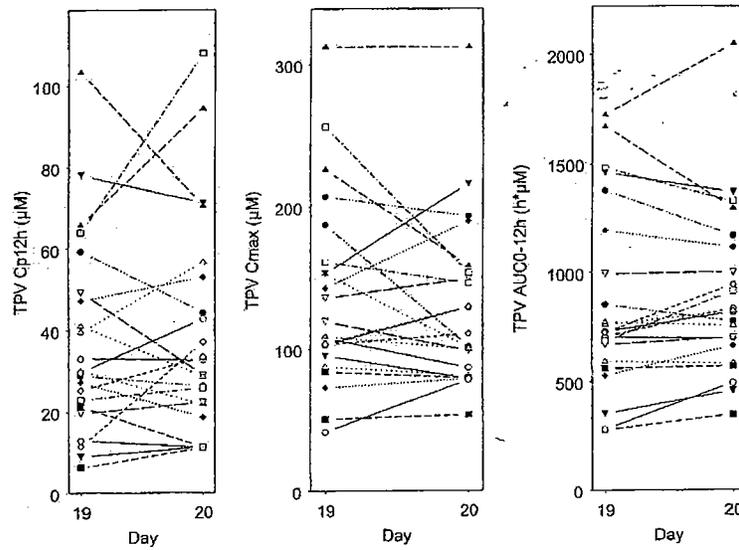


Table 6. Summary of the single-dose pharmacokinetic parameters of TPV with and without antacid

TPV PK parameter <sup>s</sup>	TPV/r alone (Day 8)	TPV/r + antacid (Day 13)
T <sub>max</sub> (h)	3.1	2.8
C <sub>max</sub> (μM)	68.82	51.39
AUC <sub>0-∞</sub> (h*μM)	634.61	462.87
Cp <sub>12h</sub> (μM)	22.46	15.93
Cl/F (L/h)	1.31	1.79
V (L)	10.32	13.50
z (h <sup>-1</sup> )	0.127	0.133
t <sub>1/2</sub> (h)	5.47	5.22

<sup>s</sup> Geometric Mean

Table 7. Summary of geometric mean ratios and 90% confidence intervals for TPV pharmacokinetic parameters with and without antacid (Day 13 versus Day 8)

Comparison	AUC <sub>0-∞</sub>			C <sub>max</sub>			Cp <sub>12h</sub>		
	% change	Ratio	90% CI	% change	Ratio	90% CI	% change	Ratio	90% CI
Day 13 versus Day 8	-27%	0.73	0.64-0.84	-25%	0.75	0.63-0.88	-29%	0.71	0.59-0.85

Figure 4. Effect of antacid on the single-dose TPV pharmacokinetic parameters ( $C_{p12h}$ ,  $C_{max}$  and AUC)

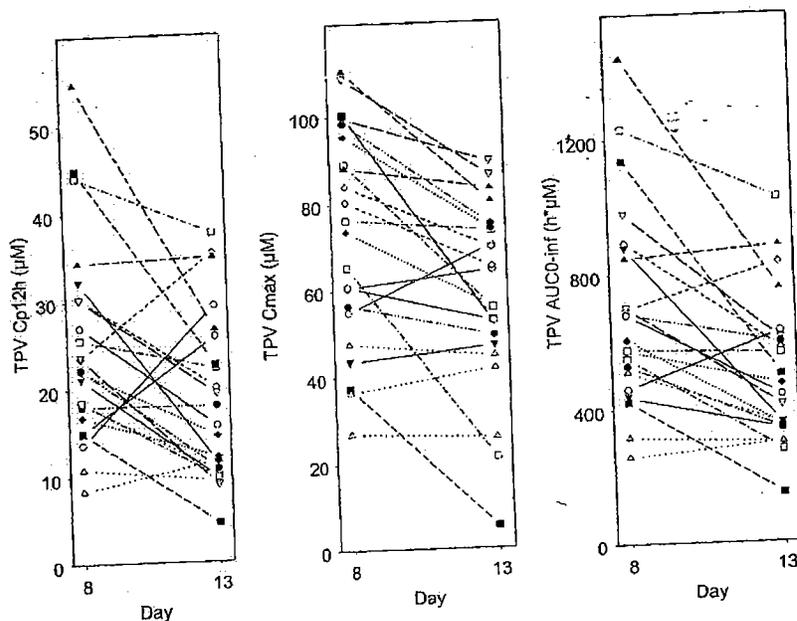
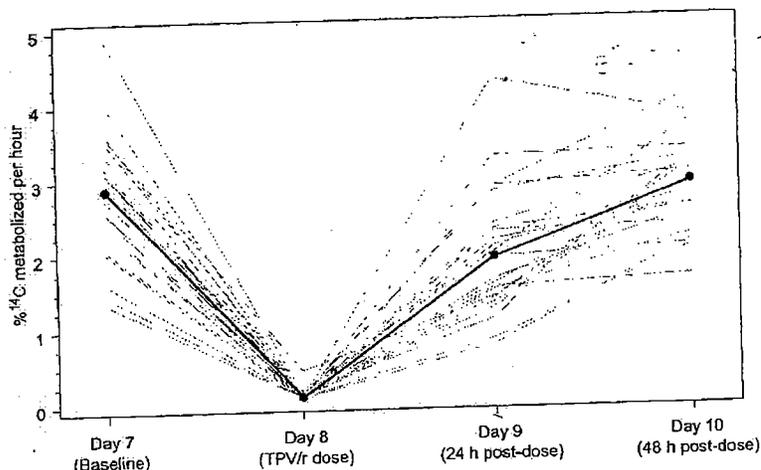


Table 8. Summary statistics of the erythromycin breath test results (%  $^{14}C$  metabolized per hour) on Study Days 7 through 10

	Study Day 7 (baseline)	Study Day 8 (TPV/r dose)	Study Day 9 (24h post-dose)	Study Day 10 (48h post-dose)
Mean	2.83	0.11	1.97	2.85
SD	0.84	0.08	0.85	0.63
Min	┌			┐
Median	2.88	0.09	1.91	2.89
Max	┌			┐
Geometric mean	2.70	0.10	1.81	2.78

Figure 5. Individual and median changes in hepatic CYP3A4 activity, as measured by erythromycin breath test, at baseline (Day 7), after a single-dose of TPV/R (500/200 mg, Day 8), 24-hour post-dose (Day 9), and 48-hour post-dose (Day 10)



**SAFETY RESULTS:**

Consistent with previous TPV trials, the most frequently observed AEs were GI-related on TPV/r treatment.

**CONCLUSIONS AND DISCUSSION:**

ATV is extensively metabolized by CYP3A4. Co-administration of steady-state TPV/r increased single dose ATV's AUC by 9.4-fold,  $C_{max}$  by 8.6-fold and  $C_{p12}$  by 5.2-fold. No effect of single-dose ATV on the steady-state PK of TPV/r was observed. Similar findings have been reported for lopinavir/ritonavir 400/100 BID, which increased ATV AUC and  $C_{max}$  by 6- and 5-fold respectively. The ATV interaction data suggest that the net effect of TPV/r 500/200 BID at steady-state is inhibition of CYP3A4 mediated metabolism.

The Erythromycin Breath Test result demonstrated that a single dose of TPV/r 500/200 mg nearly completely inhibited the hepatic CYP3A4 activity. However, CYP3A activity returned to baseline levels as TPV/r was eliminated from the body.

Simultaneous ingestion of antacid and TPV/r reduced the plasma TPV concentrations by about 25-29%. The exact mechanism of the interaction between antacid and TPV/r is not known.

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1182.22 (Reviewer: Lincy Thomas, Pharm.D.)

**Study Title:** A single center, open-label, randomized, parallel group, multiple dose comparison of the effect of Tipranavir 750 mg and Ritonavir 200 mg or Tipranavir 500 mg and Ritonavir 100 mg, administered twice daily, on the pharmacokinetic characteristics of Norethindrone-Ethinyl Estradiol (Ortho<sup>®</sup>-1/35) administered as a single dose, in healthy female adult volunteers.

**Objectives:** To characterize the effects of two dose combinations of TPV/RTV (TPV 750 mg/RTV 200 mg and TPV 500 mg/RTV 100 mg), administered twice-daily, on the pharmacokinetics of NET/EE (1 mg/0.035 mg) administered as a single dose.

**Study Design:** Open-label, randomized, parallel group, pharmacokinetic study of two dose pairs of TPV/RTV in 52 healthy female adults between the ages of 18 and 50 years. The two TPV/RTV dose arms were: TPV 750 mg/RTV 200 mg and TPV 500 mg/RTV 100 mg. All subjects were given one dose of NET/EE (1/0.035 mg) on Day 1 and post-dose plasma concentrations were obtained. On Day 4, they started a 12 day course of twice-daily TPV/RTV at one of the 2 doses to allow TPV/RTV to get to steady-state. On Day 15, subjects were given a single dose of NET/EE and post-dose plasma concentrations were obtained again. On Day 16, subjects received a final morning dose of TPV/RTV. The study was planned to end on Day 17, with no study medications being administered at that time point. Laboratory assessments and safety parameters were assessed at screening and on Days 4, 14, 17 and at the end of the study.

*Reviewer comment:* Due to the unexpected group of adverse events (skin and subcutaneous tissue disorders), which led to 19 subjects withdrawing from the study prior to completion, the sponsor decided that the final evening dose of TPV/RTV on Day 16 should not be administered. The remaining 32 patients were discontinued at the request of the sponsor prior to administration of the final dose.

**Formulation:** TPV [soft elastic capsule-Self Emulsifying Drug Delivery System (SEDDS)]: 250 mg capsules. RTV (Norvir-SEC<sup>®</sup>) soft elastic capsule: 100 mg capsules. NET/EE (Ortho<sup>®</sup>-1/35) tablet: 1mg Norethindrone; 0.035 mg ethinyl estradiol

**Pharmacokinetic Analysis:** Plasma drug samples were taken at regular intervals up to 24 – 48 hours post-dose on Study Day 1, 14 and 15.

Primary endpoints:

- Single dose pharmacokinetics of NET/EE (with and without TPV and RTV):
  - $AUC_{0-24h}$  and  $C_{max}$
- Steady state pharmacokinetics of TPV/RTV (with and without NET/EE):
  - $AUC_{0-12h}$ ,  $C_{max}$ , and  $C_{12h}$

Secondary endpoints:

- Identification of additional pharmacokinetic parameters including  $CL/F$ ,  $t_{max}$  and  $t_{1/2}$  for NET/EE and for TPV/RTV

*Reviewer comment:* Changes were made to the initial plan of conduct for the study. In order to obtain useful PK data from the second single dose of NET/EE given on Day 15, the subjects agreed to have the final PK sampling brought forward from 48 hours to 35 hours. This change was also approved by ethics board, who approved taking additional blood samples to establish the safety status of the subjects who were experiencing AEs. As a consequence of the change in timing of the final PK sampling, the analysis plan was altered, changing the NET/EE outcome of  $AUC_{0-48h}$ , to  $AUC_{0-24h}$ . This change is acceptable.

The following pharmacokinetic parameters were derived using non-compartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule), maximum observed concentration ( $C_{max}$ ), trough plasma concentration ( $C_{12h}$ ) for TPV/RTV, and concentration at a specified time after dosing (NET/EE, 24 hours; TPV and RTV, 12 hours).

**Analytical Analysis:** Plasma samples for TPV/RTV determination were measured by a validated [ ] method. The analysis for NET and EE were performed on a [ ] system.

**Pharmacokinetic Results:** NET and EE plasma concentration-time profiles were collected on Study Day 1 and on Study Day 15. TPV and RTV plasma concentration-time profiles were collected on Study Day 14 and on Study Day 15.

The addition of TPV/RTV at doses of either 500/100 or 750/200 mg BID to NET/EE (1/0.035mg) therapy reduced the total EE exposure ( $AUC_{0-24h}$ ) by 43 – 48%, and the maximal EE concentrations ( $C_{max}$ ) by approximately 50%. For both TPV/RTV doses, the suppressive effect on the  $AUC_{0-24h}$  and  $C_{max}$  of EE was statistically significant and clinically relevant. The observed reduction in  $AUC_{0-24h}$  and  $C_{max}$  can likely be explained by the net result of induction/inhibition of CYP3A4 by TPV/RTV, and increased glucuronidation due to RTV.

*Reviewer comment:* The 43 – 48% reduction in  $AUC_{0-24h}$  and 50% reduction in  $C_{max}$  indicate a drug interaction that is clinically significant and may compromise the efficacy of NET/EE (1/0.035mg). Therefore, oral contraceptives should not be the primary mode of birth control for patients taking TPV/RTV.

In contrast, repeated dosing of TPV/RTV significantly increased the single-dose  $AUC_{0-24h}$  of NET by 13.6% for the TPV/RTV dose of 500/100 mg, and by 27.1% for the TPV/RTV 750/200 mg dose. These increases are not expected to be clinically significant. There were no substantial changes in the single-dose  $C_{max}$  of NET after co-administration of either TPV/RTV dose combination. The inhibitory effects of RTV on metabolic enzymes may outweigh any inducing effects of TPV and RTV on the metabolism of NET, but not EE.

The effect of a single dose of NET/EE on steady state TPV/RTV:

For the dose combination of TPV/RTV 750/200 mg, the  $AUC_{0-12h}$ , the  $C_{max}$ , and the  $C_{12h}$  of TPV were not substantially affected by the co-administration of a single dose of NET/EE (1/0.035 mg). The lower confidence bound for RTV geometric mean ratios was less than one. However, the point estimates changed by less than 15%.

For the TPV/RTV 500/100 mg dose, the  $AUC_{0-12h}$  and the  $C_{max}$  of TPV were not substantially changed by co-administration of a single dose of NET/EE (1/0.035 mg). At this dosage, the  $AUC_{0-12h}$  and the  $C_{max}$  of RTV were reduced by 23 and 25%, respectively. However, the  $C_{12h}$  of TPV was significantly reduced by 27.3% (90% CI of the geometric mean ratio = 0.59,0.90;  $p=0.019$ ) after co-administration of a single dose of NET/EE, and the  $C_{12h}$  of RTV was reduced by 45.3%.

Administration of EE (in combination with 500 µg norgestrel) for 10 days did not affect intestinal or hepatic CYP3A activity as determined by midazolam metabolism in nine healthy women [R03-1002]. An effect of NET/EE on the PK of TPV and RTV mediated through CYP3A4 seems therefore unlikely. Even if NET/EE would induce CYP3A4 isoenzymes, an effect would not be apparent after a single dose of NET/EE. Thus, the mechanism for the decreased  $C_{12h}$  of TPV and RTV in the TPV/RTV 500/100 mg dose group requires further investigation.

*Reviewer comment:* The sponsor provided 2 sets of data analyses. For the primary PK analyses, data from 21 subjects in the TPV/RTV 500/100 mg group, and from 13 subjects in the TPV/RTV 750/200 mg group, were utilized (Table shown below). However, for completeness and sensitivity evaluation, the Sponsor also generated data including three subjects who may not have met the inclusion criteria of the trial (had measurable EE in their plasma at baseline). This data set included data from 22 subjects in the TPV/RTV 500/100 mg group, and from 15 subjects in the TPV/RTV 750/200 mg treatment group. The values from both data sets are similar.

**Summary of Geometric Mean Ratios and 90% Confidence Intervals for the  
Co-administration of TPV/RTV with NET/EE: Trial 1182.22**

(Data excluded from three subjects who had detectable plasma levels of EE pre-dose Day 1)

		TPV/RTV 500/100 mg (n=21)			TPV/RTV 750/200 mg (n=13)		
		90% CI			90% CI		
Drug name	PK parameter	Geometric Mean Ratio <sup>1</sup>	Lower	Upper	Geometric Mean Ratio <sup>1</sup>	Lower	Upper
NET	AUC <sub>0-24h</sub>	1.136	1.059	1.218	1.271	1.133	1.426
	C <sub>max</sub>	1.033	0.940	1.134	1.077	0.971	1.195
EE	AUC <sub>0-24h</sub>	0.517	0.479	0.557	0.570	0.542	0.600
	C <sub>max</sub>	0.517	0.468	0.572	0.484	0.415	0.565
TPV	AUC <sub>0-12h</sub>	0.983	0.875	1.105	0.980	0.895	1.072
	C <sub>max</sub>	1.101	0.982	1.235	1.012	0.962	1.064
	C <sub>12h</sub>	0.727	0.586	0.903	0.908	0.686	1.200
RTV	AUC <sub>0-12h</sub>	0.770	0.605	0.981	0.986	0.667	1.457
	C <sub>max</sub>	0.750	0.590	0.952	0.967	0.722	1.295
	C <sub>12h</sub>	0.547	0.326	0.920	0.864	0.388	1.922

<sup>1</sup> Ratio = (substrate + TPV/RTV)/substrate [Day 15 versus Day 1]  
Ratio = (substrate + NET/EE)/substrate [Day 15 versus Day 14]

**Safety results:** In addition to the anticipated gastrointestinal AEs, there was an unexpected constellation of skin and subcutaneous tissue disorders, variously described as 'rash' which led to subjects discontinuing from the study. Due to the unexpected occurrence of AEs, the study was discontinued prior to the administration of the final dose on the evening of Day 16.

The percentage of subjects who experienced any AEs, was the same in each group at 96.2%. There were no SAEs in the trial. Of the 501 AEs reported during the study, 464 (92.6%) were DAIDS Grade 1 (mild), and 37 (7.4%) were DAIDS Grade II (moderate). No AEs of severe intensity were reported.

In the TPV/RTV low dose group, 7 subjects were discontinued due to AEs. In the TPV/RTV high dose group, 12 subjects were discontinued due to AEs. Skin and subcutaneous system disorder AEs were the most frequent, with 7 subjects discontinued from the high-dose group due to this AE, and 4 from the low-dose group.

**Conclusions:**

- The addition of TPV/RTV at doses of either 500/100 mg BID or 750/200 mg BID to NET/EE (1/0.035 mg) therapy reduced the total EE exposure (AUC<sub>0-24h</sub>) by 43-48%, and the maximal EE concentrations (C<sub>max</sub>) by approximately 50%. This reduction of > 40% in the exposure to EE may significantly compromise the efficacy of this oral contraceptive. Therefore oral contraceptives should not be the primary method of birth control in HIV-infected women of child-bearing potential using TPV/RTV.
- The 13-27% increase in the exposure (AUC<sub>0-24h</sub>) to NET after co-administration of TPV/RTV is not expected to be clinically relevant.
- The reduction in the C<sub>12h</sub> of TPV and RTV at the TPV/RTV 500/100 mg dose suggests that inhibition of CYP3A4 is not complete at the 100 mg dose of RTV. Since this effect was not seen with the TPV/RTV 750/200 mg dose, it appears the 200 mg dose of RTV provides a more pronounced inhibition of CYP3A4.
- See Medical Review for conclusion about the adverse events.

## 1182.24

**TITLE:** A phase I multiple oral dose trial of tipranavir 500 mg/ritonavir 200 mg dosed to steady-state followed by single-dose <sup>14</sup>C-radiolabeled tipranavir co-administered with tipranavir 500 mg/ritonavir 200 mg to characterize the excretion balance and metabolite profile of <sup>14</sup>C-radiolabeled tipranavir in healthy male subjects

**OBJECTIVES:** To characterize the excretion mass balance and metabolite profiles of <sup>14</sup>C-radiolabeled tipranavir at steady-state in healthy male subjects and to isolate, identify and quantify major metabolites of tipranavir in plasma, urine and feces

**SUBJECTS AND STUDY DESIGN:** This was an open label, single arm study that administered <sup>14</sup>C-tipranavir to healthy HIV-negative subjects who had achieved tipranavir steady-state after receiving 13 doses of tipranavir 500 mg/ritonavir 200 mg bid. On Day 7, a single dose of 549 mg of unlabeled tipranavir and approximately 90 µCi of <sup>14</sup>C-tipranavir (2 mg) were coadministered with ritonavir (200mg). Subjects were to continue receiving unlabeled tipranavir 500 mg/ritonavir 200 mg bid until study termination (minimum of 14 days if at Day 14 the total radioactivity in urine and stool over a 24-hour collection period was less than 1% of the administered dose, or maximum of 21 days).

Morning and evening doses were administered two hours before breakfast and dinner, respectively. Subjects received a light snack an hour before morning and evening doses.

### INVESTIGATOR AND STUDY LOCATION: [REDACTED]

]

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. <sup>14</sup>C-radiolabeled tipranavir in ethanol with non-radiolabeled tipranavir bulk fill (SEDDS formulation) as 3 gelatin capsules containing a mean total of 551 mg of tipranavir and approximately 90 µCi of radioactivity.

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples were collected for tipranavir trough concentrations in the evenings on Days 1-6 and mornings on Days 8-18. On Day 7, two troughs were collected and a 12-hour intensive blood sampling (prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h post dose) was performed for pharmacokinetic profile after radiolabeled TPV/r administration. On Day 4, blood, urine, and stool samples were obtained to determine baseline <sup>14</sup>C radioactivity. Starting on Day 7 all stools and urine samples were collected until study termination.

**ASSAY:** Calibrated liquid scintillation counters were used to measure concentrations of radioactivity in each of the samples (blood, plasma, urine, fecal homogenate, and toilet tissue homogenate). Plasma samples for TPV and RTV were analyzed by [REDACTED]

chromatography [REDACTED] using a validated high performance liquid chromatography [REDACTED] method. The calibration curve for TPV ranged from [REDACTED] ng/mL to [REDACTED] ng/mL.

**PRIMARY ENDPOINTS:** Cumulative amount of <sup>14</sup>C-radioactivity excreted in feces and urine, identification and quantification of major tipranavir metabolites in plasma, urine and feces (presented in report U03-3555) and pharmacokinetic parameters such as C<sub>max</sub>, C<sub>p12h</sub> and AUC for <sup>14</sup>C-radiolabeled-tipranavir co-administered with RTV using non-compartmental methods.

**PHARMACOKINETIC RESULTS:**

Table 1. Total recovery of radioactivity in urine, feces and toilet tissue expressed as percent of dose

Subject	Total Cumulative Recovery as Percent of Dose			
	Urine	Feces	Toilet tissue	TOTAL
104	[			]
106				
108				
109 <sup>a</sup>				
113 <sup>b</sup>				
116				
122				
123				
127	]			
<b>Excluding 113</b>				
Median <sup>c</sup>	4.4	82.3	0.27	87.1
Range	[			]
Mean ± SD	4.6 ± 0.6	70.4 ± 24.0	0.37 ± 0.34	75.3 ± 23.7
<b>Excluding 109 and 113<sup>d</sup></b>				
Median	4.4	83.2	0.30	87.6
Range	[			]
Mean ± SD	4.44 ± 0.47	78.2 ± 10.0	0.42 ± 0.33	83.0 ± 10.0

- <sup>a</sup> Subject 109 had an unusually low total recovery, and this was associated with an unusually low fecal recovery. There was no explanation for this finding. Values for median, range, and mean ± SD were calculated with this subject's data but were also calculated without this subject's data for the reader's information only.
- <sup>b</sup> Subject 113 had an episode of diarrhea, and the sample was lost. Therefore, the results for this subject were excluded from calculations of median, range, and mean ± SD.
- <sup>c</sup> Median for results excluding Subject 113 were calculated as the average of the middle two values.
- <sup>d</sup> Summary results are presented with both Subjects 109 and 113 excluded for information only.
- Source data: Appendix 16.3.1.2.

Table 2. Summary of steady-state TPV pharmacokinetics on Day 7 following administration of <sup>14</sup>C TPV +TPV/r

Parameter	n	Mean	SD	Min	Median	Max	gMean <sup>4</sup>	hMean <sup>4</sup>
TPV Dose (mg) <sup>1</sup>	9	551	1		551			
t <sub>1/2</sub> (hr)	9	2.9	1.1		3.0		2.8	
C <sub>max</sub> (µM) observed <sup>2</sup>	9	99.39	23.37		92.08		97.09	
C <sub>max</sub> (µM) normalized <sup>3</sup>	9	90.23	21.30		83.56		88.13	
C <sub>0-12h</sub> (µM) observed <sup>2</sup>	9	25.85	18.84	/	22.49	/	21.44	
C <sub>0-12h</sub> (µM) normalized <sup>3</sup>	9	23.46	17.06	/	20.41	/	19.46	
AUC <sub>0-12h</sub> (h*µM) observed <sup>2</sup>	9	657.0	170.9		601.2		638.4	
AUC <sub>0-12h</sub> (h*µM) normalized <sup>3</sup>	9	596.5	155.7		545.5		579.4	
λ <sub>z</sub> (hr <sup>-1</sup> )	9	0.1631	0.0499		0.1713		0.1561	
t <sub>1/2</sub> (hr)	9	4.6	1.5		4.0			4.2
CL (L/hr)	9	1.47	0.36		1.52		1.43	
V (L)	9	9.6	3.2		9.2		9.2	

- <sup>1</sup> Unlabeled TPV + <sup>14</sup>C-TPV
- <sup>2</sup> Based on noncompartmental PK analysis using reported TPV concentrations
- <sup>3</sup> Based on noncompartmental PK results corrected for TPV dose: (Observed PK metric / actual TPV dose) \* nominal TPV dose, where actual TPV dose is the dose administered to each subject and the nominal TPV dose is 500 mg
- <sup>4</sup> gMean: geometric mean; hMean: harmonic mean

Table 3. Summary of steady-state RTV pharmacokinetics on Day 7 following administration of <sup>14</sup>C TPV +TPV/r

Parameter	n	Mean	SD	Min	Median	Max	gMean <sup>1</sup>	hMean <sup>1</sup>
t <sub>1/2</sub> (hr)	9	3.7	0.7		4.0		3.6	
C <sub>0</sub> (µg/mL)	9	1.2	0.5		1.2		1.2	
t <sub>1/2</sub> (hr)	9	10.7	1.7		12.0		10.5	
C <sub>12h</sub> (µg/mL)	9	0.09	0.02		0.08		0.08	
C <sub>24h</sub> (µg/mL)	9	0.05	0.05		0.05		0.08	
AUC <sub>0-12h</sub> (µg·h/mL)	9	4.90	2.15		4.55		4.52	
AUC <sub>0-24h</sub> (µg·h/mL)	9	0.4132	0.1003		0.3927		0.4030	
t <sub>1/2</sub> (hr)	9	1.76	0.41		1.76			1.68
CL (L/hr)	9	48.1	21.4		44.0		44.3	
CL <sub>R</sub> (L/hr)	9	115.5	37.8		104.1		109.9	

<sup>1</sup>gMean: geometric mean; hMean: harmonic mean

Figure 1. Cumulative recovery of radioactivity (Median ± range) in urine and feces after oral dosing of <sup>14</sup>C-tipranavir (ranges indicated by dashed line for feces and dotted line for urine)

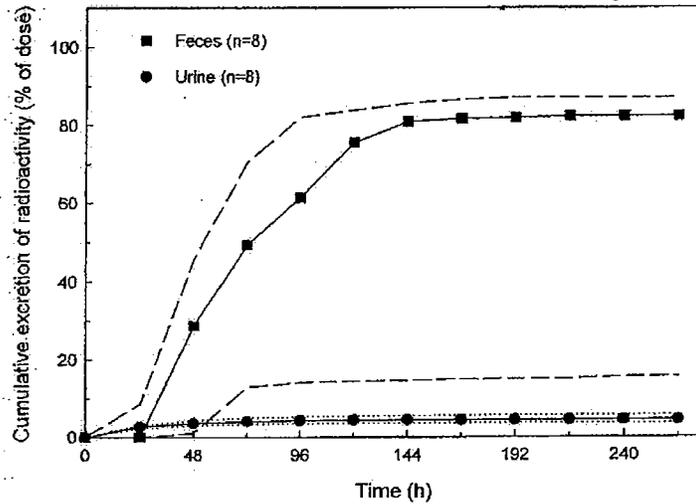
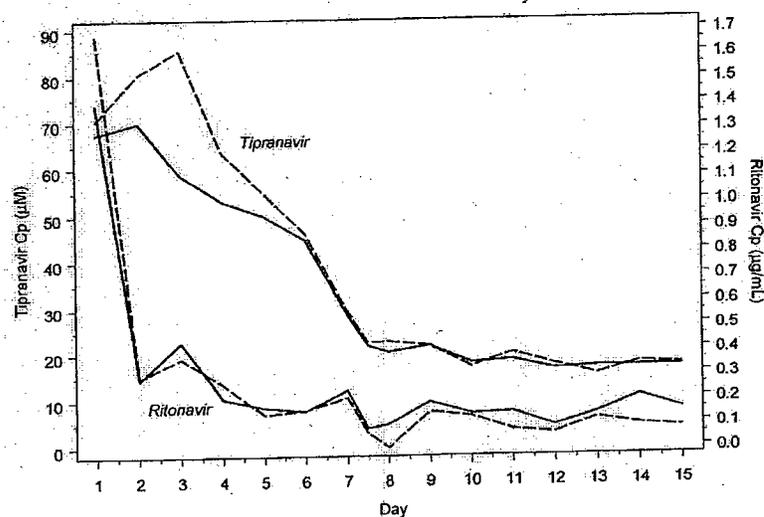


Figure 2. Comparison of daily plasma tipranavir and ritonavir trough concentrations for the subgroup of 7 subjects receiving TPV/r 500/200 mg bid for 14.5 days (Solid line: geometric mean, broken line: median)



Tipranavir metabolite profile and identification in humans was summarized in a separate report (U03-3555). In plasma, unchanged TPV was predominant and accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8 or 12 hours after dosing. Only a few metabolites were found in plasma and all were at trace levels (0.2% or less). In feces, unchanged TPV represented about 80% of fecal radioactivity. In urine, unchanged TPV was found in trace amount, about 0.5% of total urine radioactivity.

Table 4. TPV plasma metabolite profile (pooled plasma from all subjects) in human

TPV Human Plasma Metabolite Profile (Pooled Plasma from All Subjects)						
Compound	3 hour		8 hour		12 hour	
	% plasma <sup>14</sup> C	µg-Eq/mL	% plasma <sup>14</sup> C	µg-Eq/mL	% plasma <sup>14</sup> C	µg-Eq/mL
H-1	0.2	0.1	ND	ND	ND	ND
H-2	ND	ND	ND	ND	ND	ND
H-3	0.1	0.05	ND	ND	ND	ND
TPV	98.9	48.6	98.4	21.0	99.7	10.7
Total	99.2	48.8	98.4	21.0	99.7	10.7

Table 5. TPV plasma metabolite profile in human feces

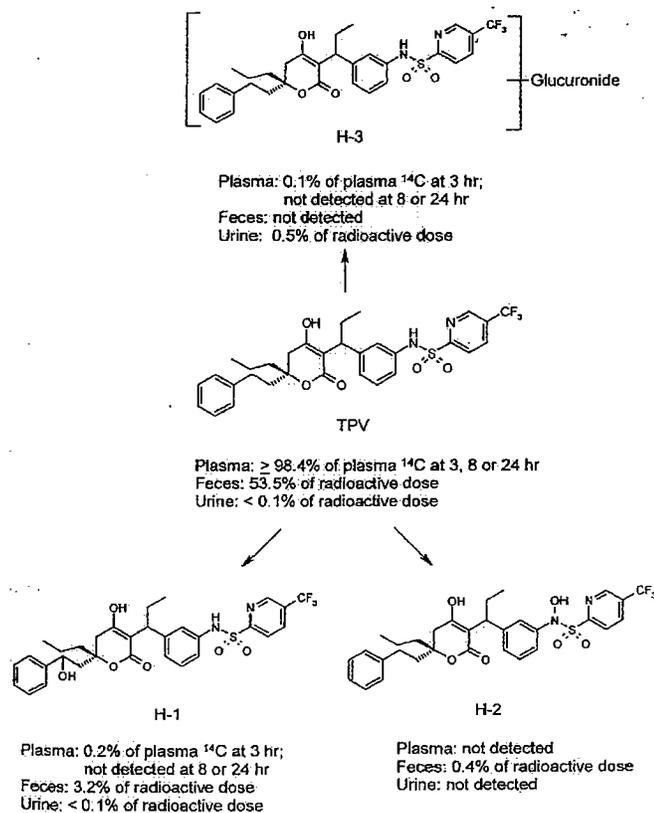
TPV Metabolite Profile in Human Feces											
Compound	Subject Number									Mean	SD
	M 104	M 106	M 108	M 109	M 113	M 116	M 122	M 123	M 127		
	Percent of Fecal Sample Radioactivity										
H-1	3.4	2.4	3.7	6.6	4.3	5.2	5.3	7.4	5.7	4.9	1.6
H-2	ND	1.0	1.0	3.1	0.7	0.5	0.7	ND	0.5	0.8	0.9
H-3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	NA
TPV	84.7	84.4	78.6	69.6	80.9	79.7	80.8	79.3	81.3	79.9	4.4
Total	88.1	87.8	83.3	79.3	85.9	85.4	86.8	86.7	87.5	85.6	2.8
Percent of Dose Radioactivity											
H-1	2.9	1.5	3.0	1.0	1.4	4.5	3.5	6.1	4.8	3.2	1.7
H-2	ND	0.6	0.8	0.5	0.2	0.4	0.4	ND	0.4	0.4	0.3
H-3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	NA
TPV	71.4	52.5	64.0	10.9	26.1	69.3	52.8	66.0	68.1	53.5	21.3
Total	74.3	54.6	67.8	12.4	27.7	74.2	56.7	72.1	73.3	57.1	22.5
Total Radioactivity Excreted in Feces (% of Dose)											
All	84.4	62.2	81.4	15.7	32.3	87.0	65.3	83.2	83.8	66.1	25.8

Table 6. TPV plasma metabolite profile in human urine

TPV Metabolite Profile in Human Urine											
Compound	Subject Number									Mean	SD
	M 104	M 106	M 108	M 109	M 113	M 116	M 122	M 123	M 127		
	Percent of Urine Sample Radioactivity										
H-1	ND	0.1	0.2	ND	ND	ND	ND	ND	ND	<0.1	NA
H-2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	NA
H-3	11.3	6.9	8.1	6.6	14.1	15.5	8.8	12.9	14.8	11.0	3.5
TPV	0.3	0.1	0.2	0.2	0.7	1.1	ND	0.6	0.9	0.5	0.4
Total	11.6	7.1	8.5	6.8	14.8	16.6	8.8	13.5	15.7	11.5	3.8
Percent of Dose Radioactivity											
H-1	ND	<0.1	<0.1	ND	ND	ND	ND	ND	ND	<0.1	NA
H-2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	NA
H-3	0.6	0.3	0.4	0.4	0.6	0.7	0.4	0.6	0.5	0.5	0.1
TPV	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	ND	<0.1	<0.1	<0.1	NA
Total	0.6	0.3	0.4	0.4	0.6	0.7	0.4	0.6	0.5	0.5	0.1
Total Radioactivity Excreted in Urine (% of Dose)											
All	5.1	4.9	4.4	5.6	3.9	4.2	4.4	4.5	3.6	4.5	0.6

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Figure 3. Proposed TPV human metabolite pathways



**CONCLUSIONS AND DISCUSSION:** At steady-state, a median of 82.3% of the radioactivity of the dose was recovered in feces indicating that the main route of excretion of tipranavir was via the feces. It could result from a combination of unabsorbed drug as well as biliary excretion of absorbed drugs and its metabolites. Since the predominant portion of fecal radioactivity was present as unchanged TPV, and the observations from an in vitro study indicate that TPV is a P-gp substrate, part of the radioactivity could be due to “excretion” into the gastrointestinal tract mediated by this efflux transporter.

Renal elimination appeared to be a minor route of excretion for TPV as only a median of 4.4% radioactivity of the dose was recovered in urine, and unchanged TPV was about 0.5% of total urine radioactivity.

Daily trough level monitoring confirmed that steady-state of TPV/r was reached after about 7 days of dosing. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1 (Figure 2.). However, in plasma, unchanged TPV was predominant and accounted for 98.4% or greater of the total plasma radioactivity at the steady-state. The decreased TPV concentrations cannot be explained by CYP3A inhibition or induction. Possible explanation is that TPV is also a potent P-gp inducer and the low dose of RTV can not compensate for P-gp induction effect caused by TPV. Since TPV is a P-gp substrate, at steady-state, more TPV is pumped back to intestinal lumen as unabsorbed drug by increased activity of intestinal P-gp.

1182.32

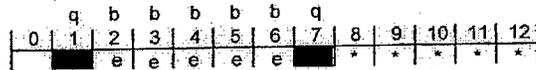
**TITLE:** An open-label study to determine the pharmacokinetics of single-dose and/or steady-state TPV/RTV 500/200 mg in subjects with mild and moderate hepatic insufficiency

**OBJECTIVES:** To determine the pharmacokinetics of single-dose and steady-state TPV/RTV 500/200 mg in subjects with mild and moderate hepatic insufficiency

**SUBJECTS AND STUDY DESIGN:** This was an open-label study in HIV negative male and female subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic insufficiency as well as healthy control subjects without hepatic insufficiency (matched by gender, race, age, weight and cigarette smoking).

Nine subjects who were enrolled into Group A (CP score: 5-6) received TPV/r until reaching steady-state with dosing and sampling scheme as follows:

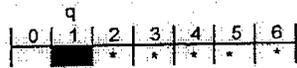
**Schematic A**  
500/200



- b = bid dosing
- q = single dose
- = TPV and RTV intensive PK sampling
- e = evening trough sample
- \* = morning sample

Three subjects who were enrolled into Group B (CP score: 7-9) received one dose of TPV/r with dosing and sampling scheme as follows:

**Schematic B**  
500/200



- q = single dose
- = TPV and RTV intensive PK sampling
- \* = morning sample

Meals were taken at least 1 hour after dosing. A light snack to minimize nausea and vomiting could be given no less than 1 hour prior to dosing.

The overall demographic characteristics of 24 subjects were as following: Male (83.3%) and female (16.7%); White (100%).

**INVESTIGATOR AND STUDY LOCATION:** Multicentre

**FORMULATION:** Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules.

**PHARMACOKINETIC SAMPLE COLLECTION:** Blood samples were collected for assay of TPV and RTV concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose on Days 1 and 7 for Group A and on Day 1 for Group B. Addition daily trough samples were also taken.

**ASSAY:** Plasma samples were analyzed for TPV and RTV by  $\square$  using a validated high performance liquid chromatography  $\square$  method. The calibration curve for TPV ranged from  $\square$  ng/mL to  $\square$  ng/mL.

**PHARMACOKINETIC DATA ANALYSIS:** Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for  $C_{max}$ ,  $C_{p12}$  and  $AUC_{0-\infty}$  were provided for TPV and RTV. The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

**PHARMACOKINETIC RESULTS:**

Table 1. Summary of the single dose TPV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with mild hepatic insufficiency to their matched controls

Parameter	Mild Controls <sup>1</sup>	Mild Hepatics <sup>1</sup>	Geometric Mean Ratio <sup>2</sup>	p-value <sup>3</sup>
$AUC_{0-\infty}$ (h· $\mu$ M)	854 $\pm$ 254 (806)	803 $\pm$ 279 (717)	0.89 (0.55, 1.45)	0.67
$C_{max}$ ( $\mu$ M)	74 $\pm$ 21 (71)	67 $\pm$ 29 (56)	0.79 (0.44, 1.43)	0.48
$C_{p12h}$ ( $\mu$ M)	24 $\pm$ 9 (22)	25 $\pm$ 9 (23)	1.03 (0.62, 1.71)	0.91

<sup>1</sup> Mean  $\pm$  SD geometric mean in parentheses  
<sup>2</sup> Geometric mean ratio of the differences, 2 90% confidence interval in parentheses  
<sup>3</sup> ANOVA

Table 2. Summary of the single dose RTV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with mild hepatic insufficiency to their matched controls

Parameter	Mild Controls <sup>1</sup>	Mild Hepatics <sup>1</sup>	Geometric Mean Ratio <sup>2</sup>	p-value <sup>3</sup>
$AUC_{0-\infty}$ (h· $\mu$ g/mL)	20 $\pm$ 9 (18)	15 $\pm$ 8 (10)	0.58 (0.23, 1.42)	0.29
$C_{max}$ ( $\mu$ g/mL)	3.9 $\pm$ 2.2 (3.4)	3.0 $\pm$ 1.7 (2.2)	0.66 (0.28, 1.58)	0.41
$C_{p12h}$ ( $\mu$ g/mL)	0.49 $\pm$ 0.44 (0.36)	0.38 $\pm$ 0.30 (0.19)	0.53 (0.15, 1.86)	0.38

<sup>1</sup> Mean  $\pm$  SD geometric mean in parentheses  
<sup>2</sup> Geometric mean ratio of the differences, 90% confidence interval in parentheses  
<sup>3</sup> ANOVA