CENTER FOR DRUG EVALUATION AND RESEARCH

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 PREACUTIONS 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 = Cmin/adjusted IC_{50}) and the probability of a ≥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 Cmin 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 ≥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 coinfected 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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kellie Reynolds
6/23/05 10:34:11 AM
BIOPHARMACEUTICS

John Lazor
6/23/05 10:40:13 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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

Table of Contents

1 Executive Summary

1.1 Recommendation

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

I. 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 Marking 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 $AUC_{0\text{-}12h}$ 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}, $AUC_{0\text{-}12h}$ and elimination half-life was 32.6 μM, 131 μM, 859 μM-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 $AUC_{0\text{-}12h}$ 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 μM) in human plasma. The degree of binding is similar over a wide concentration range from 10 to 100 μM. TPV binds to both human serum albumin and α-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 tiprnavir 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

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

Table 2: Established and Potential Drug Interactions Based on Drug Interaction Studies or Predictions

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Comment
	HIV-Antiviral Agents	
Nucleoside reverse transcriptase inhibitors: Abacavir	↓Abacavir concentrations by approx. 40%	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.
	Other Agents	
Antacids	↓ Tipranavir approx 30%	Reduced plasma concentrations of tipranavir are expected if antacids, including buffered medications, are administered with tipranavir. Tipranavir should be administered 2 h before or 1 h after these medications.
Antidepressants: SSRIs Atypical antidepressants	Expected ↑ SSRIs Expected ↑ Atypical antidepressants	Coadministration with TPV/r has the potential to produce serious adverse events and has not been studied. Patients should be monitored carefully for adverse events.
Antifungals: Fluconazole Itraconazole	↑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, nicardipine 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: • For patients with CL_{CR} 30 to 60 mL/min the dose of

2 Page(s) Withheld

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

_____ § 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_{CR} < 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.

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_{min}/corrected IC_{50}).

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:

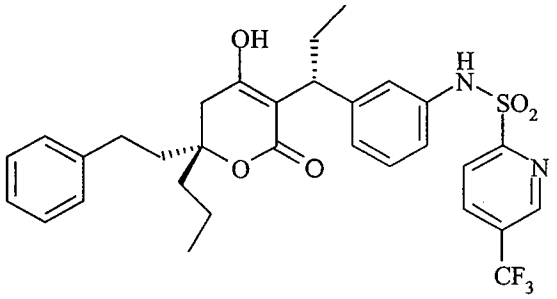
Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

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 ≥ two PIs, had a viral load of ≥ 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?

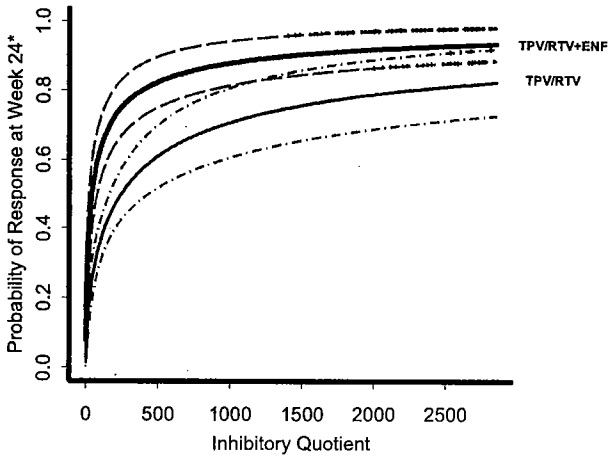
Yes, the applicant measured the appropriate moieties in clinical pharmacology studies. They measured tipranavir and ritonavir in most clinical pharmacology studies. They measured the concentrations of other moieties, as appropriate, in drug interaction studies. It was not necessary to measure concentrations 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 ≥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 log10(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 ≥ 1 log10 viral load reduction at week 24 increases with higher inhibitory quotient.

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



* response is defined as ≥ 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.

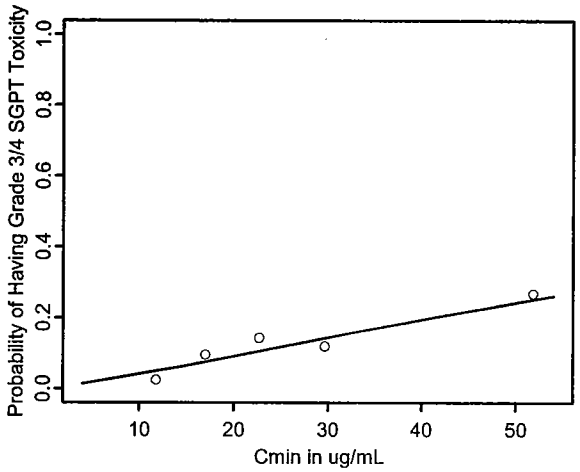
Inhibitory quotient=tipranavir trough concentration/corrected IC_{50}

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

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 log2 (tipranavir trough concentrations, TPV C_{min}), using the data from 210 patients with tipranavir concentrations. The results showed that the odds ratio associated with log2 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?

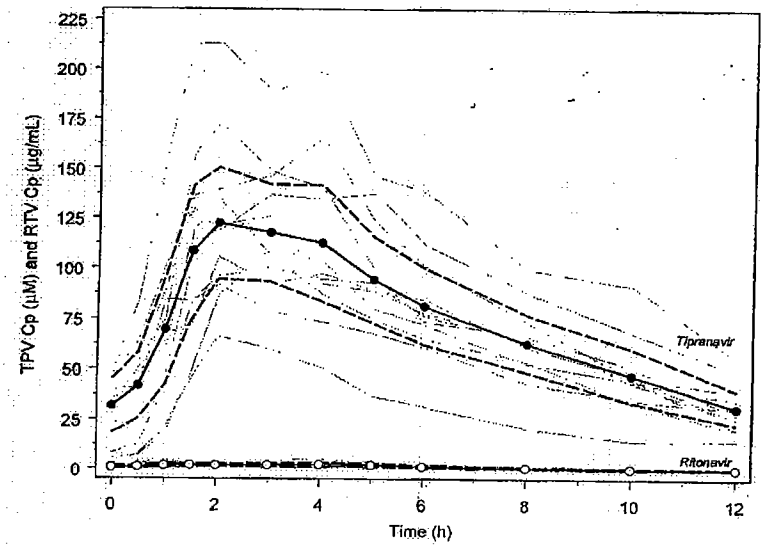
2.2.5.1. What are the single and multiple dose PK parameters?

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_{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 mg*		C_{min} (µM)	C_{max} (µM)	$AUC_{0-\tau}$ (h•µM)
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†		C_{min} (μM)	C_{max} (μM)	$AUC_{0-\tau}$ (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†		C_{min} (μM)	C_{max} (μM)	$AUC_{0-\tau}$ (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)
$Cp_{0h,12h}$ (μM)	30.94	31.63	43.26	32.97
Cmax (μM)	92.33	75.87	114.71	90.08
Tmax (h)	2.9	2.9	3.0	2.9
$AUC_{0\text{-}12h}$ (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
$t_{1/2}$ (h)	6.0		4.8	
	5.5	6.0	4.7	4.8
Ka (h^{-1})	0.5142	0.5291	0.4406	0.4780
Ke (h^{-1})	0.1354	0.1200	0.1560	0.1510

Note: Pharmacokinetic parameters are reported as geometric mean, except $t_{1/2}$ 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 ^{14}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 μM or 5 μM inhibited the metabolism of tipranavir (50 μM) 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).