CLINICAL PHARMACOLOGY REVIEW

NDA: 21-814 SE1 005, 21-822 N 000, 22-292 N 000	Submission Date(s): December 20, 2007
Brand Name	APTIVUS
Generic Name	Tipranavir
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OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Boehringer Ingelheim
Formulation; Strength(s)	Capsule (250 mg) and Solution (100 mg/mL)
Indication	Treatment of HIV-1 infection in protease inhibitor-experienced patients

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I. Executive Summary

Recommendations

The applicant submitted three separate submissions simultaneously:

1. A pediatric supplemental NDA to NDA 21-814 (APTIVUS capsules) to provide for use in children ages 2 through 18 years;
2. A new NDA to register APTIVUS oral solution for use in children;
3. A complete response to the approvable letter for original NDA 21-822 to address the bioequivalence of APTIVUS oral solution for use in adults

This submission includes pharmacokinetics, safety, and efficacy data obtained with APTIVUS in pediatric patients 2 through 18 years, pharmacokinetics (relative bioavailability) data of APTIVUS capsule vs.

solution in healthy adult subjects. The submission also supports the Pediatric Exclusivity claim for APTIVUS.

The Office of Clinical Pharmacology (OCP) reviewed the information submitted and concluded the information is adequate for the proposed indication for tipranavir oral solution and capsule in pediatric patients 2 to 18 years, the use of oral solution in adult patients, and the Pediatric Exclusivity claim.

We also proposed body weight based dosing regimens in pediatric patients in addition to the body surface area based dosing regimens.

Phase IV Commitments

None.

Summary of Clinical Pharmacology Findings

1. Pediatric Use

APTIVUS, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor (PI). The recommended adult dose of APTIVUS is 500 mg co-administered with 200 mg of ritonavir, twice daily.

The sponsor conducted the pediatric Trial 1182.14 in children ages 2 through 18 years to evaluate the use of APTIVUS, co-administered with ritonavir (TPV/r) and to support the indication for use of APTIVUS, co-administered with ritonavir in combination with other antiretroviral drugs for the treatment of HIV infection in treatment experienced patients over 2 years of age.

This was an open-label, randomized study. Children and adolescents were stratified according to age (2 to <6 years, 6 to <12 years and 12 to 18 years) and randomized to one of two doses of tipranavir/ritonavir (TPV/r) with background antiretroviral (ARV) therapy chosen by their local investigator. Children were enrolled in the study regardless of their prior antiretroviral therapy or HIV resistance status. All patients started treatment with TPV oral solution.

The primary objective of this study is to determine the safety and tolerability of TPV oral solution and soft-gel capsules together with low-dose RTV in HIV-infected children and adolescents and to provide information concerning the pharmacokinetic characteristics of TPV and RTV in this age group. The secondary objective of this study is the determination of the dose of TPV/r in children and adolescents between 2 and 18 years of age required for an adult equivalent systemic exposure of TPV/r 500/200 mg.

The two TPV/r doses used in this trial are scaled doses of the adult recommended TPV/r 500/200 mg dose. The low dose is a body surface area (BSA)-equivalent of the adult dose, derived by dividing the adult dose with mean adult BSA of 1.73 m^2 yielding doses of TPV 290 mg/m^2 + RTV 115 mg/m^2. The high dose was calculated by dividing the adult dose with 1.33 m^2 (12 year old male BSA), yielding doses of TPV 375 mg/m^2 + RTV 150 mg/m^2. BSA was calculated at randomization and at each study visit and TPV/r dosing was adjusted as needed. The maximum TPV/r dose allowed was 500/200 mg b.i.d. regardless of the patient's BSA.

Key efficacy endpoints were proportion of patients reaching and maintaining a viral load <400 copies/mL at Week 48 and change in CD4 count from baseline to Week 48. Safety endpoints were adverse events and laboratory measurements using the NIH Division of AIDS (DAIDS) standardized Toxicity Table for Grading Severity of Pediatric (>3 months) Adverse Experiences.

Overall, 43% of study patients achieved and sustained an HIV RNA level < 400 copies/mL and 33% reached an HIV RNA level < 50 copies/mL over the 48 weeks study period. The overall treatment response was slightly higher in the high dose group when compared to the low dose group (46% vs. 40%). However no differences in response rate could be identified in the youngest age group (2 to < 6 years) based on the dose of tipranavir/ritonavir given; the proportion of patients with viral load <400 copies/mL was 70% in both low and high dose groups. Please see details in Medical Officer's review.

Overall, tipranavir co-administered with ritonavir in combination with other antiretroviral drugs was safe and tolerable when administered to pediatric patients 2 to 18 years of age. The types of adverse events reported were similar to adults but the frequency of reporting was lower in pediatric patients, although vomiting and rash were more frequent in pediatric patients. When the high and low dose tipranavir are compared, the overall adverse events profile was similar for the two groups. Please see details in Medical Officer's review.

PK evaluation showed that observed TPV trough concentrations and model based estimates of TPV PK parameters were similar to those observed in adults.

Exposure following administration of the TPV/r low dose was similar the TPV exposure observed in adults. The TPV/r high dose resulted in much higher TPV exposure (about 50% higher) in the 2 to <6 and 6 to <12 age groups than the TPV/r low dose, while smaller increase was found in the 12 to 18 age group. The smaller increase in older group is the reflection of limiting the dose to 500/200 mg and many older patients in the TPV/r high dose group reached that maximum.

The results of the 48-week analysis showed that TPV/r in combination with other antiretroviral agents is effective and well tolerated for treatment of HIV in children 2 to 18 years of age. The efficacy of the higher dose was better than the lower dose for pediatric patients 6 to 18 years old who have multiple tipranavir mutations. Therefore, for the older age group, the benefit of 375/150mg/m^2 dose outweighs the potential higher risks associated with it. In contrast to the older age groups, no added benefit was observed in the youngest age group (2 to 6 years of age) with the administration of the higher tipranavir dose. However some patients enrolled in the youngest age group (2 to 6 years of age) are less treatment experienced and have less drug resistance than the population for whom the drug is indicated. The labeled indication for APTIVUS will continue to be in "patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor". In this patient population, regardless of age, the high dose seems appropriate in order to avoid resistance.

Thus we concur with the sponsor's APTIVUS/ritonavir pediatric dosing recommendation: 375/150 mg/m^2 b.i.d., up to a maximum of 500 mg/200 mg b.i.d. for pediatric patients (age ≥ 2 to <18 years).

Weight based dosing was also explored because it is more convenient than BSA-based dosing in some healthcare settings. Based on Cmin-body weight relationship, 10,000 patients were simulated (nonparametric simulations from observed weights) to assess potential distribution of Cmin following administration of various dose levels of TPV (9 mg/kg, 10 mg/kg, 12 mg/kg and 14 mg/ kg). A working therapeutic window (17.4 μM and 57.2 μM) was selected based on exposure-response for efficacy and safety.

A dose of 14 mg/kg TPV + 6 mg/kg RTV that would match the dose of BSA based dosing (375/150 mg/m^2) would result in 6% and 5% below window, 34% and 41% above window, for pediatric patients ≤ 20 Kg and >20 kg, respectively. Based on benefit-risk assessment, this distribution of C_{min} is acceptable.

However, patients who develop toxicity or intolerance while receiving recommended dose of TPV/r and who do not have multiple baseline protease inhibitor mutations, the dose may be reduced to 290/115 mg/m^2 or 12/5 mg/kg.

2. Oral solution formulation

APTIVUS oral solution formulation (under NDA 21-822) was not approved at the time of the APTIVUS capsule NDA approval. The biopharmaceutics information submitted to NDA 21-822 was not acceptable. Tipranavir solution was about 30% more bioavailable than tipranavir capsules when the dosage forms were administered with ritonavir under fasted conditions; thus, the solution and capsules were not bioequivalent. The relative bioavailability study design (single dose) did not provide definitive results, as discussed below.

Tipranavir is a dual substrate of CYP3A and P-glycoprotein (P-gp). The steady state concentrations of tipranavir depend on the net effect (induction or inhibition) on CYP3A and P-gp. The capsules and solution contain different excipients that may have different effects on CYP3A and P-gp- the capsules contain Cremophor EL and the solution contains vitamin E polythylene glycol succinate. Thus, it is difficult to predict relative bioavailability of these two dosage forms at steady-state from single-dose data due to the complex enzyme/transporter interactions during absorption. It is necessary to evaluate the relative bioavailability of the two dosage forms at steady-state.

In addition to the lack of acceptable relative bioavailability data, the NDA 21-822 did not include adequate pharmacokinetic data from pediatric patients who received the oral solution. Thus a dose for pediatric patients could not be determined.

The current application includes results of an open-label, single-site, one-sequence cross-over study that was conducted to assess the relative bioavailability of TPV/r 500 mg/200 mg at steady state when TPV and RTV were administered as oral solutions vs. capsules in the fed and fasted state.

The primary objective was to establish the relative bioavailability of the TPV oral solution formulation (500 mg co-administered with RTV oral solution 200 mg) to the TPV capsule formulation (500 mg co-administered with RTV capsules 200 mg), with both treatments at steady-state under fasted and fed conditions in healthy male and female volunteers.

At steady-state and under fed conditions, TPV/r oral solution formulation administered as a 500/200 mg dose twice-daily was slightly more bioavailable ($AUC_{0\text{-}12h}$ increased by 23%, C_{max} increased by 14%) than the marketed TPV/r capsule formulation.

At steady-state and under fasted conditions, TPV/r oral solution formulation administered as a 500/200 mg dose twice-daily was more bioavailable ($AUC_{0\text{-}12h}$ increased by 27%, C_{max} increased by 36%) than the marketed TPV/r capsule formulation.

Food did not affect tipranavir steady-state C_{p12h} and $AUC_{0\text{-}12h}$ for subjects that received TPV/r 500/200 mg as the oral solution formulations, however, C_{max} was about 17% lower when TPV/r oral solutions are administered with food compared to the fasted state. Food did not affect tipranavir steady-state C_{p12h}, C_{max}, and $AUC_{0\text{-}12h}$ for subjects that received TPV/r 500/200 mg as the capsule formulations. These results indicate that both TPV capsule and oral solution formulations can be administered to patients either with food or without food.

The current label recommends the tipranavir capsules be taken with food. At the time of the accelerated NDA approval, the finding of food effect on TPV capsule formulation was not conclusive. For the 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. However, 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.

Based on TPV known exposure-response for efficacy and safety, the differences between oral solution and capsule formulation are not sufficient to change the dose regimen from the current recommended dose of TPV/r 500/200 mg bid. Thus oral solution and capsule can be used interchangeably.

II. Question Based Review

A. General Attributes of the Drug

i. What is the proposed therapeutic indication?

APTIVUS, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor (PI).

ii. What is the proposed dosage and route of administration?

The data provided in this submission support the Applicant's proposed dosing recommendations for treatment experienced pediatric patients from 2 – 18 years of age:

375 mg/m^2 APTIVUS co-administered with 150 mg/m^2 ritonavir twice daily with food. Dose based on age and should not exceed adult dose.

We also proposed body weight based dosing regimens in pediatric patients in addition to the body surface area based dosing regimens.

The recommended dosage of APTIVUS is 14 mg/kg co-administered with 6 mg/kg of ritonavir, twice daily.

However, in patients who develop toxicity or intolerance while receiving recommended dose of TPV/r and who do not have multiple baseline protease inhibitor mutations, the dose may be reduced to 290/115 mg/m^2 or 12/5 mg/kg.

The approved APTIVUS capsule and solution are used for pediatric patients.

iii. What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

For pediatric dosing instructions for HIV drugs, safety and PK are required. The proposed dose in pediatric provide exposures similar to observed in adult patients with no new safety concerns.

Study 1182.14 provided relevant safety, PK and efficacy data.

B. General Clinical Pharmacology

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

The surrogate efficacy endpoints for HIV-1 infection are

1. plasma HIV viral load

2. CD4 cell counts.

The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for Study 1182.14 was the proportion of subjects with a treatment response (HIV RNA < 400 c/mL) through Week 48.

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

The plasma concentrations of tipranavir were determined by a validated LC/MS/MS method. The method is acceptable.

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

1. exposure-virologic success relationship

Genotypic Inhibitory Quotient (GIQ) was found to be one of the major predictors of virologic success (proportion of patients with viral load below 400 copies/mL and 50 copies/mL) at week 48. GIQ was calculated by dividing geometric mean TPV plasma trough concentration (Cmin) by number of TPV related mutations, a measure of drug resistance virus. The virologic success at week 48 increased with higher TPV exposure. For example, proportion of patients with virologic success (VL < 400 copies/mL) increased from 11.5% in the lowest quartile (GIQ range 0.48-6.05) to 69.2% in the highest quartile (GIQ range 36.48-215.38). For a given mutation score additional benefit was seen with higher exposures.

2. exposure-safety relationship

The analysis of safety and exposure conducted focused on rash, bleeding and liver function test (LFT) abnormality. There was no apparent relationship shown between rash or bleeding and exposure, but LFT abnormalities seemed to increase as exposure increases. The LFTs were analyzed from adverse event as well as lab dataset. The proportion of patients with $\geq$ grade 2 LFTs increased from 16% in the lowest quartile (median Cmin=14 μM) to 53.8% in the highest quartile (median Cmin= 74 μM).

Figure 1. The predicted probability of virologic response rate overall and by TPV mutation score as a function of TPV trough concentration with observed proportion of virologic response at median of concentration quartiles

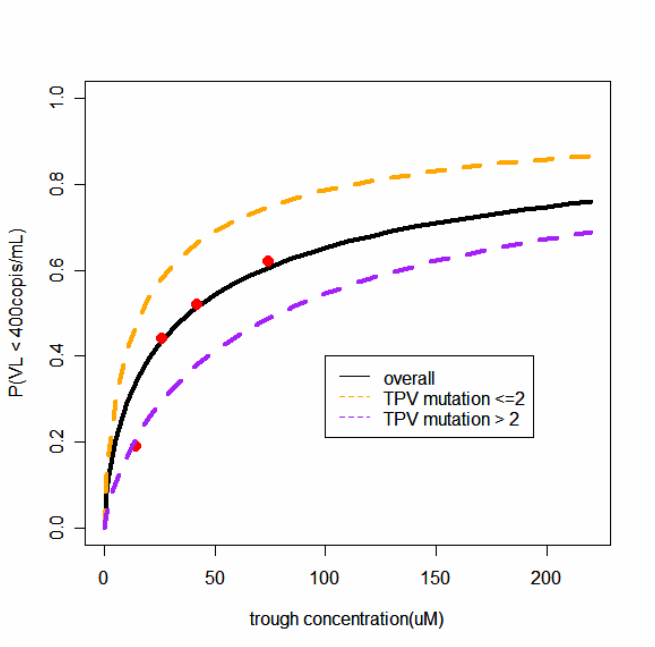
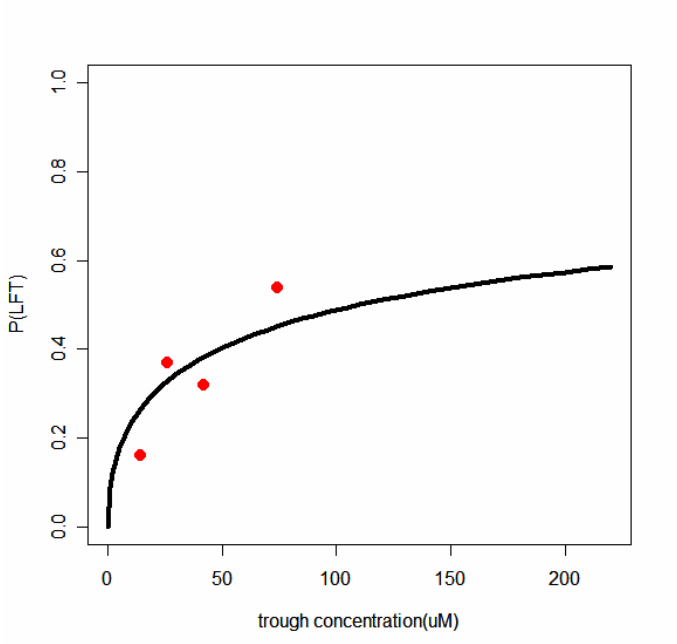


Figure 2. The relationship between exposure (Cmin) and the predicted probability of LFT (black solid line) with observed proportion of LFT incidence at the median of each concentration quartile (red dots)



See details in Pharmacometrics review.

C. Intrinsic Factors

i. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups

Age effect

In pediatric patients, TPV exposure for the TPV/r low dose closely resembled the TPV exposure observed in adults. The TPV/r high dose resulted in much higher TPV exposure in the 2 to <6 and 6 to <12 age groups than the TPV/r low dose, while smaller increase was found in the 12 to 18 age group. The smaller difference between doses for the 12 to 18 age group is the reflection of limiting the dose to 500/200 mg and many older patients in the TPV/r high dose group reached that maximum.

Table 1. Summary of tipranavir steady-state pharmacokinetics for pediatric patients receiving TPV/r 290/115 mg/m^2 or 375/150 mg/m^2

Parameter	TPV/r (mg/m2)	2 to <6 years (n=12 each dose)	6 to <12 years (n=8 each dose)	12 to 18 years (n=5 at 290/115, n=6 at 375/115)
Predicted AUC0-12h (mean ± SD) (h•μM)	290/115	710 ± 223	971 ± 469	1102 ± 526
	375/150	1190 ± 332	1354 ± 256	1194 ± 517
Predicted Cmax [geo mean (min - max)] (μM)	290/115	77.51 (35.21 - 119.84)	97.74 (46.52 - 189.58)	120.73 (66.85 - 183.35)
	375/150	127.91 (61.47 - 230.20)	147.39 (83.06 - 182.51)	125.58 (43.04 - 182.22)
Predicted Cp0,12h (μM) (geo mean (min - max))	290/115	29.36 (15.24 – 66.14)	42.17 (18.60 – 125.18)	36.29 (11.14 – 116.38)
	375/150	55.18 (28.56 – 94.35)	65.32 51.78 – 91.19)	39.02 (4.85 – 97.31)
Observed geo mean concentrations 10-14h post-dosing (μM) (min – max)	290/115	28.23 (8.74 – 111.59)	43.81 (BLQ – 116.85)	35.31 (9.23 – 119.12)
	375/150	48.69 (26.57 – 111.53)	63.89 (28.68 – 97.82)	46.09 (BLQ – 104.35)
CL/F (mean ± SD) (L/h)	290/115	0.45 ± 0.16	0.55 ± 0.30	0.78 ± 0.44
	375/150	0.34 ± 0.11	0.45 ± 0.08	0.99 ± 0.96
Elimination half-life (mean ± SD) (h)	290/115	7.6 ± 5.1	7.5 ± 3.7	8.3 ± 9.0
	375/150	8.1 ± 3.3	7.1 ± 2.1	5.17 ± 2.3

Predicted values were calculated from the population PK model and the observed trough values were directly from the measured plasma concentrations.

D. Extrinsic Factors

Please refer to the Clinical Pharmacology and Biopharmaceutics review of tipranavir capsule formulation (NDA 21-814).

E. General Biopharmaceutics

Please refer to the Clinical Pharmacology and Biopharmaceutics review of tipranavir capsule formulation (NDA 21-814).

Table 2. Composition of tipranavir 100 mg/mL oral solution used in clinical trials and intended for market authorization

Ingredient	Function	mg/mL
Tipranavir	Active Ingredient	100.0
Polyethylene Glycol 400		
Propylene Glycol		
Vitamin E Polyethylene Glycol Succinate		
Purified Water		
Buttermint	Flavor	
Butter Toffee	Flavor	
Total Weight		

F. Analytical Section

See details in individual study reports. The analytical method is acceptable.

III. Labeling Recommendations

The Proposed Key Labeling Changes Pertinent to Clinical Pharmacology

The rationale of the change is that midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, APTIVUS should not be given with orally administered midazolam.

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IV. Individual Clinical Pharmacology Reports (2)

1182.14

TITLE: Multiple-dose, open-label, randomized, safety and pharmacokinetic study of tipranavir in combination with low-dose ritonavir in HIV-infected pediatric patients – 48 week report

BACKGROUND: The two TPV/r doses used in this trial were scaled doses of the adult recommended TPV/r 500/200 mg dose. The low dose was a body surface area (BSA)-equivalent of the adult dose, derived by dividing the adult dose with mean adult BSA of 1.73 m2 yielding doses of TPV 290 mg/m2 + RTV 115 mg/m2. The high dose was calculated by dividing the adult dose with 1.33 m2 (12 year old male BSA), yielding doses of TPV 375 mg/m2 + RTV 150 mg/m2. BSA was calculated at randomization and at each study visit and TPV/r dosing was adjusted as needed. The maximum TPV/r dose allowed was 500/200 mg b.i.d. regardless of the patient's BSA.

OBJECTIVES: The primary objective of this study was to determine the safety and tolerability of TPV oral solution and soft-gel capsules together with low-dose RTV in HIV-infected children and adolescents and to provide information concerning the pharmacokinetic characteristics of TPV and RTV in this age group. The secondary objective of this study was the determination of the dose of TPV/r in children and adolescents between 2 and 18 years of age required for an adult equivalent systemic exposure of TPV/r 500/200 mg.

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized study. Children and adolescents were stratified according to age (2 to <6 years, 6 to <12 years and 12 to 18 years) and randomized to one of two doses of tipranavir/ritonavir (TPV/r) with background ARV therapy chosen by their local investigator. Children were enrolled in the study regardless of their prior antiretroviral therapy or HIV resistance status. All patients started treatment with TPV oral solution.

Key efficacy endpoints were proportion of patients reaching and maintaining a viral load <400 copies/mL at Week 48 and change in mean CD4 count from baseline to Week 48. Safety endpoints were adverse events and laboratory measurements using the DAIDS standardized Toxicity Table for Grading Severity of Pediatric (>3 months) Adverse Experiences.

Sparse pharmacokinetic sampling was performed on a subset of 52 patients at Week 2. An interim analysis (utilizing PK, and 4-week safety and efficacy data) was performed to determine the TPV/r dose required for an adult-equivalent systemic exposure on 52 patients from each age group. Equal number of patients were randomized to the TPV/r low dose group (n = 26) and TPV/r high dose group (n = 26). All patients included in this analysis completed 4 weeks of treatment.

Children who were 12 years or older and reached TPV/r 500/200 mg dose were eligible to switch to TPV soft-gel capsules after Study Week 4.

A total of 132 were screened and 115 were treated including 58 in TPV 290 mg/m^2 + RTV 115 mg/m^2 bid cohort and 57 in TPV 375 mg/m^2 + RTV 150 mg/m^2 bid cohort.

The objective of the interim analysis was to select one of the two doses based on these data and switch all patients to that dose. Both doses met the protocol defined criteria for dose selection: <20% severe AEs; <20% DAIDS Grade 3 or 4 laboratory abnormalities; median viral load decrease greater than 0.5 log10 copies/mL; geometric mean TPV Cmin >16 μM and geometric mean TPV AUC0-12h >483 h*μM. Overall, both doses showed a similar early safety profile although there appeared to be slightly more study drug-related adverse events and Grade 3 or 4 laboratory abnormalities in the TPV/r high dose group. In addition, the TPV/r low dose group showed similar early efficacy as the TPV/r high dose group. Finally, the PK characteristics of the TPV/r low dose group more closely resembled the PK characteristics observed in adults who receive the approved dose of 500 mg/200 mg b.i.d. and the TPV/r high dose achieved higher exposure levels. Based on these results a low dose, TPV/r 290/115 mg/m2 BID, was

selected as the optimal dose. Following the interim analysis for optimal dose selection, patients in the TPV/r high dose group were supposed to be switched to the TPV/r low dose group. Only 4 patients in the TPV/r high dose group actually switched to the TPV/r low dose group prior to the 48-week cut-off for this analysis. These patients had less than 16 weeks of exposure to the TPV/r low dose group. Since the TPV/r low dose exposure is relatively smaller compared to the total TPV/r high dose exposure, these patients were not separately analyzed for this period and were analyzed based on the initial randomization to TPV/r high dose.

Table 1. Demographics of patients in interim analysis

	TPV/r low dose	TPV/r high dose	Total
Total Treated [N(%)]	26(100.0)	26(100.0)	52(100.0)
Gender [N(%)]			
Male	11(42.3)	16(61.5)	27(51.9)
Female	15(57.7)	10(38.5)	25(48.1)
Race [N(%)]			
White	21(80.8)	16(61.5)	37(71.2)
Black	5(19.2)	8(30.8)	13(25.0)
Asian	0(0.0)	2(7.7)	2(3.8)
Ethnicity [N(%)]			
Hispanic/Latino	19(73.1)	13(50.0)	32(61.5)
Mixed race	0(0.0)	2(7.7)	2(3.8)
Age(years)			
2 to <6	12(46.2)	12(46.2)	24(46.2)
6 to <12	8(30.8)	8(30.8)	16(30.8)
12 to 18	6(23.1)	6(23.1)	12(23.1)

Table 2. Demographics of patients in 48-week analysis

	TPV/r low dose N (%)	TPV/r high dose N (%)	Total N (%)
Total Treated	58 (100.0)	57 (100.0)	115 (100.0)
Age group			
2 to <6	13 (22.4)	12 (21.1)	25 (21.7)
6 to <12	19 (32.8)	19 (33.3)	38 (33.0)
12 to 18	26 (44.8)	26 (45.6)	52 (45.2)
Gender			
Male	32 (55.2)	33 (57.9)	65(56.5)
Female	26 (44.8)	24 (42.1)	50(43.5)
Race			
White	45 (77.6)	35 (61.4)	80 (69.6)
Black	13 (22.4)	20 (35.1)	33 (28.7)
Asian	0 (0.0)	2 (3.5)	2 (1.7)
Ethnicity			
Hispanic/Latino	35 (60.3)	26 (45.6)	61(53.0)
Mixed race	3 (5.2)	2 (3.5)	5 (4.3)
Unknown	20 (34.5)	29 (50.9)	49 (42.6)

TPV/r low dose = TPV 290 mg/m^2 + RTV 115mg/m^2
TPV/r high dose = TPV 375 mg/m^2 + RTV 150mg/m^2

FORMULATION: Tipranavir: Oral solution (100 mg/mL) or 250 mg soft-gel capsules; Ritonavir: Oral solution (80 mg/mL) or 100 mg capsules. Oral dosing syringes (up to 5 rnL with 0.1 mL increments) were used in the study.

PK SAMPLE COLLECTION: A subset of 52 patients, including patients from each age group as specified in the Written Request for pediatric studies issued by Food and Drug Administration (FDA), was included in the PK cohort:

- 2 to <6 years of age - 24 patients (12 patients in TPV/r low dose group and 12 patients in TPV/r high dose group)
- 6 to <12 years of age - 16 patients (8 patients in TPV/r low dose group and 8 patients in TPV/r high dose group)
- 12 to 18 years of age - 12 patients (6 patients in TPV/r low dose group and 6 patients in TPV/r high dose group)

Sparse pseudorandom PK sampling was performed in these patients at steady state (Week 2) to determine the PK parameters of TPV and RTV in this population.

Pseudorandom population pharmacokinetic blood-sampling scheme based on the month of birth of the patient

Month of birth	Sample collection window (hours after TPV/r administration)			
	Sample 1	Sample 2	Sample 3	Sample 4
January	0.5 - 1.5	3 - 4	5.5 - 6.5	8 - 9
February	1 - 2	3.5 - 4.5	6 - 7	8.5 - 9.5
March	1.5 - 2.5	4 - 5	6.5 - 7.5	9 -10
April	0.5 - 1.5	3 - 4	5.5 - 6.5	8 - 9
May	1 - 2	3.5 - 4.5	6 - 7	8.5 - 9.5
June	1.5 - 2.5	4 - 5	6.5 - 7.5	9 -10
July	0.5 - 1.5	3 - 4	5.5 - 6.5	8 - 9
August	1 - 2	3.5 - 4.5	6 - 7	8.5 - 9.5
September	1.5 - 2.5	4 - 5	6.5 - 7.5	9 -10
October	0.5 - 1.5	3 - 4	5.5 - 6.5	8 - 9
November	1 - 2	3.5 - 4.5	6 - 7	8.5 - 9.5
December	1.5 - 2.5	4 - 5	6.5 - 7.5	9 -10

Patients who are ≥12 years and whose BSA-adjusted TPV/r dose is equivalent to TPV/r 500/200 mg had option to switch to capsules at Study Day 28 (Week 4, Visit 4). For patients from this group who were designated as a PK cohort, on Study Day 14 (Week 2, Visit 3) and Study Day 42 (Week 6, Visit 5), 10 additional blood samples were collected after administration of TPV/r in addition to the morning trough sample collected prior to TPV/r administration at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 hours post dose.

For all patients, TPV and RTV trough plasma levels were collected at every visit starting from Week 2 (Visit 3) to Week 16 (Visit 8) and then at every other visit starting from Week 24 (Visit 10) to Week 48 Visit 16): collected 10-14 hours after dosing and prior to the next scheduled dose of TPV/r.

BIOANALYTICAL ASSAYS: A validated LC/MS/MS method was established to measure plasma concentrations of tipranavir and ritonavir at [redacted]. The analytical method is acceptable. Divisi [redacted] bioanalytical site. They inspection report concluded that no significant findings were observed.

Summary of tipranavir and ritonavir bio-analytical assay

Analyte	Tipranavir	Ritonavir
Internal Standard	[redacted]	[redacted]
Matrix / Anticoagulant	Li-Hep human plasma	
Assay Volume Required	50 µl	
Extraction Method	[redacted]	
% Mean Recovery	65.6 – 73.4 43.2 ($^{13}C_6$-TPV)	84.4 – 105.4 87.1 (D_5-SQV)
Detection Method	Tandem mass spectrometric detection	
Standard Curve Range (ng/ml)	1,000 – 100,000	25.0 – 2,500
Regression Type	Linear (y = A+Bx), weight (1/x)	
Retention time (min)	1.9 – 2.4	2.6 – 3.2
Peak height/area ratio	>0.07	>0.07
Carry-over (%)	<0.2	<0.2
Quantitation Method	Peak area ratio	
Parameters		
Mean accuracy (QC results) (%)	100.6 – 103.0	89.2 – 94.4
Precision (QC results) (%) Intra-batch (min – max)	2.2 – 3.4	4.7 – 9.6
Precision (QC results) (%) Inter-batch (min – max)	0.4 – 6.7	1.4 – 12.5
Stability in plasma after 3 times freeze-thaw cycles (100% is the theoretical value)	106.5 – 110.5	99.8 – 107.1
Heat treatment stability (100% is the theoretical value) at 55°C, 4h	96.7 – 106.9	84.1* – 92.4
Dilution (100% is the theoretical value)	89.5	97.4
Mean matrix effect (100% is the theoretical value)	116.8-123.3 101.0-105.3 ($^{13}C_6$-TPV)	114.9 – 127.0 101.1 – 106.9 (D_5-SQV)
Stability in plasma at room temperature (100% is the theoretical value) during 88h	103.6 – 109.2	103.3 – 105.0
Long-term freezer stability in plasma (100% is the theoretical value), -15°C, 92 days	96.5 – 101.1	111.5 – 115.5
Autosampler extract stability (100% is the theoretical value), 96h at 4°C	103.9 – 110.3	108.2 – 108.5
Stability in extracts at room temperature (100% is the theoretical value) , 96 h	106.5 – 110.0	93.0 – 107.2
Stability stock solution , 6.4 h (100% is the theoretical value)	107.6 – 109.9 97.9 ($^{13}C_6$-TPV)	89.6 – 102.1 99.8 (D_5-SQV)

PHARMACOKINETIC DATA ANALYSIS:

In addition to the observed C_{p12hr} values, tipranavir pharmacokinetic parameters were calculated using the nonlinear mixed effects modeling program NONMEM® Version 5 (GloboMax LLC, Ellicott City, Maryland USA). A one-compartment, oral absorption, steady-state model was fitted to the tipranavir plasma concentration-time data to provide estimates of individual patient and population tipranavir pharmacokinetic parameters (C_{p12h}, C_{max}, t_{max}, $AUC_{0\text{-}12h}$, Ka, Ke, CL/F, V and $t_{1/2}$).

PHARMACOKINETIC RESULTS:

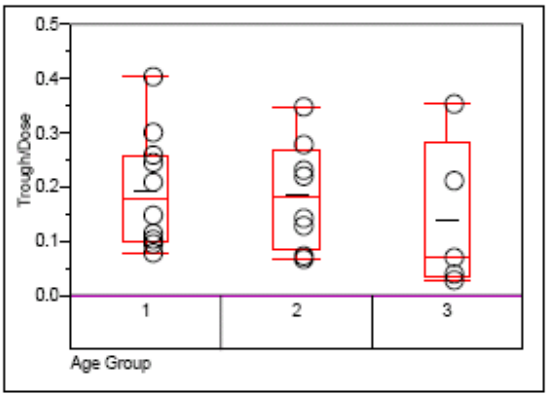
Table 1. Summary of tipranavir steady-state pharmacokinetics for pediatric patients receiving TPV/r 290/115 mg/m^2 or 375/150 mg/m^2

Parameter	TPV/r (mg/m2)	2 to <6 years (n=12 each dose)	6 to <12 years (n=8 each dose)	12 to 18 years (n=5 at 290/115, n=6 at 375/115)
Predicted AUC0-12h (mean ± SD) (h•μM)	290/115	710 ± 223	971 ± 469	1102 ± 526
	375/150	1190 ± 332	1354 ± 256	1194 ± 517
Predicted Cmax [geo mean (min - max)] (μM)	290/115	77.51 (35.21 - 119.84)	97.74 (46.52 - 189.58)	120.73 (66.85 - 183.35)
	375/150	127.91 (61.47 - 230.20)	147.39 (83.06 - 182.51)	125.58 (43.04 - 182.22)
Predicted Cp0,12h (μM) (geo mean (min - max))	290/115	29.36 (15.24 – 66.14)	42.17 (18.60 – 125.18)	36.29 (11.14 – 116.38)
	375/150	55.18 (28.56 – 94.35)	65.32 51.78 – 91.19)	39.02 (4.85 – 97.31)
Observed geo mean concentrations 10-14h post-dosing (μM) (min – max)	290/115	28.23 (8.74 – 111.59)	43.81 (BLQ – 116.85)	35.31 (9.23 – 119.12)
	375/150	48.69 (26.57 – 111.53)	63.89 (28.68 – 97.82)	46.09 (BLQ – 104.35)
CL/F (mean ± SD) (L/h)	290/115	0.45 ± 0.16	0.55 ± 0.30	0.78 ± 0.44
	375/150	0.34 ± 0.11	0.45 ± 0.08	0.99 ± 0.96
Elimination half-life (mean ± SD) (h)	290/115	7.6 ± 5.1	7.5 ± 3.7	8.3 ± 9.0
	375/150	8.1 ± 3.3	7.1 ± 2.1	5.17 ± 2.3

Figure 1. Variability of trough tipranavir concentrations for the two dose levels studied

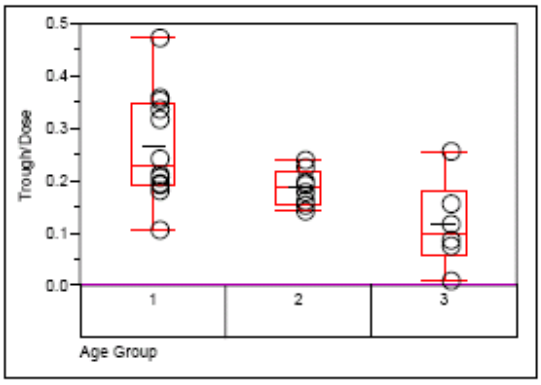
Dose Group=290 mg/m2

Variability Chart for Trough/Dose



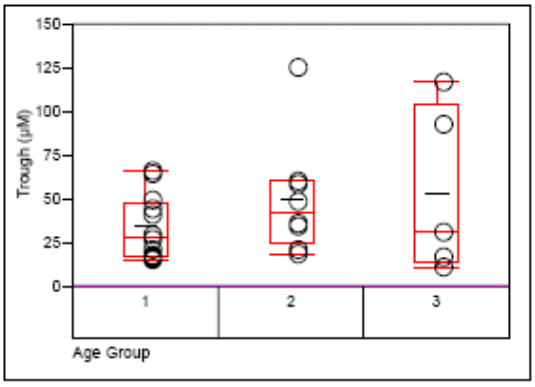
Dose Group=375 mg/m2

Variability Chart for Trough/Dose



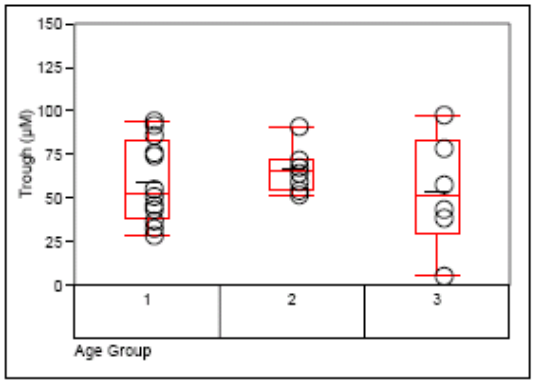
Dose Group=290 mg/m2

Variability Chart for Trough (µM)



Dose Group=375 mg/m2

Variability Chart for Trough (µM)



Age Group 1 = 2 to <6 years of age, Age Group 2 = 6 to <12 years of age, Age Group 3 = 12 to 18 years of age

Table 2. Comparison of tipranavir steady-state pharmacokinetics for HIV+ pediatric patients receiving TPV/r 290/115 mg/m2 or 375/150 mg/m2 to HIV+ adult patients receiving TPV/r 500/200 mg

Pharmacokinetic Parameter	Adult HIV+ Females	Adult HIV+ Males	All Pediatric Patients
	(n = 14)[a]	(n = 106)[a]	(n = 51)
Cp0,12h (µM)	41.6 ± 24.3	35.6 ± 16.7	29.36 – 42.17[b] 39.02 – 65.32[c]
Cmax (µM)	94.8 ± 22.8	77.6 ± 16.6	77.51 – 120.73[b] 125.58 – 147.39[c]
Tmax (h)	2.9	3.0	2.6 – 2.7[b] 2.5 – 2.7[c]
AUC0-12h (h•µM)	851 ± 309	710 ± 207	710 – 1102[b] 1190 – 1354[c]
CL/F (L/h)	1.15	1.27	0.45 – 0.78[b] 0.34 – 0.99[c]
V/F (L)	7.7	10.2	4.53 – 6.14[b] 3.98 – 5.29[c]
t1/2 (h)	5.5	6.0	7.5 – 8.3[b] 5.2 – 8.1c

a. Arithmetic mean ± standard deviation
b. 290/115 mg/m^2 dose group
c. 375/150 mg/m^2 dose group

A subset of eight patients in this trial received both drug formulations and had tipranavir trough concentrations measured while on tipranavir solution and capsule formulations.

Figure 2. Comparison of tipranavir trough concentrations for patients who switched from tipranavir solution to tipranavir capsule formulation

EXPOSURE-RESPONSE ANALYSIS: Please see details in the Pharmacometrics review.

1. exposure-virologic success relationship

Genotypic Inhibitory Quotient (GIQ) was found to be one of the major predictors of virologic success (proportion of patients with viral load below 400 copies/mL and 50 copies/mL) at week 48. GIQ was calculated by dividing geometric mean TPV plasma trough concentration (Cmin) by number of TPV related mutations. The virologic success at week 48 increased with higher TPV exposure. For example, proportion of patients with virologic success (VL < 400 copies/mL) increased from 11.5% in the lowest quartile (GIQ range 0.48-6.05) to 69.2% in the highest quartile (GIQ range 36.48-215.38). For a given mutation score additional benefit was seen with higher exposures.

2. exposure-safety relationship

The analysis of safety and exposure conducted, focused on rash, bleeding and liver function test (LFT) abnormality. There was no apparent relationship shown between rash or bleeding and exposure, but LFT seemed to increase as exposure increases. The LFTs were analyzed from adverse event as well as lab dataset. The proportion of patients with ≥ grade 2 LFTs increased from 16% in the lowest quartile (median Cmin=14 μM) to 53.8% in the highest quartile (median Cmin= 74 μM).

Figure 3. The predicted probability of virologic response rate by overall and TPV mutation score as a function of TPV trough concentration with observed proportion of virologic response at median of concentration quartiles

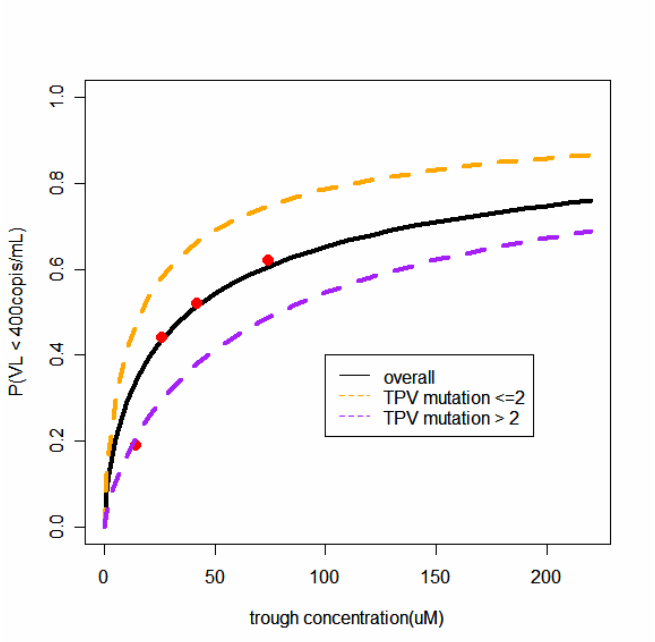
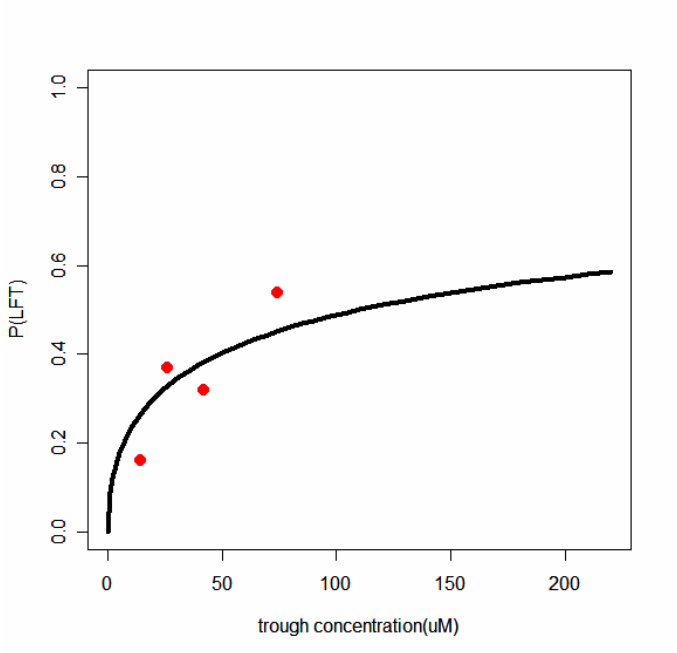


Figure 4. The relationship between exposure (Cmin) and the predicted probability of LFT (black solid line) with observed proportion of LFT incidence at the median of each concentration quartile (red dots)



EFFICACY RESULTS: Overall, 43% of study patients achieved and sustained an HIV RNA level < 400 copies/mL and 33% reached an HIV RNA level < 50 copies/mL over the 48 weeks study period. The overall treatment response was slightly higher in the high dose group when compared to the low dose group (46% vs. 40%). However, no differences in response rate could be identified in the youngest age group (2 to < 6 years) based on the dose of tipranavir/ritonavir given; the proportion of patients with viral load <400 copies/mL was 70% in both low and high dose groups. Please see details in Medical Officer's review.

SAFETY RESULTS: Overall, tipranavir co-administered with ritonavir in combination with other antiretroviral drugs was safe and tolerable when administered to pediatric patients 2 to 18 years of age. The types of adverse events reported were similar to adults but the frequency of reporting was lower in pediatric patients, although vomiting and rash were more frequent in pediatric patients. When the high and low dose tipranavir are compared, the overall adverse events profile was similar for the two groups. Please see details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS:

PK evaluation showed that observed TPV trough concentrations and model based estimates of TPV PK parameters were similar to those observed in adults.

Exposure following administration of the TPV/r low dose more closely resembled the TPV exposure observed in adults. The TPV/r high dose resulted in much higher TPV exposure (about 50% higher) in the 2 to <6 and 6 to <12 age groups than the TPV/r low dose, while smaller increase was found in the 12 to 18 age group. The smaller increase in older group is the reflection of limiting the dose to 500/200 mg and many older patients in the TPV/r high dose group reached that maximum.

The results of the 48-week analysis showed that TPV/r in combination with other antiretroviral agents is effective and well tolerated for treatment in children 2 to 18 years of age. The efficacy of the higher dose was better than the lower dose for pediatric patients 6 to 18 years old who have multiple tipranavir mutations. Therefore, for the older age group, the benefit of 375/150mg/m2 dose outweighs the higher risks associated with it. In contrast to the older age groups, no added benefit was observed in the youngest age group (2 to 6 years of age) with the administration of the higher tipranavir dose. However some patients enrolled in the youngest age group (2 to 6 years of age) are less treatment experienced and have less drug resistance than the population for whom the drug is indicated. The labeled indication for APTIVUS will continue to be in "patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor". In this patient population, regardless of age, the high dose seems appropriate in order to avoid resistance.

Thus we concur with the sponsor's APTIVUS/ritonavir pediatric dosing recommendation: 375/150 mg/m^2 b.i.d., up to a maximum of 500 mg/200 mg b.i.d. for pediatric patients (age ≥ 2 to <18 years).

Weight based dosing was also explored because it is more convenient than BSA-based dosing in some healthcare settings. Based on Cmin-body weight relationship, 10,000 patients were simulated (nonparametric simulations from observed weights) to assess potential distribution of Cmin following administration of various dose levels of TPV (9 mg/kg, 10 mg/kg, 12 mg/kg and 14 mg/ kg). A working therapeutic window (17.4 μM and 57.2 μM) was selected based on exposure-response for efficacy and safety.

A dose of 14 mg/kg that would match the dose of BSA based dosing (375/150 mg/m^2) would result in 6% and 5% below window, 34% and 41% above window, for pediatric patients ≤ 20 Kg and >20 kg, respectively.

The treatment experienced pediatric patients who will receive tipranavir have limited treatment options. Thus, the benefit/risk assessment favors a higher proportion of patients above the window rather than below the window.

However, patients who develop toxicity or intolerance while receiving recommended dose of TPV/r and who do not have multiple baseline protease inhibitor mutations, the dose may be reduced to 290/115 mg/m^2 or 12/5 mg/kg. (See details in Pharmacometrics review).

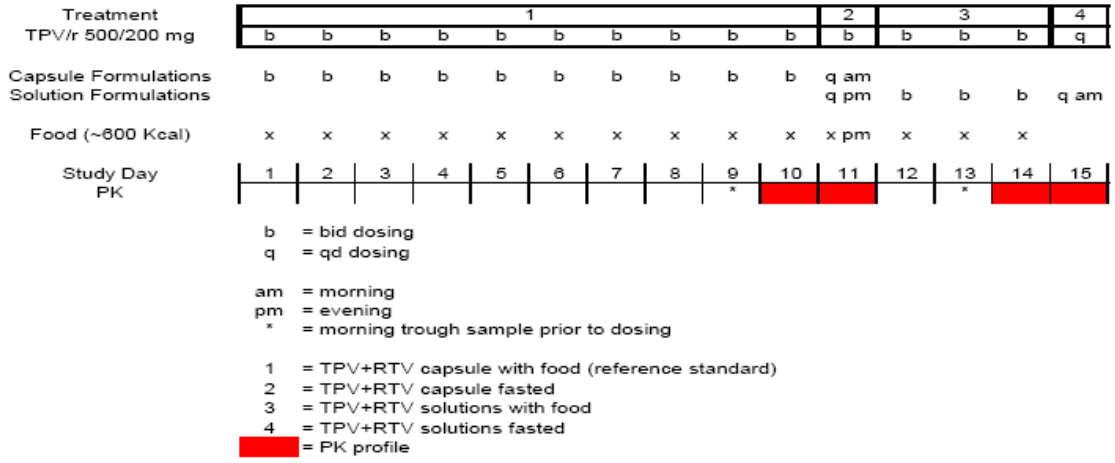
1182.100

TITLE: An open-label, single-site, one-sequence cross-over study to assess the relative bioavailability of TPV/r 500 mg/200 mg at steady state when TPV and RTV are administered as oral solutions vs. capsules in the fed and fasted state

OBJECTIVES: The primary objective was to establish the relative bioavailability of the TPV oral solution formulation (500 mg co-administered with RTV oral solution 200 mg) to the TPV capsule formulation (500 mg co-administered with RTV capsules 200 mg), with both treatments at steady-state under fasted and fed conditions in healthy male and female volunteers.

BACKGROUND: The current clinical study was undertaken to compare the bioavailability of the oral solution of TPV at steady state, compared to capsules, in fed and fasted conditions. This information was required to support the use of TPV oral solution in patients who may not be able to swallow TPV capsules.

SUBJECTS AND STUDY DESIGN: The study was a multi-dose (steady state), open-label, non-randomized, one-sequence, cross-over, single site study.



Each subject acted as their own control, having PK (fed and fasted) performed following 10.5 days of TPV/r capsules, and then switching to oral solution for 3.5 days before further PK (fed and fasted) was performed. Comparisons were as following:

- Capsule fasted to Capsule fed: Day 11 to Day 10
- Solution fed to Capsule fed: Day 14 to Day 10
- Solution fasted to solutions fed: Day 15 to Day 14

Investigator:
Study center,

Thirty-five healthy male and female volunteers were enrolled in the study and thirty-two completed the study.

Table 1. Subject Demographic and Disease Characteristics at Baseline

Total Treated [N(%)]	35(100.0)
Sex [N(%)]	
Male	17(48.6)
Female	18(51.4)
Race [N(%)]	
White	35(100.0)

FORMULATION: Tipranavir: soft elastic capsule 250 mg, oral solution 100 mg/ml; Ritonavir: soft elastic capsules 100 mg, oral solution 80 mg/ml

PK SAMPLE COLLECTION: Blood samples for the determination of TPV and RTV plasma concentrations were obtained according to the following plasma sampling scheme:

Study Day	Analyte	Nominal Sample Time (h) relative to drug administration
9	TPV and RTV	Trough: 10 minutes before 8:00 AM study drug administration
10	TPV and RTV	0 (actual -10 min), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12
11	TPV and RTV	0 (actual -10 min), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12
13	TPV and RTV	Trough: 10 minutes before 8:00 AM study drug administration
14	TPV and RTV	0 (actual -10 min), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12
15	TPV and RTV	0 (actual -10 min), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12

BIOANALYTICAL ASSAYS: A validated LC/MS/MS assay was used to determine the plasma concentrations of tipranavir and ritonavir by [redacted], [redacted] The analytical method is acceptable.

Determination of Tipranavir and Ritonavir in human plasma (High Calibration Range)

Analytes	Tipranavir and Ritonavir	
Internal Standard	[redacted]	
Matrix / Anticoagulant	K3 EDTA/human plasma	
Assay Volume Required	0.050 mL	
Extraction Method	[redacted]	
% Recovery	Tipranavir: 70.7 Ritonavir: 92.2	
Detection Method	LC/MS/MS detection	
Standard Curve Range	1000 ng/mL to 20000 ng/mL	
Regression Type	Quadratic with 1/concentration^2 weighting	
Quantitation Method	Peak area ratio	
Parameters	Intra-day	Inter-day
Accuracy (QC results)	Ritonavir –14.4% to 2.1%	Ritonavir –5.4% to 0.3%
	Tipranavir –13.8% to 7.6%	Tipranavir –7.6% to 4.0%
Precision (QC results)	Ritonavir 1.0% to 6.8%	Ritonavir 5.6% to 8.7%
	Tipranavir 1.9% to 9.6%	Tipranavir 4.8% to 7.2%
Stability in plasma after 5 freeze-thaws (% difference from theory)	Ritonavir –8.2% to –5.3% Tipranavir –8.4% to –5.4% (5 cycles at ~ -20°C)	
Heat treatment stability (% difference from theory)	Ritonavir –5.8% to 0.2% Tipranavir –1.4% to 1.5% (45 minutes at ~ 56°C)	
Stability in plasma at room temperature (% difference from theory)	Ritonavir –7.1 % to –0.5% Tipranavir –7.6% to –1.4% (24 Hours)	
Autosampler extract stability (% difference from theory)	Ritonavir –3.4% to 2.5% 123 hours under refrigeration Tipranavir 2.9% to 8.2% 145 hours under refrigeration	
Matrix stability (% difference from theory)	Ritonavir –8.2% to 1.4% Tipranavir –7.3% to –1.8% (room temperature for 48 hours)	
Long-term freezer stability in plasma (% difference from theory)	At ~ -20°C for 21 days Ritonavir –11.0% to –7.5% Tipranavir –13.3% to –1.1 %	

Determination of Tipranavir and Ritonavir in human plasma (Low Calibration Range)

Analytes	Tipranavir and Ritonavir	
Internal Standard		
Matrix / Anticoagulant	K3 EDTA/human plasma	
Assay Volume Required	0.050 mL	
Extraction Method		
% Recovery	Tipranavir: 53.7 Ritonavir: 84.2	
Detection Method	LC/MS/MS detection	
Standard Curve Range	25.0 ng/mL to 2000 ng/mL	
Regression Type	Quadratic with 1/concentration^2 weighting	
Quantitation Method	Peak area ratio	
Parameters	Intra-day	Inter-day
Accuracy (QC results)	Ritonavir –9.4% to 6.0%	Ritonavir –8.3% to 2.4%
	Tipranavir –10.3% to 7.9%	Tipranavir –5.2% to –1.6%
Precision (QC results)	Ritonavir 1.6% to 6.9%	Ritonavir 5.4% to 6.9%
	Tipranavir 1.6% to 7.7%	Tipranavir 5.1 % to 7.0%
Stability in plasma after 5 freeze-thaws (% difference from theory)	Ritonavir –11.3% to 0.0% Tipranavir –10.5% to –7.2% (5 cycles at ~ -20°C)	
Heat treatment stability (% difference from theory)	Ritonavir –6.4% to –5.3% Tipranavir –10.7% to –9.9% (45 minutes at ~ 56°C)	
Stability in plasma at room temperature (% difference from theory)	Ritonavir –10.4% to –7.2% Tipranavir –9.9% to –6.8% (24 Hours)	
Autosampler extract stability (% difference from theory)	-2.5% to 2.6% (27 hours at room temperature, tipranavir only)	
	Ritonavir –13.3% to 2.0% 123 hours under refrigeration Tipranavir –6.1 % to 4.6% 145 hours under refrigeration	
Matrix stability (% difference from theory)	Ritonavir –9.3% to 3.3% Tipranavir –7.2% to –4.9% (room temperature for 48 hours)	
Long-term freezer stability in plasma (% difference from theory)	(At ~ -20°C for 26 days) Ritonavir –10.9% to-10.5% Tipranavir –6.1 % to –3.9%	

PHARMACOKINETIC DATA ANALYSIS:

Pharmacokinetic parameters were calculated using non-compartmental methods. Pharmacokinetic parameters, including $AUC_{0\text{-}12hr}$, C_{max}, T_{max} and C_{12hr} for each subject under each treatment were calculated.

PHARMACOKINETIC RESULTS:

Table 1. Summary of geometric mean ratios and 90% confidence intervals for subjects administered TPV/r 500/200 mg solutions vs. capsule under fed conditions

PK parameter	n	Geometric mean ratio (%) TPV/r Oral Solutions vs. Capsules	90% Confidence Interval
TPV pharmacokinetic parameters			
AUC0-12h	32	122.64	111.18, 135.28
Cmax	32	114.33	103.40, 126.41
Cp12h	32	128.26	109.73, 149.92
RTV pharmacokinetic parameters			
AUC0-12h	32	96.11	78.61, 117.50
Cmax	32	86.77	70.25, 107.17
Cp12h	32	71.77	60.12, 85.68

Table 2. Summary of geometric mean ratios and 90% confidence intervals for subjects administered TPV/r 500/200 mg oral solutions with and without food

PK parameter	n	Geometric mean ratio (%) TPV/r solutions Fasted vs. Fed	90% Confidence Interval
TPV pharmacokinetic parameters			
Cp12h	32	95.60	89.68, 101.91
Cmax	32	120.74	115.87, 125.81
AUC0-12h	32	102.91	99.70, 106.23
RTV pharmacokinetic parameters			
Cp12h	32	89.84	80.98, 99.67
Cmax	32	182.36	165.30, 201.18
AUC0-12h	32	135.43	124.85, 146.91

Table 3. Summary of geometric mean ratios and 90% confidence intervals for subjects administered TPV/r 500/200 mg capsules with and without food

PK parameter	n	Geometric mean ratio (%) TPV/r capsules Fasted vs. Fed	90% Confidence Interval
TPV pharmacokinetic parameters			
Cp12h	32	101.50	83.59, 123.23
Cmax	32	101.64	90.90, 113.64
AUC0-12h	32	99.17	88.21, 111.48
RTV pharmacokinetic parameters			
Cp12h	32	83.11	66.90, 103.27
Cmax	32	126.55	95.35, 167.95
AUC0-12h	32	103.88	78.85, 136.87

Table 4. Steady-state pharmacokinetics of tipranavir when administered orally as TPV/r 500/200 mg bid

Pharmacokinetic Parameter	Treatment	N	Mean	SD	Median	Geo. Mean
Tmax (h)	TPV/r capsules (fasted)	32	2.3	0.8	2.0	2.2
	TPV/r capsules (fed)	32	2.3	0.7	2.0	2.2
	TPV/r solutions (fasted)	32	1.8	0.6	1.5	1.7
	TPV/r solutions (fed)	32	2.5	1.0	2.0	2.3
Cmax (μM)	TPV/r capsules (fasted)	32	124.7	54.7	125.5	114.6
	TPV/r capsules (fed)	32	124.6	60.3	110.9	112.7
	TPV/r solutions (fasted)	32	162.1	47.6	161.1	155.6
	TPV/r solutions (fed)	32	134.9	43.2	130.3	128.9
Cp12h (μM)	TPV/r capsules (fasted)	32	27.6	22.7	22.0	21.3
	TPV/r capsules (fed)	32	29.8	29.6	23.1	21.0
	TPV/r solutions (fasted)	32	30.8	19.6	29.2	25.7
	TPV/r solutions (fed)	32	33.3	27.1	27.0	26.9
AUC0-12h (h-μM)	TPV/r capsules (fasted)	32	789	395	774	708
	TPV/r capsules (fed)	32	820	479	744	714
	TPV/r solutions (fasted)	32	959	351	943	901
	TPV/r solutions (fed)	32	936	370	909	875
CL/F (L/h)	TPV/r capsules (fasted)	32	1.30	0.60	1.07	1.17
	TPV/r capsules (fed)	32	1.33	0.73	1.11	1.16
	TPV/r solutions (fasted)	32	0.98	0.36	0.88	0.92
	TPV/r solutions (fed)	32	1.01	0.37	0.91	0.95
Vz/F (L)	TPV/r capsules (fasted)	32	7.6	2.9	6.7	7.1
	TPV/r capsules (fed)	32	7.3	2.9	6.5	6.8
	TPV/r solutions (fasted)	32	5.7	1.5	5.4	5.5
	TPV/r solutions (fed)	32	5.7	1.4	5.6	5.5
t1/2 (h)	TPV/r capsules (fasted)	32	4.4	1.7	4.0	4.2
	TPV/r capsules (fed)	32	4.2	1.3	4.0	4.1
	TPV/r solutions (fasted)	32	4.3	1.5	4.3	4.2
	TPV/r solutions (fed)	32	4.2	1.3	4.0	4.0

Figure 1. Effect of formulation on tipranavir steady-state pharmacokinetics for subjects administered TPV/r 500/200 mg bid capsules and solutions with food

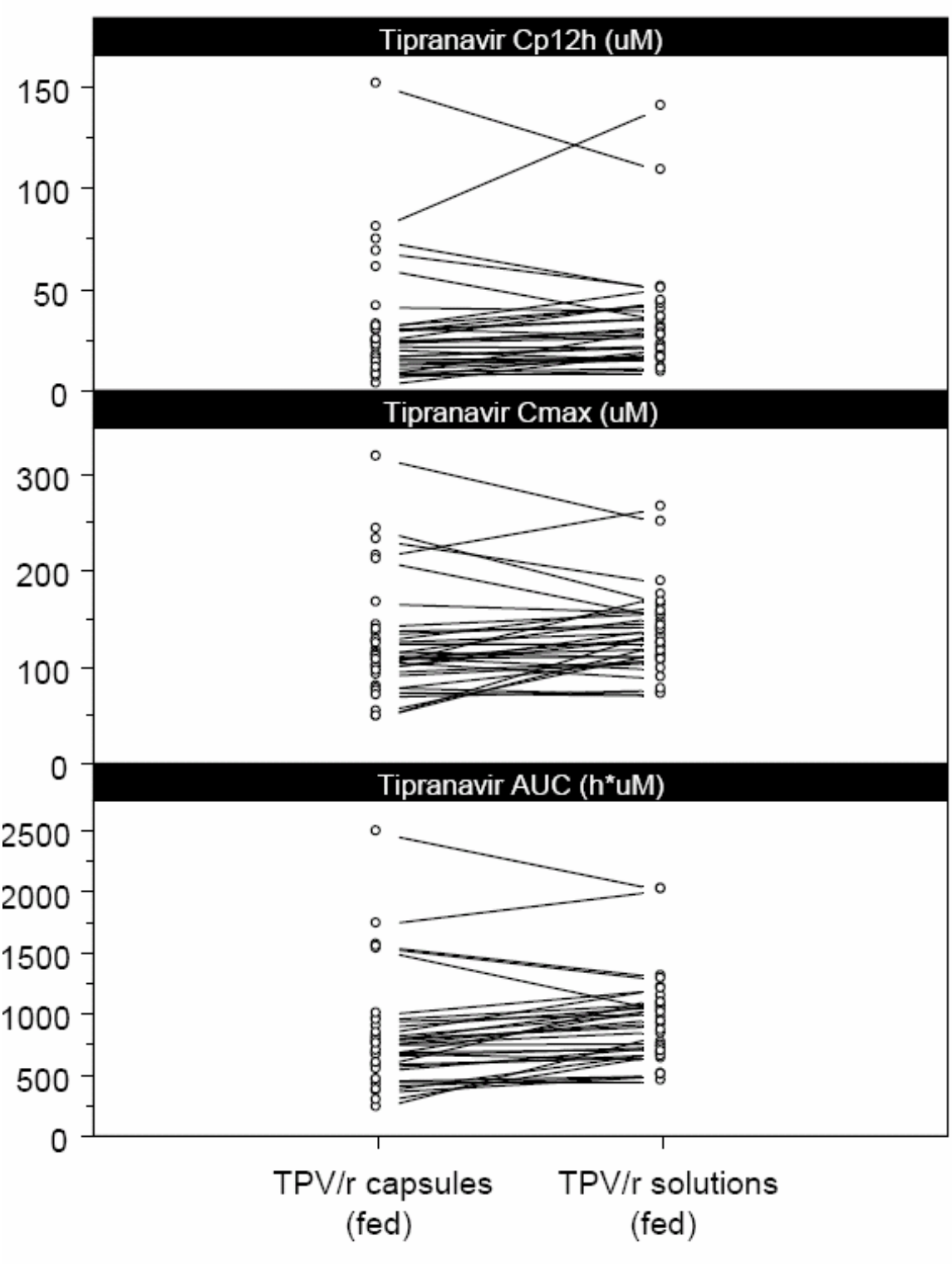
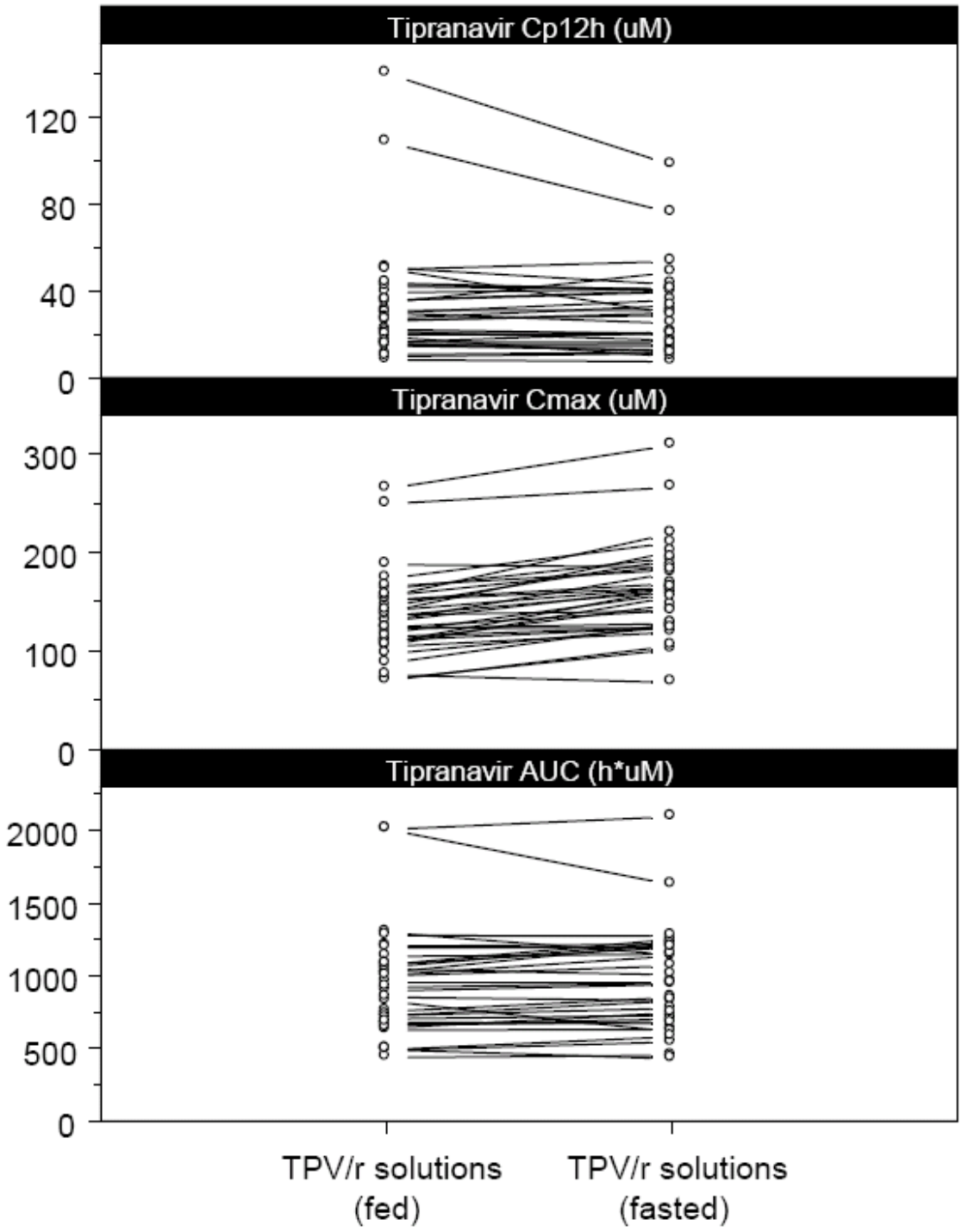


Figure 2. Effect of food on tipranavir steady-state pharmacokinetics for subjects administered TPV/r 500/200 mg bid solution formulations



SAFETY RESULTS: No unexpected safety issues arose during conduct of the study. See details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS: At steady-state and under fed conditions, TPV/r oral solution formulation administered as a 500/200 mg dose twice-daily was slightly more bioavailable (AUC_{0-12h} increased by 23%, Cmax increased by 14%) than the marketed TPV/r capsule formulation.

At steady-state and under fasted conditions, TPV/r oral solution formulation administered as a 500/200 mg dose twice-daily was more bioavailable (AUC_{0-12h} increased by 27%, Cmax increased by 36%) than the marketed TPV/r capsule formulation.

Food did not affect tipranavir steady-state C_{p12h} and AUC_{0-12h} for subjects that received TPV/r 500/200 mg as the oral solution formulations, however, C_{max} was about 17% lower when TPV/r oral solutions are administered with food compared to the fasted state. Food did not affect tipranavir steady-state C_{p12h}, C_{max}, and AUC_{0-12h} for subjects that received TPV/r 500/200 mg as the capsule formulations. These results indicate that both TPV capsule and oral solution formulations can be administered to patients either with food or without food.

The current label recommends the tipranavir capsules be taken with food. At the time of the accelerated NDA approval, the finding of food effect on TPV capsule formulation was not conclusive. For the 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. However, 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.

Based on TPV known exposure-response for efficacy and safety, the differences between oral solution and capsule formulation are not sufficient to change the dose regimen from the current recommended dose of TPV/r 500/200 mg bid. Thus oral solution and capsule can be used interchangeably.

V. Pharmacometric Consult

PHARMACOMETRIC REVIEW

NDA	21-814 SE1 005, 21-822 N 000, 22-292 N 000
Generic name:	Tipranavir
Indication:	Treatment experienced pediatric patients with HIV
Proposed Regimen (Sponsor):	Tipranavir / Ritonavir 375 / 150mg/ m^2 BID
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc
OCP Reviewer	Derek Zhang, Ph.D.
OCP Team Leader	Kellie Reynolds, Pharm.D.
PM Reviewer:	Joo Yeon Lee, Ph.D
Secondary PM Reviewer	Pravin Jadhav, Ph.D
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	NDA
Submission Date:	December 21, 2007
PDUFA Date:	June 21, 2008

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APPENDIX **58**

Executive Summary

Tipranavir (APTIVUS; TPV) capsule, a non-peptidic protease inhibitor (PI), was granted accelerated approval in June 2005 and traditional approval in October 2007 as an HIV-1 PI with demonstrated efficacy in adult patients. Sponsor submitted NDA 22-292 and 21-814 seeking an approval of APTIVUS oral solution (OS) and capsule for pediatric use.

The sponsor conducted a 48 week, open-label, parallel, randomized clinical trial (1182.14) with two doses of TPV oral solution with low-dose ritonavir (RTV) in HIV-infected children 2 to 18 years of age (N=115). The trial was extended to 100 weeks after 48 week analysis. The doses were scaled from recommended adult TPV/RTV (TPV/r) 500/200 mg dose. The low dose was a BSA-adjusted equivalent of the adult dose, derived by dividing the adult dose by the mean adult BSA of $1.73m^2$, yielding a dose of TPV 290 mg/m^2 + RTV 115 mg/m^2. The high dose was determined to be 30% higher than the low dose, yielding TPV 375mg/m2 + RTV 150mg/m2. The sponsor proposed high dose (TPV 375 mg/m^2 + RTV 150 mg/m^2) for approval based on benefit / risk profile.

The pharmacometrics review focused on three main questions:

1. Is there an exposure-virologic success relationship for TPV?

Genotypic Inhibitory Quotient (GIQ) was found to be one of the major predictors of virologic success (proportion of patients with viral load below 400 copies/mL and 50 copies/mL) at week 48. GIQ was calculated by dividing geometric mean TPV plasma trough concentration (Cmin) by number of TPV related mutations. The virologic success at week 48 increased with higher TPV exposure. For example, proportion of patients with virologic success (VL < 400 copies/mL) increased from 11.5% in the lowest quartile (GIQ range 0.48-6.05) to 69.2% in the highest quartile (GIQ range 36.48-215.38). For a given mutation score additional benefit was seen with higher exposures.

2. Is there an exposure-safety relationship for TPV?

The analysis of safety and exposure focused on rash, bleeding and liver function test (LFT) abnormalities. There was no apparent relationship between rash or bleeding and TPV exposure, but incidence of LFT seemed to increase with TPV exposure. The LFTs were analyzed from adverse event as well as lab dataset. The proportion of patients with ≥ grade 2 LFTs increased from 16% in the lowest quartile (median Cmin=14uM) to 53.8% in the highest quartile (median Cmin= 74uM).

3. What is the appropriate dose of TPV based on exposure-virologic success and exposure-safety relationship?

The geometric mean plasma trough concentration of TPV was compared between adult and pediatric patients. The low dose ($290/115mg/m^2$) reasonably matched exposures to that of adult's approved dose ($500/200mg/m^2$). According to the sponsor, a high dose should offer more benefit compared to low dose. Based on exposure-response analysis and the medical reviewer's observation, the benefit with higher exposures was mostly seen in patients with high number of TPV mutations. There was a relationship between age and number of TPV mutations (Pearson's chi-square test: p-value=0.009), and as shown in Table 4, the number of TPV mutation scores increased with age. Thus the

benefit of higher dose was observed in older (≥ 6 years) children more than in younger (< 6 years) children. Therefore, higher dose (375/150 mg/m^2) was deemed appropriate for older children and lower dose (290/115 mg/m^2) for younger children, based on the subjects in study 1182.14.

The pharmacokinetics (clearance and volume of distribution) of TPV are dependent on body weight and not age. According to the above proposal, older children with lower weight could get the higher dose, leading to higher exposures than in children of identical age but higher body weight. Hence, the weight based dosing was investigated to handle patients at the age cut-off boundary.

Based on Cmin-body weight relationship, 10,000 patients were simulated (nonparametric simulations from observed weights) to assess potential distribution of Cmin under various dose levels of TPV (9 mg/kg, 10 mg/kg, 12 mg/kg and 14 mg/ kg). A working therapeutic window (17.4 μM and 57.2 μM) was selected based on the upper bound of the first quartile and the lower bound of the last quartile through efficacy and safety analysis. Proportions of patients in different weight categories (<20 kg, 20-40 kg, 40-60 kg and >60 kg) with Cmin outside of the working therapeutic window were calculated.

As shown in **Table 10**, a dose 10 mg/kg (body weight ≤20 kg) and 9 mg/kg (body weight >20 kg) would be appropriate, if equal weight is given to safety and effectiveness. These doses result in 15-17% patients below 17.4 μM and above 57.2 μM thresholds. In the discussion with medical and clinical pharmacology colleagues (May 21, 2008 meeting), a preference was given more toward maximizing benefit at the potential expense of safety. This was justified from the clinical experience that patients with more resistance require higher exposures and those with fewer future treatment options may be willing to accept risk. The dosing scheme of TPV/r 12/5 mg/kg for children ≤ 20 kg and 14/6 mg/kg for children >20kg was proposed based on overall risk-benefit consideration.

The population evaluated in study 1182.14 may not represent the target population as the inclusion criteria allowed subjects with less treatment experience to enroll. In particular, the younger age group may not well represent target population. TPV is indicated for patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor, the actual target population would be likely to have multiple mutation scores even in younger or lighter children population. The discrepancy between target and study population was discussed at the June 10, 2008 meeting after the sponsor's request to further discuss the dosing proposal. If the target population is likely to have multiple PI resistance and thus higher TPV mutations, a higher dose (14/6 mg/kg) can be justified across the entire age and weight range.

Recommendations

Given pharmacokinetic profile, efficacy and safety analyses results we propose the following dosing scheme;

TPV/r of 14/6 mg per kilogram BID

However, patients who develop toxicity or intolerance while receiving recommended dose of TPV/r and who do not have multiple baseline PI resistance, the dose may be

reduced to 12/5 mg/kg A dose reduction in patients with multiple baseline protease inhibitor mutations is not recommended.

Source of Data: Trial 1182.14

Trial 1182.14 was an open-label, parallel, randomized trial of two doses of TPV OS with low-dose RTV in HIV-infected children 2 to 18 years of age. The initial duration of this trial was 48 weeks. After completing 48 weeks, patients were able to continue in an extension of the trial up to 100 weeks. Of the 115 patients who entered in this trial, 97 patients were treated with TPV/r more than 24 weeks.

In addition to Trial 1182.14, there were 25 patients from the Expanded Access Program (EAP) / Emergency Use Program (EUP) (1182.58, 1182.67 and 1182.16), and clinical trials 1182.48 and 1182.53, which contributed data and the data from these sources were also used for safety analysis. But the primary sources of data were taken from the clinical trial reports for Trial 1182.14.

Two TPV/r doses were used in Trial 1182.14, a low dose and high dose. These doses were allometrically scaled from the recommended adult (TPV/r 500/200 mg) dose. The low dose was a BSA-adjusted equivalent of the adult dose, derived by dividing the adult dose by the mean adult BSA of 1.73m2, yielding a dose of TPV 290 mg/m2 + RTV 115 mg/m2. A high dose was chosen because children may require higher doses of PIs than adults, due to an increased rate of drug metabolism. The high dose was determined to be 30% higher than the low dose, yielding TPV 375mg/m2 + RTV 150mg/m2. The maximum TPV/r dose allowed was 500/200mg BID regardless of the patient's BSA-calculated dose. Based on study design, all patients were required to begin the study by taking TPV/r as an OS for the first 4 weeks of treatment. Thereafter, patients who were 12 years or older and whose BSA-calculated dose was equivalent to TPV/r 500/200mg were permitted to switch from TPV OS to TPV capsules, if they want.

Table 1: The baseline demographics

	TPV/r low dose N (%)	TPV/r high dose N (%)	Total N (%)
Total Treated	58 (100.0)	57 (100.0)	115 (100.0)
Age group			
2-<6	13 (22.4)	12 (21.1)	25 (21.7)
6-<12	19 (32.8)	19 (33.3)	38 (33.0)
12-18	26 (44.8)	26 (45.6)	52 (45.2)
Gender			
Male	32 (55.2)	33 (57.9)	65 (56.5)
Female	26 (44.8)	24 (42.1)	50 (43.5)
Race			
White	45 (77.6)	35 (61.4)	80 (69.6)
Black	13 (22.4)	20 (35.1)	33 (28.7)
Asian	0 (0.0)	2 (3.5)	2 (1.7)
Ethnicity			
Hispanic/Latino	35 (60.3)	26 (45.6)	61 (53.0)
Mixed race	3 (5.2)	2 (3.5)	5 (4.3)
Unknown	20 (34.5)	29 (50.9)	49 (42.6)

TPV/r low dose = TPV 290 mg/m^2 + RTV 115mg/m^2
TPV/r high dose = TPV 375 mg/m^2 + RTV 150mg/m^2

Source: sponsor's report U07-3541 Table 2.5.4.2: 1 page 16

QUESTION BASED REVIEW

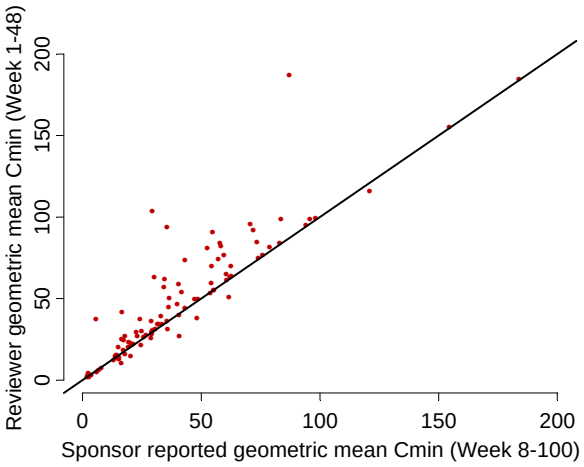
Is there an exposure-virologic success relationship for TPV?

Yes, there is a relationship between exposure and virologic success (confirmed viral load below 400 copies/mL at week 48). Genotypic Inhibitory Quotient (GIQ) was found to be a predictor of virologic success. GIQ was calculated by dividing geometric mean TPV plasma trough concentration (Cmin) by number of TPV related mutations.

GIQ-Response analysis

The total of 115 patients was used for efficacy analysis. For 48 week analysis, the sponsor used geometric mean trough concentration. It was calculated using data collected from weeks 8 through 100. It was not obvious if post 48 weeks pharmacokinetics data due to dose changes during the course of the trial were relevant to week 48 exposure-response analysis. In order to confirm the sponsor's calculation on GIQ, the reviewer compared geometric mean of trough concentration during weeks 1- 48 with the sponsor's geometric mean trough concentrations. As shown in Figure 1, reviewer's calculation was reasonably consistent with sponsor's, hence throughout the analyses the sponsor's reported geometric mean trough concentrations are used.

Figure 1. The comparison of trough concentration between the sponsor's calculation and the reviewer's calculation.



With reasonable agreement on calculation of GIQ, Table 2 presented virologic response rate from observed data. Virologic responses increased with increasing GIQ quartile. Specifically patients with GIQ in the higher quartile tended to show better response rates than lower quartile . For example, proportions of patients with virologic success for VL <

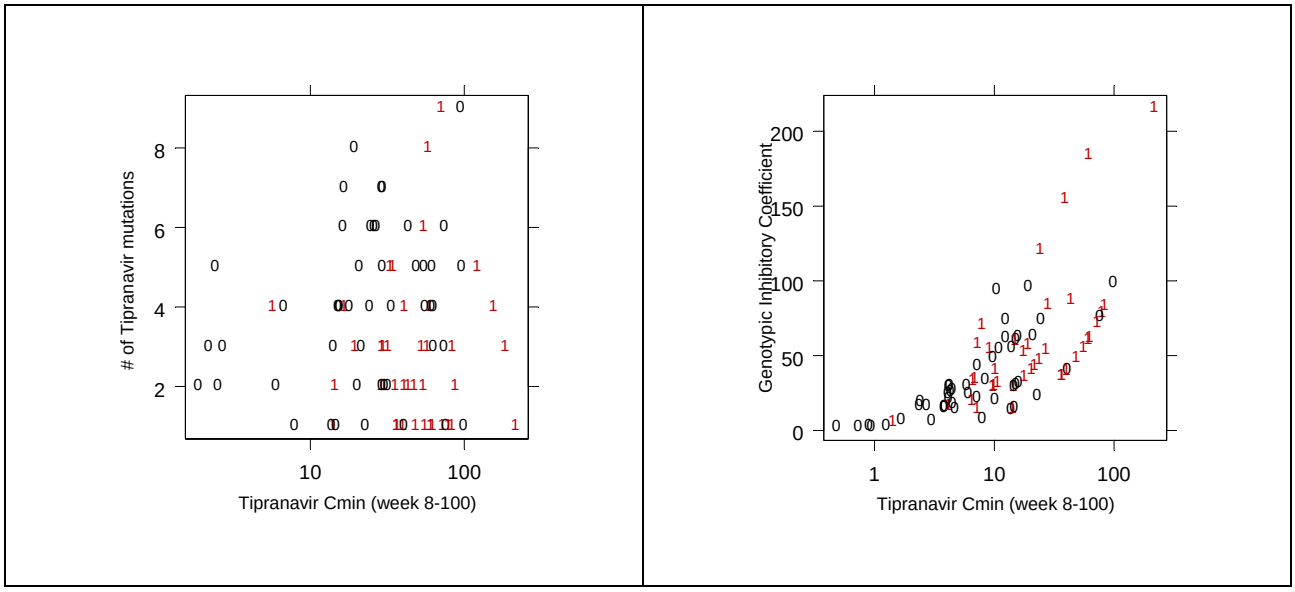
400 copies/mL and VL < 50 copies/mL increased from 11.5%, 7.7% in the lowest quartile (GIQ range 0.48-6.05) to 69.2%, 57.7% in the higher quartile (GIQ range 36.48-215.38), respectively. For a given mutation score, additional benefit was seen with higher exposures. For both variables, a trend appeared to be similar so a reviewer did proceed the analysis focused on VL < 400 copies/mL.

Table 2: The proportion of virologic response rates by GIQ quartiles.

GIQ quartiles	HIV RNA count < 400 copies/mL	HIV RNA count < 50 copies/mL
Q1 (0.48 – 6.05)	3 (11.5%) 26	2 (7.7%) 26
Q2 (6.05 – 14.38)	13 (50.0%) 26	10 (38.5%) 26
Q3 (14.38 – 36.48)	14 (56.0%) 25	12 (48.0%) 25
Q4 (36.48 – 215.38)	18 (69.2%) 26	15 (57.7%) 26

However, it was important to know if the Cmin or TPV mutations was the major contributor to virologic success. The left panel of Figure 2 shows the response with viral load < 400 copies/mL at week 48 (noted '1' for virologic success and '0 for failure) by both TPV mutation score and trough concentration. A slightly higher propotion of patients with virologic success were observed with lower TPV mutation score at the baseline. In terms of the relationship between trough concentration and response, there appeared to be obvious trend of higher virologic success with higher concentration for a given mutation score. Furthermore, there is the relation between GIQ and trough concentration as shown in the right panel of Figure 2. The importance of the Cmin over number of TPV mutations was also confirmed by logistic regression analysis. The Akaike's Information Criteria (AIC) value from a model with Cmin as a predictor (AIC=134) was lower than the AIC value from a model number of TPV mutations as a predictor (AIC=145)

Figure 2.The relationship between TPV mutation score and TPV trough concentration (left panel) and GIQ and TPV trough concentration (right panel) for patients with virologic success (1) and failure (0).



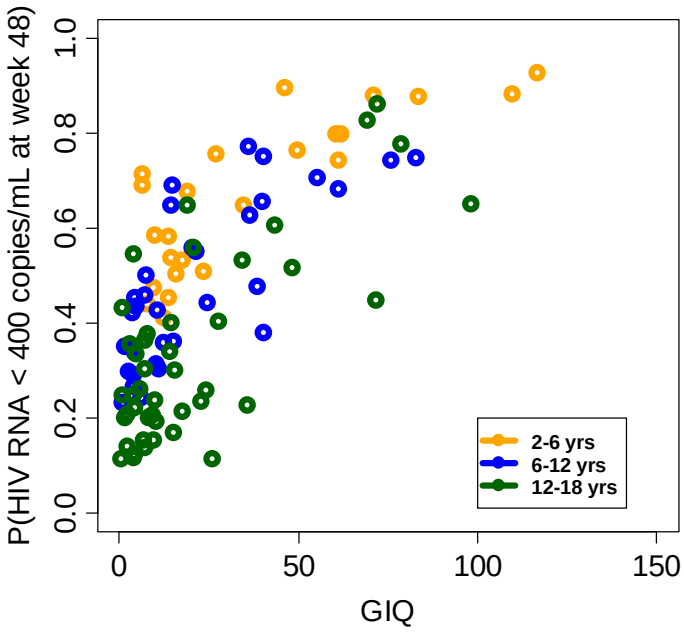
In addition, the sponsor conducted logistic regression analysis using virologic response at week 48 (if HIV RNA count < 400 copies/mL or not) as a response variable and dose group, GIQ quartiles, baseline viral load, age, adherence and Genotype Susceptibility Score (GSS) score as predictors after converting continuous scale to categorical scale. The sponsor concluded that GIQ quartile is the only significant factor for predicting response rate at week 48. However, there should be multicollinearity between dose group and GIQ quartiles and there was no advantage of the use of categorical variable rather than continuous variables. Hence, reviewer refitted logistic model including age, baseline viral load and GIQ as continuous variables and the result is shown in Table 3. Unlike the sponsor's conclusion, baseline viral load and age also are significant factors in virologic response rate at week 48.

Table 3: The parameter estimates with p-value of reviewer's logistic regression model.

	Estimate (SE)	P-value
Baseline log10 HIV RNA count (copies/mL)	-0.8 (0.35)	0.024
AGE	-0.13(0.05)	0.013
GIQ	0.02 (0.01)	0.029

Figure 3 shows the predicted probability of VL < 400 copies/mL at week 48 by GIQ stratified by age group from the reviewer's model. Clearly as GIQ increases and a patient is younger, there would be higher probability of getting virologic response at week 48.

Figure 3. The predicted probability of virologic response rates at week 48 as a function of GIQ from a logistic regression model.



TPV trough concentration – response analysis

As GIQ is a function of TPV mutation score as well as TPV trough concentration, higher response rate by increasing GIQ could result from not only higher TPV concentration (high dose) but also less TPV mutation at the baseline. In this analysis reviewer aimed to assess the effect of TPV concentration rather than GIQ on the response rate.

First the reviewer examined the distribution of TPV mutation score at the baseline by dose and age groups and it is shown in Table 4 . Slightly more patients in high dose group had TPV mutation score of zero at the baseline than those in low dose group. However, overall there is no specific trend in mutation score by dose group, which is also supported by Pearson chi-square test (p-value=0.41). However, there existed a relationship between age of patients and the number of TPV mutation score (p-value=0.009); older patients appeared to have higher TPV mutation score.

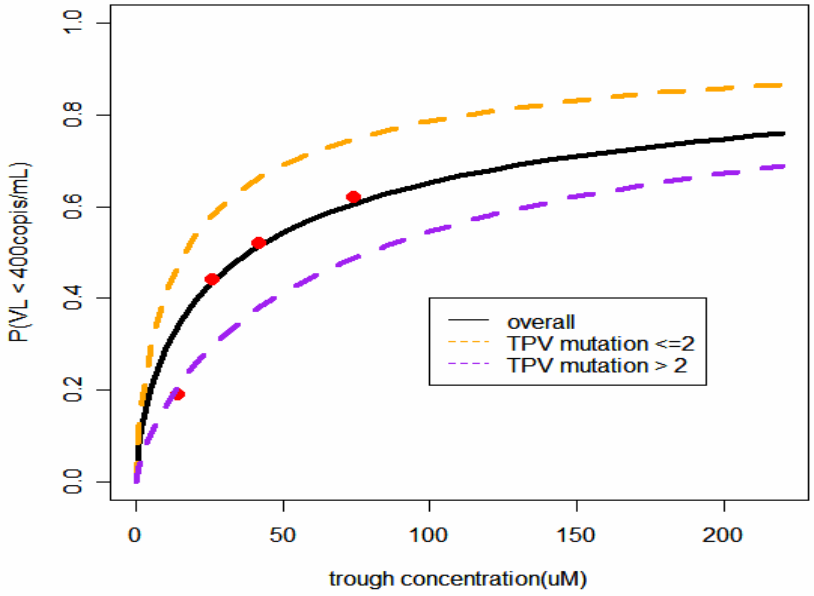
Table 4: The TPV mutation score at the baseline by dose and age groups

	Dose Group		Age group		
TPV mutation score	290/115mg/m2 (58)	375/150mg/m2 (57)	2-<6 (25)	6-<12 (37)	12-18 (53)
0	7 (12.1%)	12 (21.1%)	8 (32.0%)	4 (10.8%)	7 (13.2%)
1-4	36 (62.1%)	33 (57.9%)	15 (60.0%)	27 (73.0%)	27 (50.9%)
>4	15 (25.8%)	12 (21.0%)	2 (8.0%)	6 (16.2%)	19 (35.9%)

The effect of TPV exposure after adjusting baseline log(viral load) and TPV mutation score as a dummy variable (0 if TPV mutation score <=2, 1 if > 2) on virologic success (VL < 400 copies/mL) at week 48 was analyzed using logistic regression. Figure 4 shows the predicted probability of virologic success at week 48 from logistic model by overall and TPV mutation score with observed proportion of virologic success at each quartile of concentration.

The results from logistic regression show that the predicted likelihood of virologic response increases as an exposure to TPV increases, but it seemed to reach a plateau. The observed proportion of patients with virologic success were 19% in the 1st quartile with median of 13.7 (range 1.8 – 17.4), 44% in the 2nd quartile with median of 25.7 (range 17.8-32.9), 52% in the 3rd quartile with median of 41.8 (range 33.4 – 55.3) and 62% in the 4th quartile of median of 73.7 (range 57.2 – 215.4). Also it is shown that the patients with lower TPV mutation score seemed to have higher probability of success at a given concentration than those with higher TPV mutation score. In conclusion, higher TPV exposure increases the overall likelihood of virologic response rate (VL < 400 copies/mL) up to 60 -70%. From a patient viewpoint, it is advantageous not to be in the first quartile i.e. Cmin <17.5 μM compared to other quartiles. For patients with TPV mutations ≤2, Cmin >17.5 μM did not seem to yield additional benefit.

Figure 4. The predicted probability of virologic response rate by overall and TPV mutation score as a function of TPV trough concentration with observed proportion of virologic response at median of concentration quartiles.



Is there exposure-safety relationship for TPV?

Yes, there appeared to be signal on liver function abnormality related to TPV exposure.

Adverse events

In the exposure-safety analysis, there were 115 patients included. Table 5 below presents overall summary of adverse events by dose group. Overall frequency of events appears to be similar for both dose group.

Table 5: Overall summary of adverse events at week 48 by dose group.

	Number (%) of Patients		
	TPV/r low dose[1]	TPV/r high dose[2]	Total
Total treated	58 (100.0)	57 (100.0)	115 (100.0)
Total with any AE	54 (93.1)	54 (94.7)	108 (93.9)
Total with any severe AE	15 (25.9)	14 (24.6)	29 (25.2)
Total with any study drug-related AE	28 (48.3)	34 (59.6)	62 (53.9)
Total with any AE leading to discontinuation of study drug	6 (10.3)	4 (7.0)	10 (8.7)
Total with any SAE	16 (27.6)	13 (22.8)	29 (25.2)
Total with protocol-defined significant AE	5 (8.6)	6 (10.5)	11 (9.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

1 TPV/r low dose = TPV 290 mg/m^2 + RTV 115 mg/m^2.
2 TPV/r high dose = TPV 375 mg/m^2 + RTV 150 mg/m^2.

Source: Sponsor's report U07-3462 table 2.1.1:1, page 30

Based on the experiences from adult studies, three adverse events, rash, bleeding and liver function test abnormality, were selected for exposure-safety evaluation. Table 6 presents the specific events included in each category.

Table 6: The selected adverse events and preferred terminology.

Adverse event	Preferred terms
Rash	Dermatitis papular, Drug rash, Localised rash, Macular rash, Maculopapular rash, Neck rash, Papular rash, Papular rash on hands, Papule, Pruritic rash, Pruritus, Rash, Rash macular, Rash on face, Swelling face, Swelling of eyelid, Urticaria, Urticarial rash
Liver Function Test abnormality (LFT)	ALT increased, AST increased, GGT increased, GPT increased, Liver function test abnormal
Bleeding	Bleeding from ears, Blood in stool, Bloody diarrhea, GI bleed, Gum

	bleeding, Nose bleed, Haematoma, Coagulation time prolonged, Bruise, Contusion, Dysmenorrhea, Epistaxis, Menstruation increased, Thrombocytopenia, Thrombotic thrombocytopenic purpura, Transient ischaemic attack

The observed plasma trough concentration was used an exposure variable. It was determined to be reasonable based on correlation between TPV pharmacokinetic variables (Cmin and Cmax as well as Cmin and AUC) (Figure 5).

Figure 5. The relationship of Cmin .vs. Cmax (right panel) and Cmin .vs. AUC (left panel). Each parameter was estimated from population PK model with 52 patients.

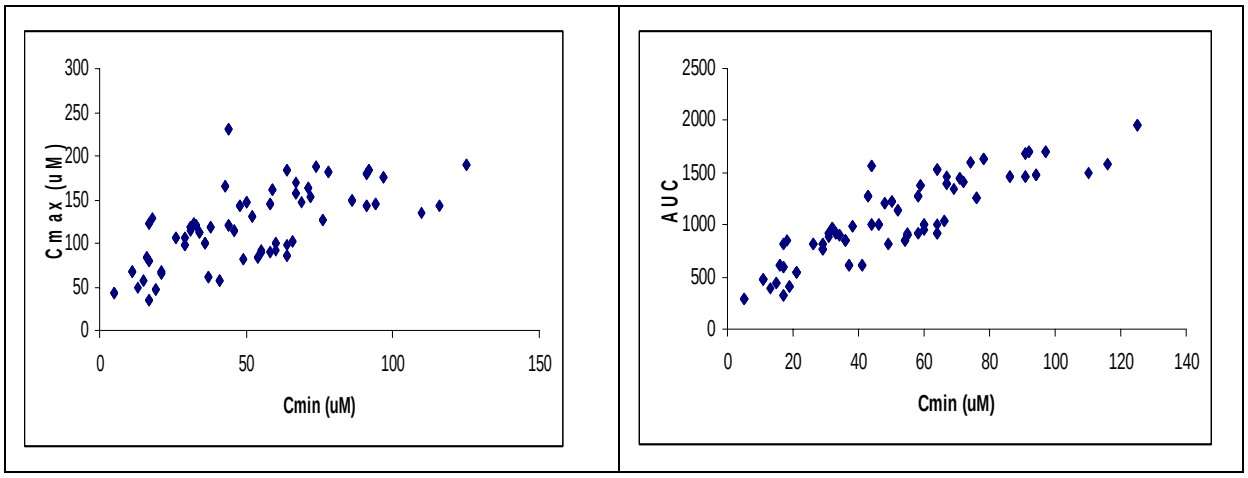
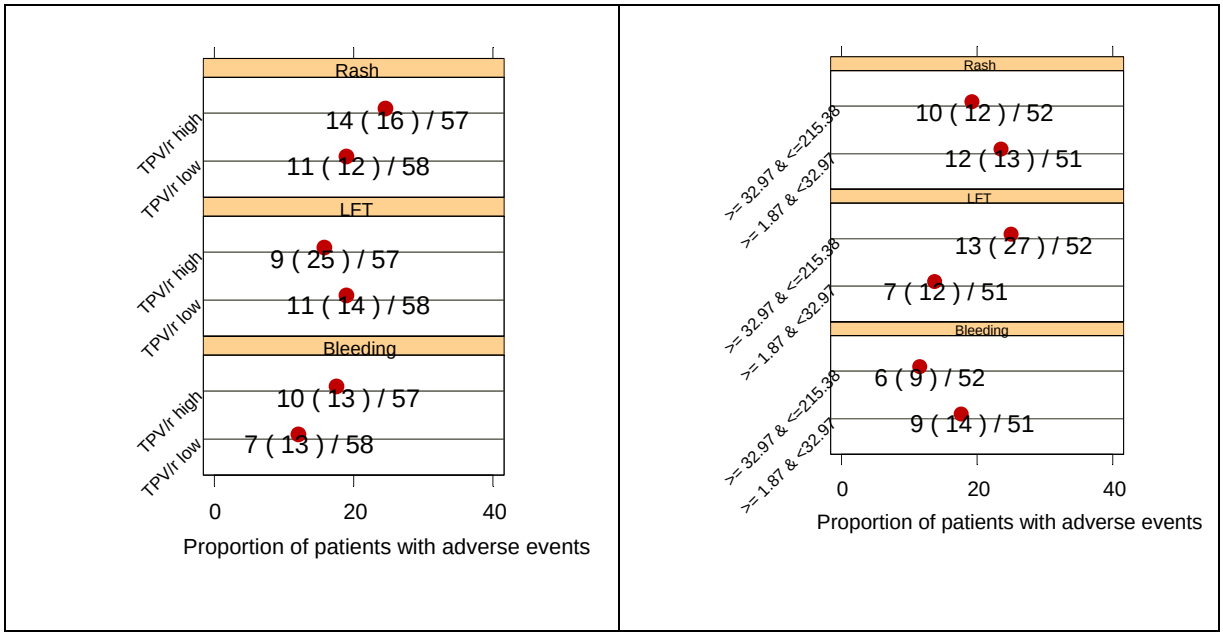


Figure 6 shows the proportions of patients who experienced each adverse event with an actual number of multiple incidences in a parenthesis by dose group (left panel) and trough concentration (right panel) which was divided based on median. No specific trend was seen for rash and bleeding events for either dose group or concentration comparisons. But more incidences related to liver function abnormality happened in the patients with high concentration.

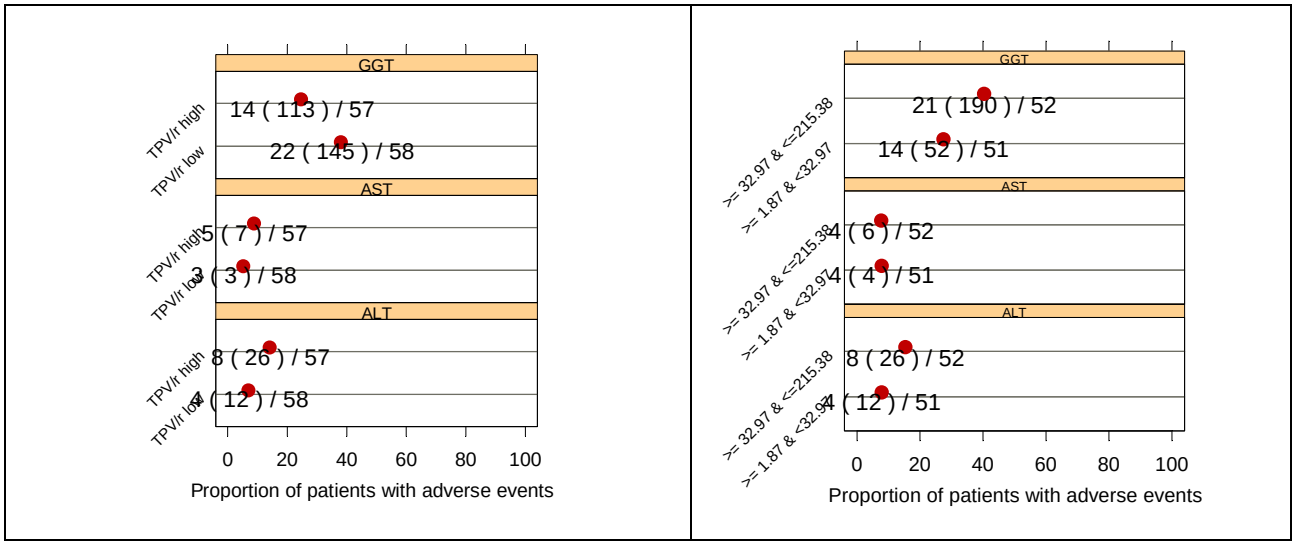
Figure 6. Proportions of patients with bleeding, LFT and rash by dose groups and Cmin groups. The numbers associated with each symbol represent the number of patient (number of actual events)/ total number of patients per group.



Liver function test abnormality (LFT)

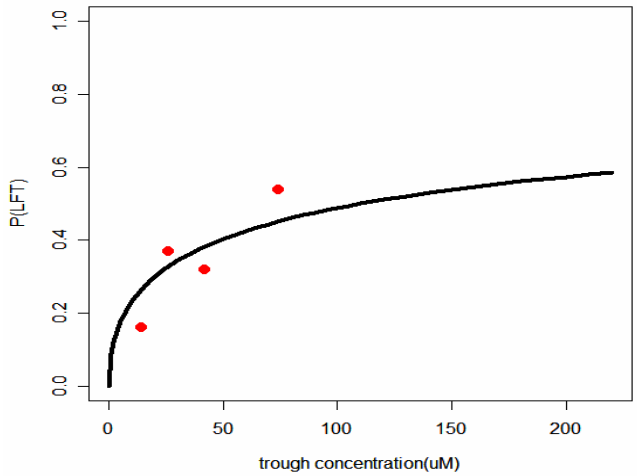
It was shown that there could be a signal with liver function abnormality, so we further analyzed exposure and safety focused on LFT laboratory result data (grade level 2 and greater). The Figure 7 shows the frequency and proportion of patients who had incidences of LFT. The GGT increase seems to be the biggest cause in LFT and it shows higher incidences in low dose (24.5% .vs. 37.9%) but in higher concentration (40.4% .vs. 27.5%). Hence it is natural to believe that there should be overlapping range of exposures between patients with and without events. Therefore, rather than just comparing the descriptive statistics by dose group or two categories of concentration, the reviewer conducted logistic regression analysis to see more systematic relationship between LFT and exposure.

Figure 7. Proportion of patients with LFTs (grade >=2) from laborotory data. The numbers associated with each symbol represent the number of patient (number of actual events)/ total number of patients per group.



The proportion of patients with ≥ grade 2 LFTs increased from 16% in the lowest quartile (median Cmin= 14uM) to 53.8% in the highest quartile (median Cmin= 74uM). **Figure 8** shows the predicted probability of LFT as a function of trough concentration with an observed proportion of LFT at each median of quartiles of concentration. There was a good agreement between observed proportion and predicted values from the logit model. There appeared to be higher likelihood of LFT incidences (mostly driven by GGT) with increasing exposure and the relationship is statistically significant (p-value=0.04).

Figure 8. The relationship between exposure (Cmin) and the predicted probability of LFT (black solid line) with observed proportion of LFT incidence at the median of each concentration quartile (red dots).



What is the appropriate dose of TPV based on exposure-virologic success and exposure-safety relationship?

The focus was to analyze appropriateness of the sponsor's proposal of 375/150 mg/m^2 across the pediatric age range based on GIQ-response analysis and safety profile.

The sponsor conducted population PK analysis using 1-compartment model with first-order absorption using non-linear mixed effect model among 52 children in trial 1182.14, during the first 4 weeks of TPV/r oral solution administration. The summary of PK parameters is presented in Table 7. Most parameters look reasonably comparable among the age groups and dose groups, although clearance appeared to be a bit higher for the 12-18 years age group with also large variability.

Table 7: Steady-state TPV PK parameters (mean, SD) following twice-daily dosing with OS in pediatric patients during the first 4 weeks.

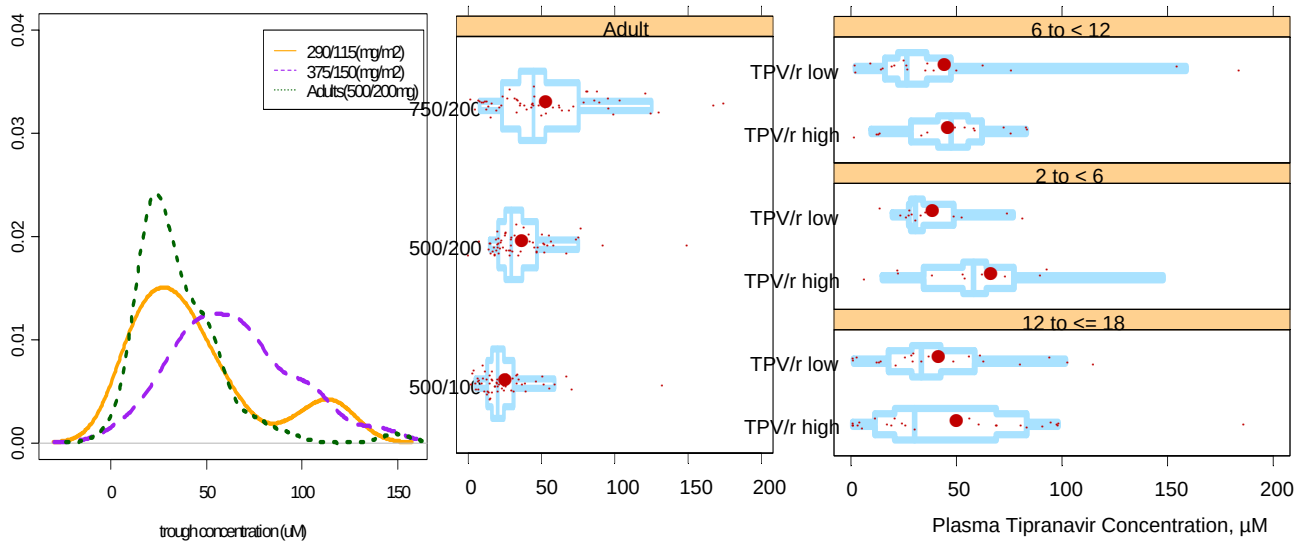
Parameter	Dose Regimen	2 to <6 years	6 to <12 years	12 to 18 years
Oral Clearance (L/h)	Low Dose[1] High Dose[2]	0.45 ± 0.16 0.34 ± 0.11	0.55 ± 0.30 0.45 ± 0.08	0.78 ± 0.44 0.99 ± 0.96
Elimination Half-Life (h)	Low Dose High Dose	7.6 ± 5.1 8.1 ± 3.3	7.5 ± 3.7 7.1 ± 2.1	8.3 ± 9.0 5.2 ± 2.3
Predicted $AUC_{0\text{-}12h}$ (μM•h)	Low Dose High Dose	710 ± 223 1190 ± 332	971 ± 469 1354 ± 256	1102 ± 526 1194 ± 517
Geometric mean observed concentrations (μM)	Low Dose High Dose	28.2 48.7	43.8 63.9	35.3 46.1

[1]TPV/r low dose = TPV 290 mg/m^2 + RTV 115mg/m^2
[2]TPV/r high dose = TPV 375 mg/m^2 + RTV 150mg/m^2

Source: sponsor's report U07-3541, table 2.5.3.1:1, page 11

Figure 9 presents the distribution of trough concentration with 52 patients who were used for population PK analysis. A dose of 290 mg/m^2 gave approximately the same exposure as compared to approved dose for adults use (500/200ng), although large variability is shown in the distribution. Especially, high dose in 2-<6 years age group may yield high exposures compared to other subgroups of age.

Figure 9. The distribution of geometric mean of trough concentration collected 10 to 14 hours after dosing by dose group from trial 1182.14 and approved adult dose (500/200mg) from the data of study 52 by overall and age group.



Also, the sponsor collected steady-state trough concentrations from all subjects, which were obtained between 10-14 hours after the prior dose, during week 8 through week 124. As shown in Table 8, trough concentration remained similar to those calculated from the population PK model throughout the extended follow-up trial.

Table 8: Summary of steady-state TPV trough concentrations collected 10-14 hours after dosing during week 8 through week 124.

Plasma tipranavir concentrations				
		TPV/r dose (mg/m^2)		
Age (years)	Summary Statistic	290/115	375/150	Ratio[1]
2 to <6	N (patients)	17	11	
	Geometric Mean (µM) (%CV)	32.69 (99)	46.91 (66.8)	1.4
6 to <12	N (patients)	37	16	
	Geometric Mean (µM) (%CV)	33.08 (92)	61.32 (86)	1.9
12 to 18	N (patients)	27	23	
	Geometric Mean (µM) (%CV)	49.79 (115)	55.06 (124)	1.1

[1]Ratio of geometric mean concentrations of high dose (375/150) : low dose (290/115);

Source: sponsor's report U07-3541, table 2.5.3.2:1 page 13

Overall, low dose (290/115mg/m^2) reasonably matched exposures to that of adult approved dose (500/200mg/m^2). However, the sponsor proposed a higher dose with an argument to offer more benefit compared to low dose. Based on observed exposure-

response analysis presented before, the benefit with higher exposures was mostly seen in patients with high number of TPV mutations. The age and number of TPV mutations were correlated and the benefit was thus translated to older (≥ 6 years) children more than younger (< 6 years) children as older children were observed to have more mutation score than younger children (Table 4).

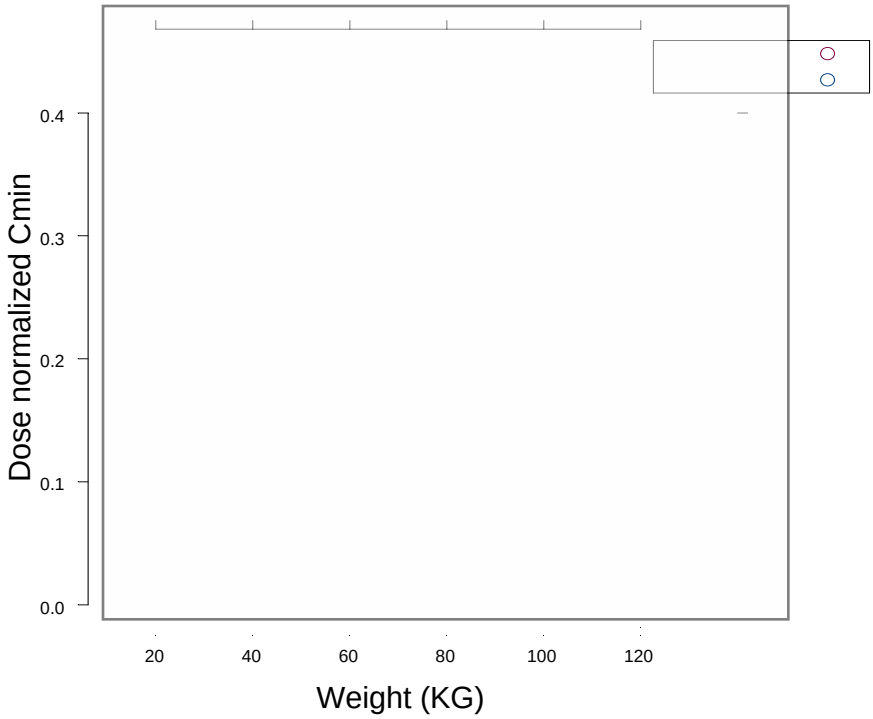
Pharmacokinetics (clearance and volume of distribution) of TPV are dependent on body weight. The weight based dosing was investigated to handle patients at the age cut-off boundary. For example, the age-BSA based dosing recommendation will lead to different dosing in a 6 year old 20 kg patient than 6.5 year old 20 kg patient, thus exposing the latter patient to relatively high concentrations from safety viewpoint (Table 9).

Table 9. The number of patients by age and body weight categories.

		Body weight		
AGE		≤ 20 kg (N=33)	20 – 40 kg (N=44)	> 40kg (N=38)
	2-<6 years (N=25)	25	0	0
	6- < 12 years (N=37)	8	28	1
	12-18 years (N=53)	0	16	37

The reviewer pooled the adult dataset (study 52) and pediatric dataset. The sponsor's population PK model was extended to include body weight as a covariate on clearance and volume of distribution (see appendix 2). The Figure 10 shows the relationship between body weight and dose normalized trough concentration from the model (solid line) with observed data (dot). The simple linear regression analysis was used to derive relationship between Cmin and body weight. Log of dose normalized Cmin and log of bodyweight were used for better fit. The derived relationship (log (Cmin) = 0.602 - 0.799*log (body weight)) was mechanistically (allometrically) appropriate. The relationship appeared to drop substantially up to 20kg and bodyweight > 40kg does not give much difference.

Figure 10. The relationship between body weight and dose normalized trough concentration. The black solid line is mean model prediction and red solid lines represent 5% and 95% quartiles. The red and blue dots indicate the observed data from adults and pediatric patients.



To find most reasonable dosing scheme based on body weight the reviewer conducted the simulation using 10,000 bootstrap samples of the original dataset (nonparametric simulations from observed weights). The dosing schemes of 9, 10, 12, 14 mg/kg were tested and maximum dose was capped to 500 mg (equal to adult dose) to generate potential distribution of Cmin under various dose levels. Based on previous exposure-virologic success relationship, TPV Cmin of 17.5 uM (the upper bound of the 1st quartile) was the minimum required concentration to achieve virologic success. It was also established that incidence of LFT increases with increasing exposure. A working therapeutic window (17.4 μM and 57.2 μM) was selected based on the upper bound of the first quartile and the lower bound of the last quartile. Proportion of patients by different weight categories (<20 kg, 20-40 kg, 40-60 kg and >60 kg) in the outside of the working therapeutic window were calculated. The aim of this simulation was to find optimal dosing scheme and minimize the number of patients in the 1st quartile (efficacy) and 4th quartile (safety), if equal weight was to be given to effectiveness and safety (Figure 11).

Figure 11. The mean predicted Cmin by body weight from regression model for various dosing scheme. Inner doted lines: lower (upper bound of 1st quartile) and upper (lower bound of 4th quartile) thresholds of Cmin, dashed lines: range of Cmin from observed data.

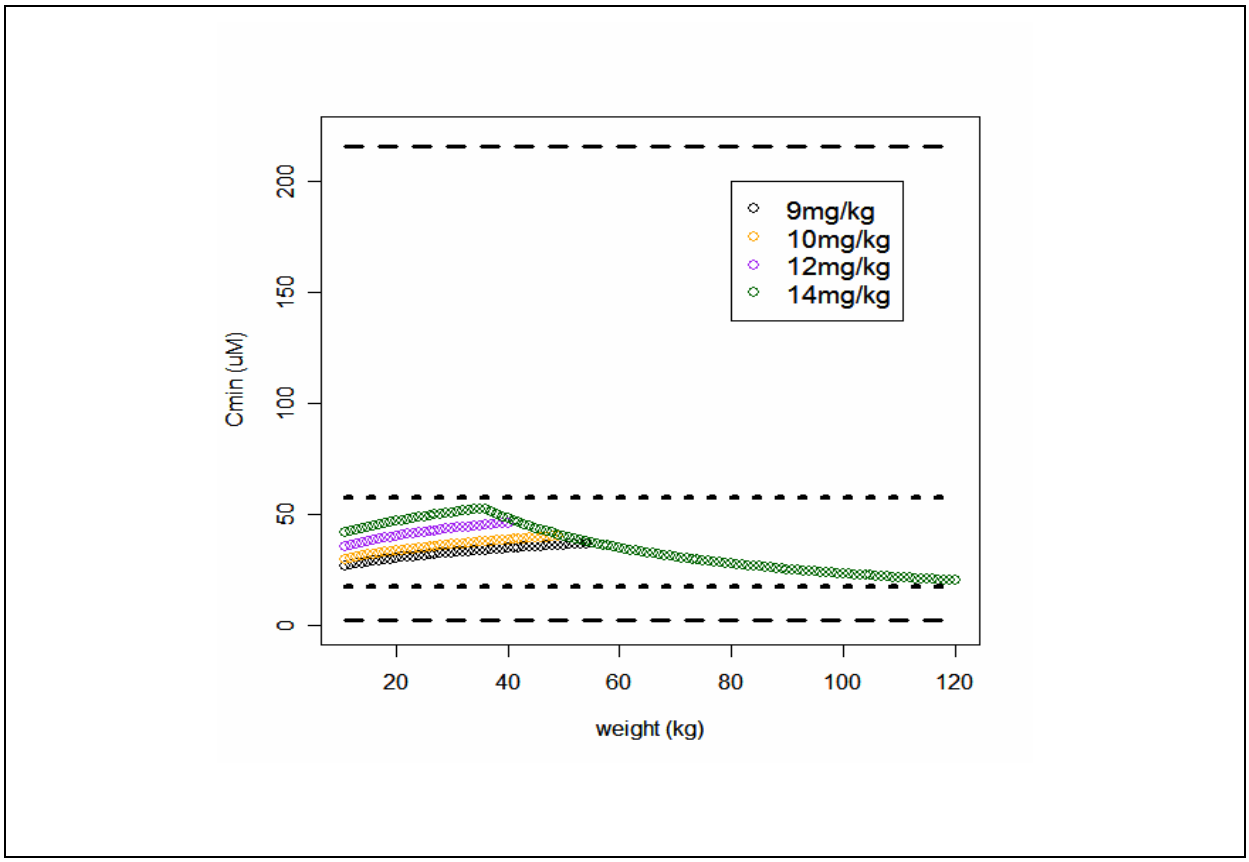


Table 10 presents the simulation results from four dosing schemes by body weight groups. Regardless of body weight, as dose increase the proportion of patients in the 1st quartiles decreases, meaning that more benefit (efficacy) is achieved with increasing doses. Also with higher dose the more patients fall in the 4th quartile, meaning that more patients can be at risk of adverse events or toxicity.

Table 10 : The proportion of patients who fall in the 1st and 4th quartiles by body weight according to various dosing scheme based on simulation.

Body weight	Threshold of concentration	9mg/kg	10mg/kg	12mg/kg	14mg/kg
≤ 20 kg	1st quartile (17.4uM)	22.1%	16.9%	9.7%	6.2%
	4th quartile (57.2uM)	12.4%	15.6%	24.4%	33.9%
> 20 kg	1st quartile (17.4uM)	14.7%	11.1%	6.1%	4.5%
	4th quartile (57.2uM)	17.2%	22.0%	33.0%	40.9%

A dose 10 mg/kg (≤20 kg) and 9 mg/kg (>20 kg) would be appropriate, if equal weight is given to safety and effectiveness. These doses result in 15-17% patients below 17.4 μM and above 57.2 μM thresholds. In the discussion with medical and clinical pharmacology colleagues (May 21, 2008 meeting), a preference was given toward maximizing benefit at the potential expense of safety. This can be justified from the clinical experience that patients using TPV/r as a part of antiretroviral regimen are more likely to have failed on other protease inhibitors due to safety or efficacy problems. In other words, the patients with more resistance require higher exposure and those with fewer future treatment options may be willing to accept risk. Table 11 indicates that about 45% of children who weigh less than 20 kg were observed to have less than 2 mutation score.

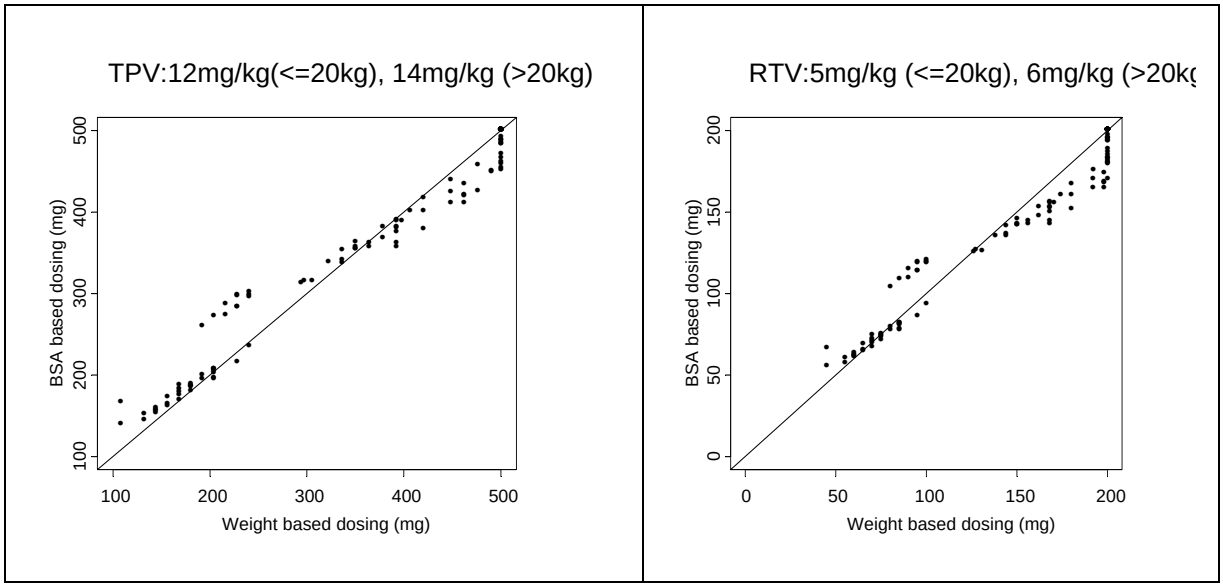
Table 11. TPV mutation score by body weight

TPV mutation score	≤ 20 kg (N=33)	>20 kg (N=82)
0	8 (24.2%)	11 (13.4%)
1	7 (21.2%)	14 (17.1%)
2	8 (24.2%)	8 (9.8%)
>2	10 (30.3%)	49 (59.8%)

As discussed previously, most benefit would be more likely to happen in the heavier children who have more mutation score than lighter children, which can be translated to the dosing scheme of TPV/r 12/5 mg/kg for children with ≤ 20 kg and 14/6 mg/kg for children with >20kg based on overall risk-benefit consideration.

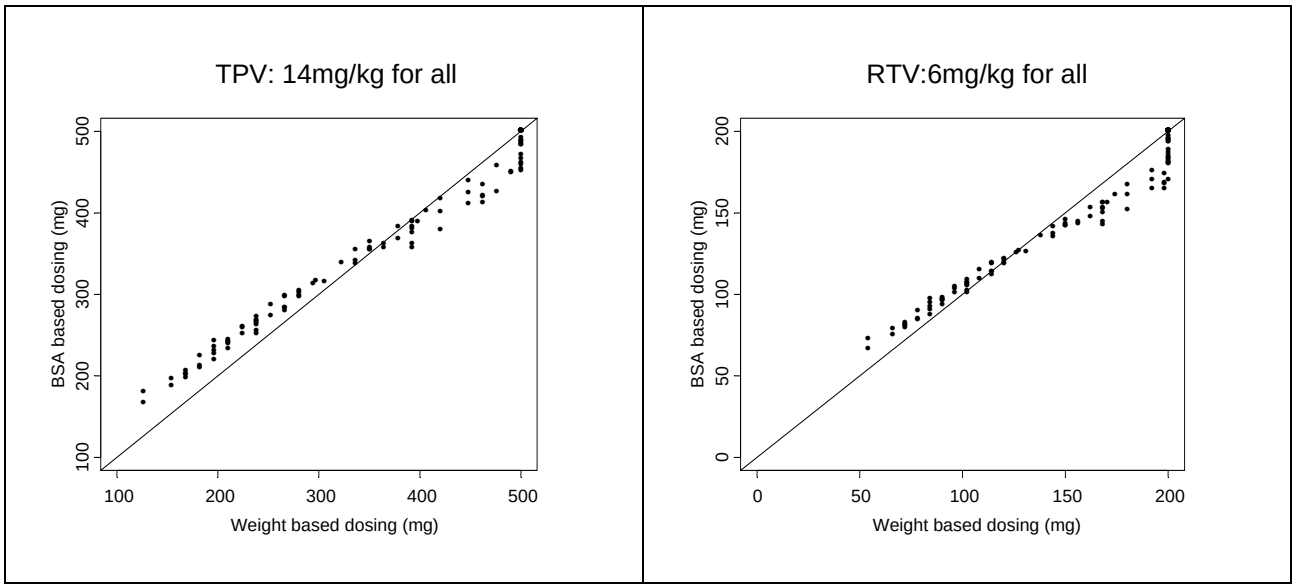
Figure 12 shows the comparison between BSA-based dosing and weight-based dosing when 2-tier dosing scheme was applied. The BSA-based dosing was calculated by multiplying 290mg by the BSA of patients 2-<6 years old and 375mg by the BSA of patients 6-18 years old in the dataset. The weight based dosing was computed by multiplying 12 mg and 14 mg by the body weight of patients with ≤ 20 kg and > 20kg, respectively.

Figure 12. The straight line represents the same dose by BSA and weight based dosing scheme, and dots above and below the line indicate lower and higher dose by weight-based dosing scheme than BSA-based dosing scheme, respectively.



The population evaluated in study 1182.14 may not represent the target population as the inclusion criteria allowed subjects with less treatment experience to enroll. In particular, the younger age group may not well represent target. TPV is indicated for patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor, the actual target population would be likely to have multiple mutation scores even in younger or lighter children population. The discrepancy between target and study population was discussed at the June 10, 2008 meeting after the sponsor's request to further discuss the dosing proposal. If the target population is likely to have multiple PI resistance and thus higher TPV mutations, a higher dose (14/6 mg/kg) can be justified. The final dosing recommendation of TPV/r of 14/6 mg/kg for all children reasonably matches with BSA-based dosing (375/150 mg/m^2 for all patients)(Figure 13). Patients who develop toxicity or intolerance while receiving recommended dose of TPV/r and who do not have multiple baseline PI resistance, the dose may be reduced to 12/5 mg/kg up to 10/4 mg/kg. A dose reduction in patients with multiple baseline protease inhibitor mutations is not recommended.

Figure 13. The comparison of total dose for a give patient based on age-BSA based dosing (TPV/r: 375/150 mg/m^2 for all children) and weight-based doing (TPV/r: 14/6 mg/kg for all children). The straight line represents the same dose by BSA and weight based dosing schemes, and dots above and below the line indicate lower and higher dose by weight-based dosing scheme than BSA-based dosing scheme, respectively.



Appendix

1. RTV concentration by dose and age groups

Ritonavir (RTV) works as a pharmacokinetic booster of Tipranavir (TPV). As shown in Table 12, RTV concentration appeared to be lower than those shown in adult dose of 200mg except for 12-18 years old in high dose (375/150mg/ m^2). It was assumed that as long as the concentration of TPV matches adult exposures across all age groups (see **Figure 9**), lower RTV concentration should not be of concern. In a given patient, however, lower RTV concentration could be responsible for lower TPV concentrations.

Table 12: The RTV geometric mean plasma steady-state trough concentration by dose and age groups.

	Age group		
	2-<6 yrs	6-<12 yrs	12-18 yrs
290/115mg/ m^2	0.15 (BLQ, 0.78)	0.20 (BLQ, 0.69)	0.12 (BLQ, 0.13)
375/150mg/ m^2	0.22 (BLQ, 0.92)	0.24 (0.08, 0.46)	0.35 (BLQ, 1.17)
Adults (500/200mg)	0.25 (0.04, 0.89)		

2. Reviewer's population PK model

A reviewer modified a sponsor's population PK model (1- compartment model with first-order absorption) to investigate the effect of body weight on Clearance (CL) and Volume of distribution (V) using NONMEM. The were comprised of 52 pediatric patients from Trial 1182.14 sampled during the first 28 days on 290/115 and 375/150 mg/m^2 TPV/r dose and 141 adult patients on 500/200mg or 750/200mg in study 52).

The body weight was included as a power function, normalized by the reference weight of 70 kg (see the code below) and it was significant on both CL and V.

The pharmacokinetic parameters are summarized in the table below.

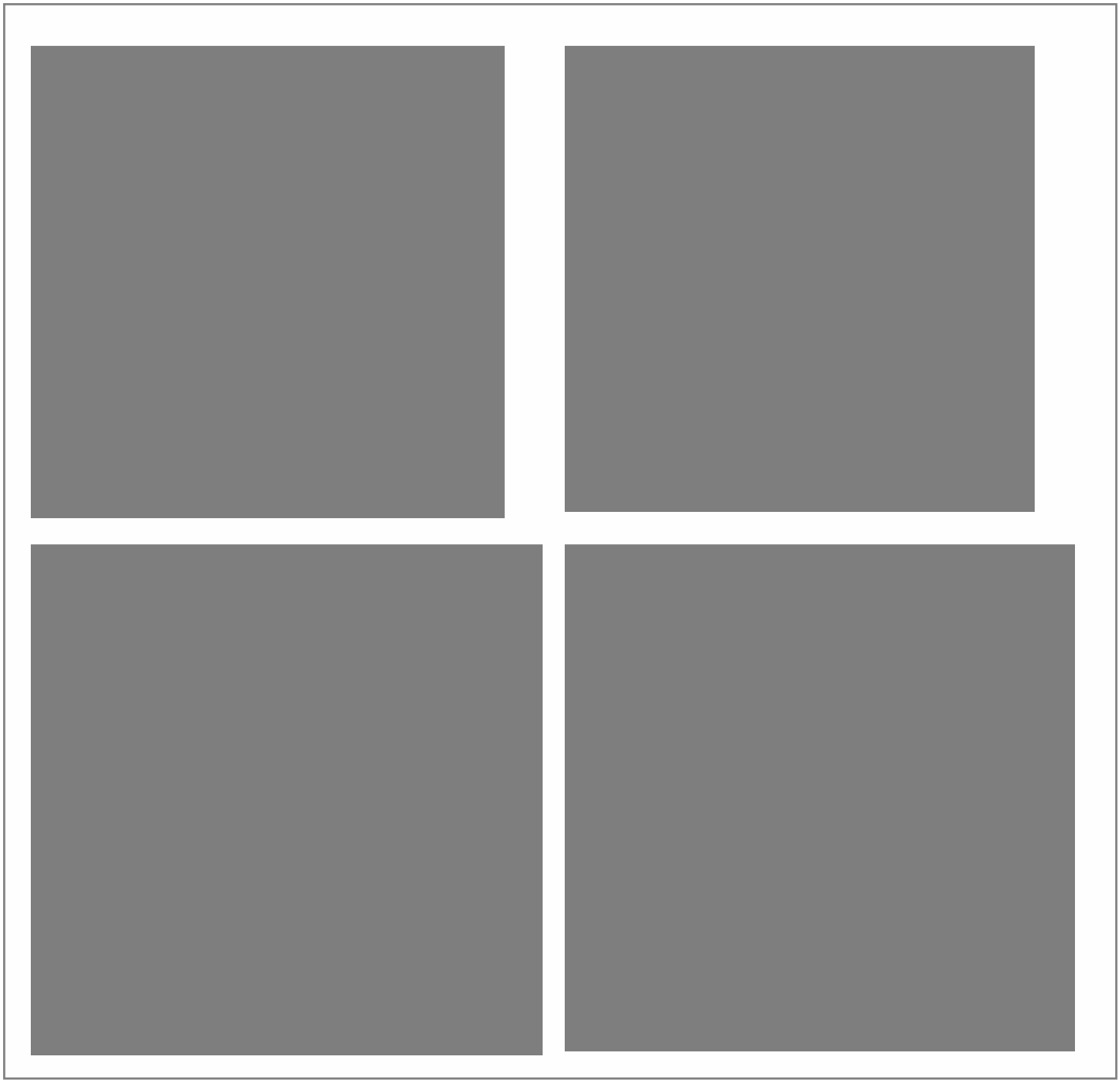
Table 13. The population PK parameter estimates.

Fixed effect (SE %)	
Ka (θ1)	0.76 (12.0%)
CL (θ2)	1.25 (4.7%)
(WTkg/70)^θ4	0.83 (6.1%)
V (θ3)	1.30 (10.5%)
(WTkg/70)^θ5	0.88 (10.4%)
Inter-subject variability (SE%)	
Ω_ka	0 (fixed)
Ω_CL	0.35 (15.3%)
Ω_V	0.27 (75.9%)
Residual variability (SE%)	0.39 (10.1%)

Model diagnostics for reviewer's population PK model

The model was qualified based on diagnostic plots. All diagnostic plots revealed that model was reasonable. Figure 15 illustrates reasonable agreement between observed and predicted data (top panel) and bottom panel shows agreement between observed and model predictions at individual level for representative adult and pediatric patients.

Figure 14. The comparison between observed and model predicted concentration; the top panels represent the relationship between observed and predicted concentrations (red dots : individual predicted values, green squares : population predicted values) and the relationship between weighted residuals and population predicted values, respectively; the comparison at individual level is shown in bottom panel (red dots : observed data, blue solid line : population predicted value, blue dotted line : individual predicted value).



The NONMEM control stream is provided below.

NONMEM code

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Derek Zhang
6/18/2008 03:21:31 PM
BIOPHARMACEUTICS

Joo-Yeon Lee
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Pravin Jadhav
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Joga will not sign off due to unavailability

Kellie Reynolds
6/19/2008 12:50:16 PM
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