

Table 3. Summary of the steady-state TPV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with mild hepatic insufficiency to their matched controls

Parameter	Mild Controls ¹	Mild Hepatics ¹	Geometric Mean Ratio ²	p-value ³
AUC _{0-12h} (h·μM)	962 ± 554 (848)	1144 ± 347 (1103)	1.30 (0.88, 1.92)	0.24
C _{max} (μM)	136 ± 57 (127)	150 ± 49 (145)	1.14 (0.83, 1.56)	0.46
Cp _{12h} (μM)	42 ± 48 (25)	51 ± 23 (47)	1.84 (0.81, 4.20)	0.20

¹ Mean ± SD geometric mean in parentheses

² Geometric mean ratio of the differences, 2.90% confidence interval in parentheses

³ ANOVA

Table 4. Summary of the steady-state RTV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with mild hepatic insufficiency to their matched controls

Parameter	Mild Controls ¹	Mild Hepatics ¹	Geometric Mean Ratio ²	p-value ³
AUC _{0-12h} (h·μg/mL)	13 ± 7 (10)	14 ± 9 (11)	1.07 (0.42, 2.73)	0.90
C _{max} (μg/mL)	3.6 ± 2.1 (2.8)	3.8 ± 2.0 (3.3)	1.17 (0.52, 2.65)	0.73
Cp _{12h} (μg/mL)	0.09 ± 0.11 (0.05)	0.12 ± 0.11 (0.08)	1.67 (0.37, 7.50)	0.54

¹ Mean ± SD geometric mean in parentheses

² Geometric mean ratio of the differences, 2.90% confidence interval in parentheses

³ ANOVA

Table 5. Summary of the single dose TPV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with moderate hepatic insufficiency to their matched controls

Parameter	Moderate Controls ¹	Moderate Hepatics ¹	Geometric Mean Ratio ²	p-value ³
AUC _{0-∞} (h·μM)	724 ± 261 (695)	1016 ± 514 (939)	1.35 (0.47, 3.90)	0.50
C _{max} (μM)	79 ± 29 (76)	57 ± 28 (52)	0.69 (0.25, 1.91)	0.40
Cp _{12h} (μM)	24 ± 8 (24)	36 ± 21 (32)	1.38 (0.44, 4.30)	0.50

¹ Mean ± SD geometric mean in parentheses

² Geometric mean ratio of the differences, 90% confidence interval in parentheses

³ ANOVA

Table 6. Summary of the single dose RTV (TPV/RTV 500 mg/200 mg) pharmacokinetic parameters comparing subjects with moderate hepatic insufficiency to their matched controls

Parameter	Moderate Controls ¹	Moderate Hepatics ¹	Geometric Mean Ratio ²	p-value ³
AUC _{0-∞} (h·µg/mL)	15 ± 3 (15)	13 ± 14 (8)	0.52 (0.04, 6.08)	0.52
C _{max} (µg/mL)	3.5 ± 0.3 (3.5)	3.8 ± 4.8 (1.9)	0.54 (0.03, 8.34)	0.58
C _{p12h} (µg/mL)	0.28 ± 0.20 (0.24)	0.30 ± 0.33 (0.17)	0.72 (0.05, 11.42)	0.76

¹ Mean ± SD geometric mean in parentheses
² Geometric mean ratio of the differences, 90% confidence interval in parentheses
³ ANOVA

Figure 1. Plasma tipranavir and ritonavir C_{p12h} for subjects with mild or moderate hepatic insufficiency and their matched controls following a single dose of TPV/r

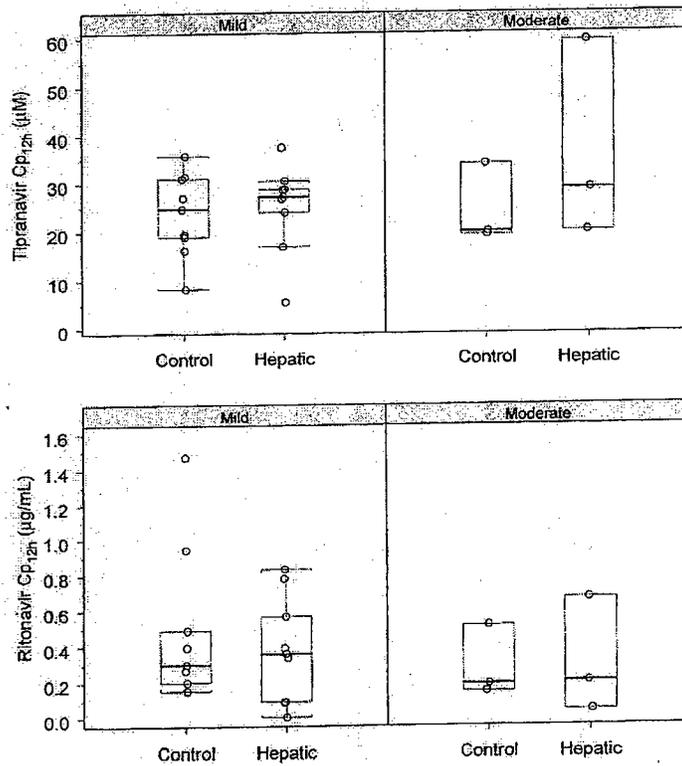


Figure 2. Plasma tipranavir and ritonavir C_{max} for subjects with mild or moderate hepatic insufficiency and their matched controls following a single dose of TPV/r

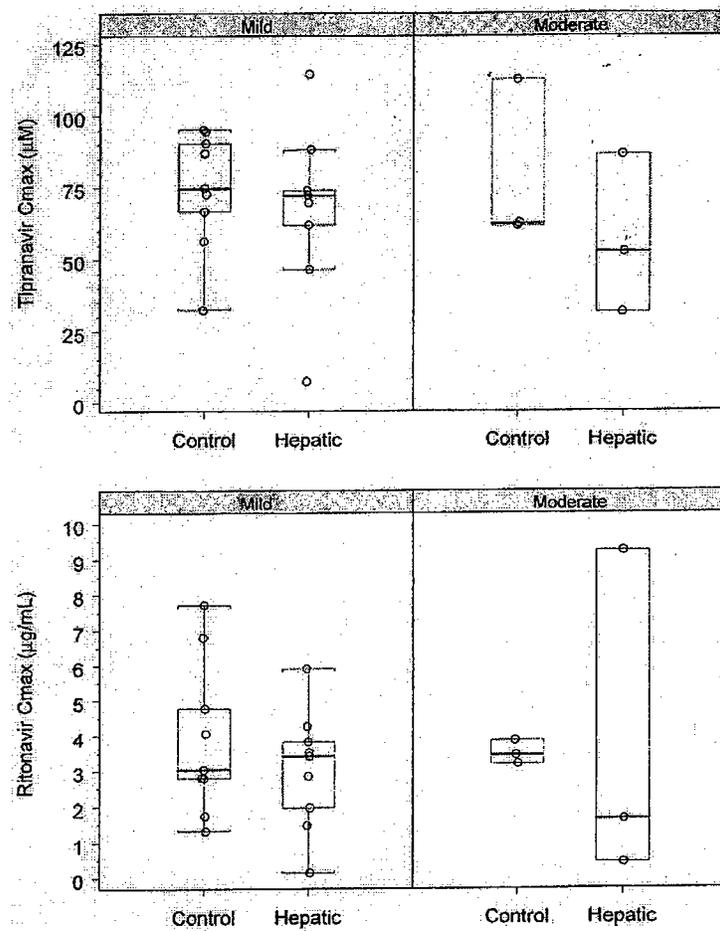


Figure 3. Plasma tipranavir and ritonavir AUC for subjects with mild or moderate hepatic insufficiency and their matched controls following a single dose of TPV/r

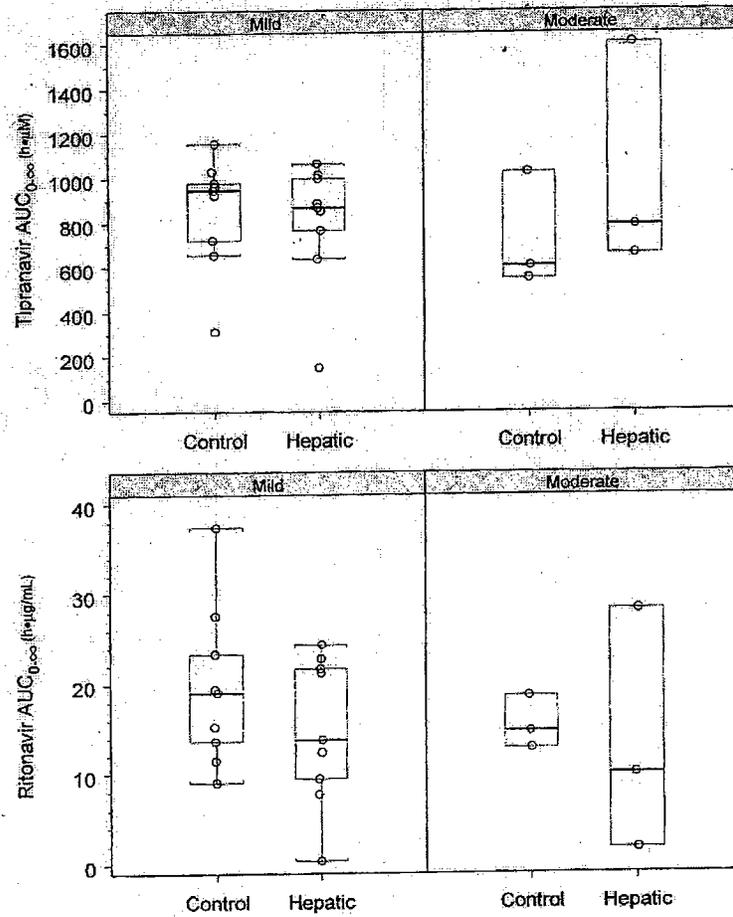


Figure 4. Steady-state plasma tipranavir and ritonavir C_{p12h} for subjects with mild hepatic insufficiency and their matched controls

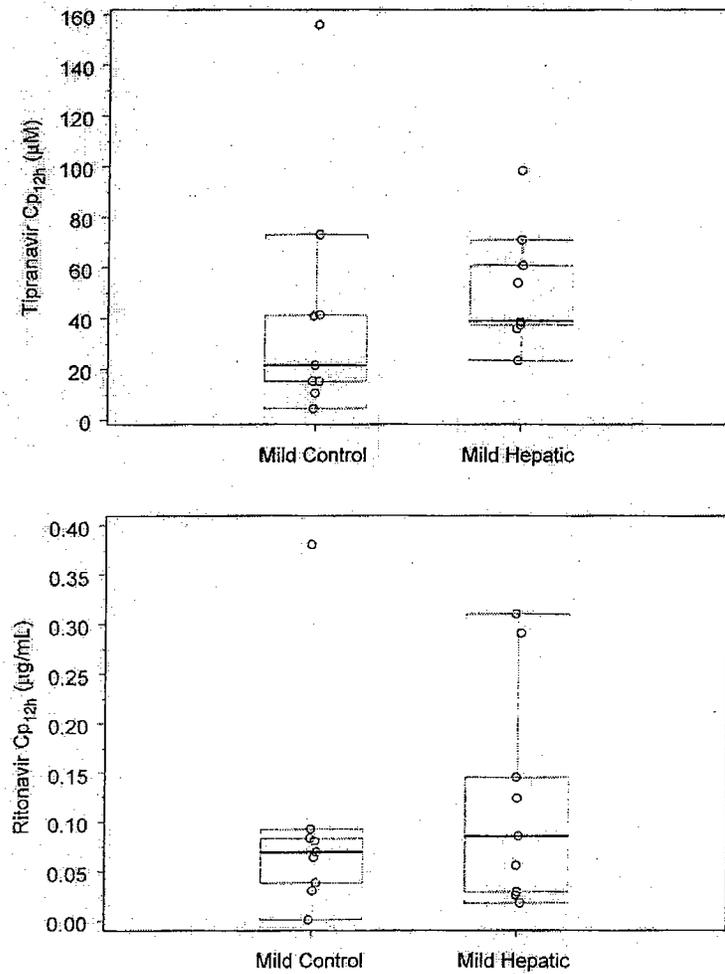


Figure 5. Steady-state plasma tipranavir and ritonavir C_{max} for subjects with mild hepatic insufficiency and their matched controls

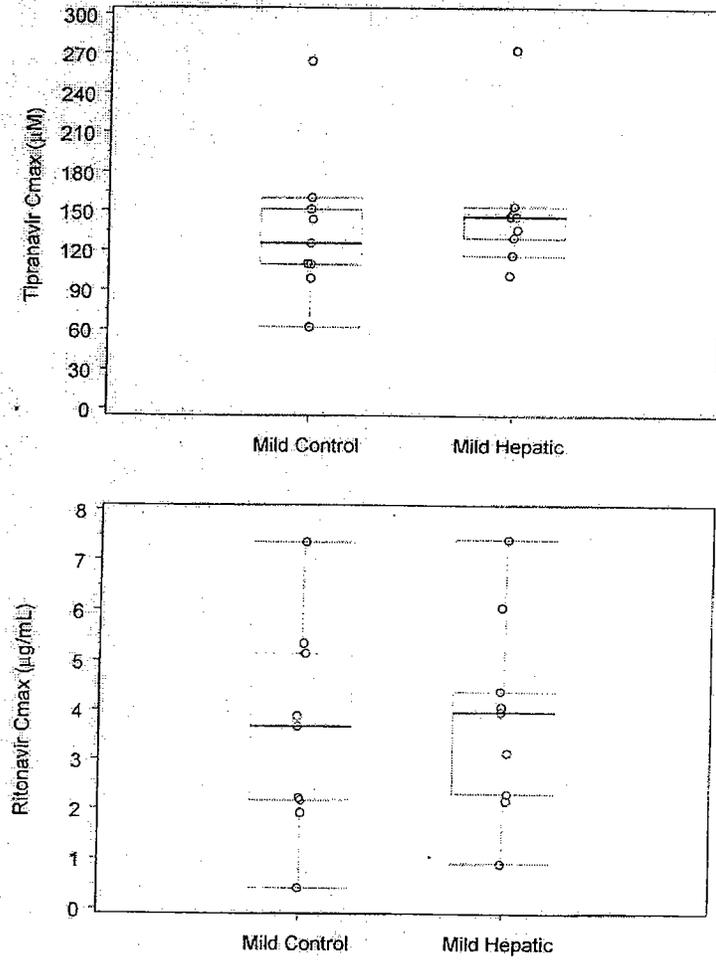
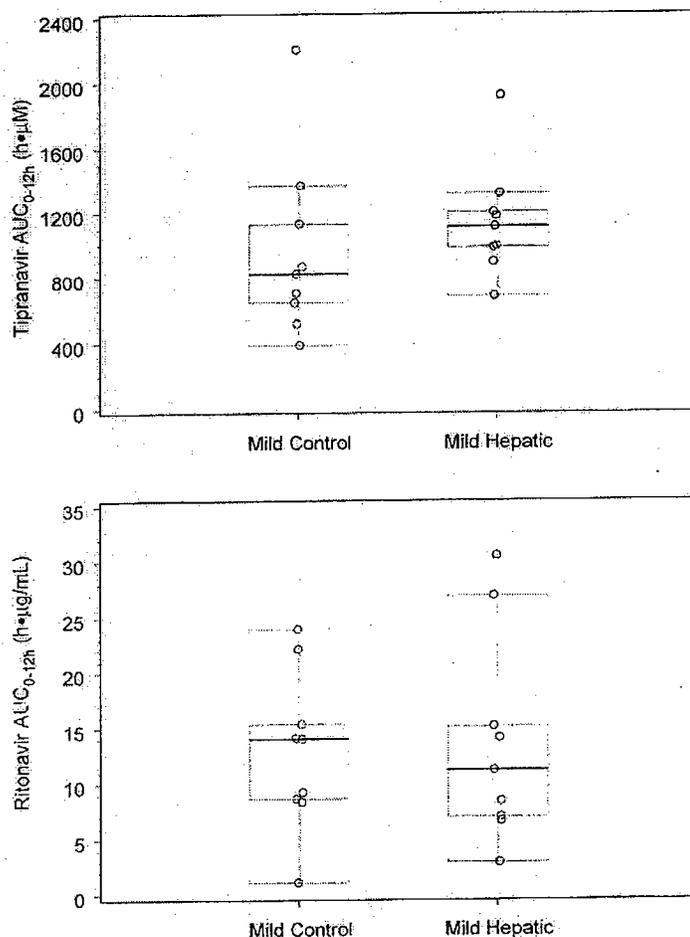


Figure 6. Steady-state plasma tipranavir and ritonavir AUC for subjects with mild hepatic insufficiency and their matched controls



SAFETY RESULTS: No new and unexpected safety issues were reported in the study. No subjects discontinued trial drug due to an AE and no subject experienced a serious AE in this trial (See details in Medical Officer's review).

CONCLUSIONS AND DISCUSSION: Following a single dose of TPV/RTV 500mg/200mg in 9 subjects with mild hepatic insufficiency, the mean systemic exposure of tipranavir was comparable to that of 9 matched controls. e.g., geometric mean ratios with 90% CIs for AUC, C_{max} and C_{min} were 0.89 (0.55, 1.45), 0.79 (0.44, 1.43) and 1.03 (0.62, 1.71), respectively. After 7 days of bid dosing, at the steady-state, the mean systemic exposure of tipranavir in subjects with mild hepatic impairment was higher than that of 9 matched controls and the ranges of 90% CI were quite large, e.g., geometric mean ratios with 90% CIs for AUC, C_{max} and C_{min} were 1.30 (0.88, 1.92), 1.14 (0.83, 1.56) and 1.84 (0.81, 4.20), respectively. Similar change of ritonavir exposure was also observed comparing mild hepatic insufficiency to healthy control. Dosage adjustment may not be warranted for this group of patients based on the moderate tipranavir and ritonavir systemic exposure and safety profiles observed in this study. There was insufficient data (lack of data at the steady-state) from moderate hepatic insufficiency group to reach any conclusion. Decisions regarding dosing in this

population will be made based on safety considerations as discussed in the Medical Officer's review. Since liver is considered as the major organ to eliminate tipranavir from systemic circulation, for anticipated safety concerns, tipranavir/ritonavir should be contraindicated for patients with severe hepatic insufficiency.

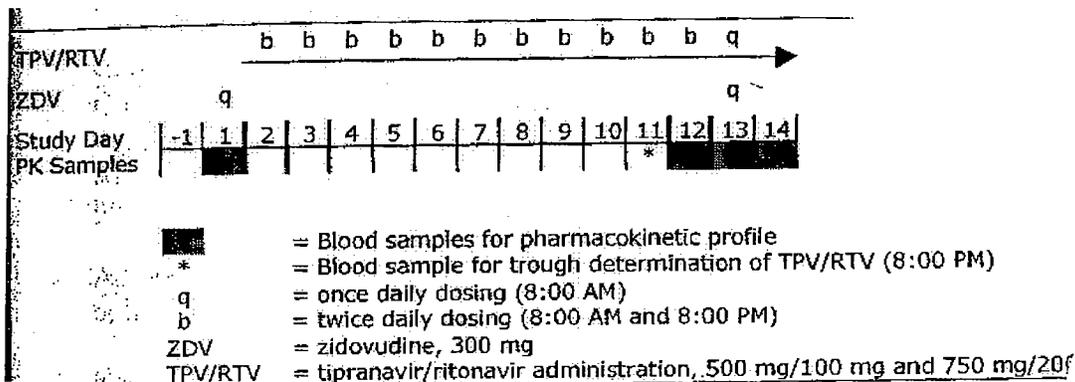
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TITLE: A single-center, open-label, randomized, parallel, multiple dose comparison of the effect of tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg twice a day for 11.5 days on the pharmacokinetic characteristics of zidovudine 300 mg in healthy volunteers

OBJECTIVES: To characterize the effect of two dose combinations of tipranavir/ritonavir (tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg twice a day) on the pharmacokinetics of zidovudine and zidovudine glucuronide as well as the effects of zidovudine on the pharmacokinetics of TPV/RTV in healthy volunteers

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, parallel, multiple dose study. A total of 60 healthy subjects were evenly randomized to either 500 mg/100 mg TPV/RTV or 750 mg /200 mg TPV/RTV dose group. 54 subjects completed the study. The scheme of the study design is shown below:



The overall demographic characteristics of 60 subjects were as following: Male (46.7%) and female (53.3%); White (86.7%) and Black (13.3%).

INVESTIGATOR AND STUDY LOCATION: []

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

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

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

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max} , C_{p12h} and AUC_{0-12h} were provided for TPV/RTV (with and without ZDV) and geometric means and coefficients of variation for C_{max} , C_{p6h} and AUC_{0-12h} were provided for ZDV and GZDV

(with and without TPV/RTV). The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

PHARMACOKINETIC RESULTS:

Table 1. Summary of the single-dose pharmacokinetic parameters of ZDV with and without TPV/RTV and their geometric means with 90% confidence intervals

PK PARAMETER	LAB UNIT	TREATMENT	DAY	N	Mini-mum	Med-ian	Maxi-mum	Geometric		
								Mean	Range Lower Limit	Range Upper Limit
AUC 0-12h	h*ug/mL	ZDV WITH TPV 500MG/RTV 10	13	29		1.49		1.53	1.13	2.06
		ZDV WITHOUT TPV 500MG/RTV 1	29		2.61		2.66	1.96	3.61	
	h*ug/mL	ZDV WITH TPV 750MG/RTV 20	13	25		1.71		1.75	1.42	2.17
		ZDV WITHOUT TPV 750MG/RTV 1	25		2.60		2.61	2.03	3.35	
C6h	ug/mL	ZDV WITH TPV 500MG/RTV 10	13	29		0.03		0.03	0.02	0.04
		ZDV WITHOUT TPV 500MG/RTV 1	29		0.03		0.03	0.02	0.05	
	ug/mL	ZDV WITH TPV 750MG/RTV 20	13	25		0.04		0.04	0.03	0.06
		ZDV WITHOUT TPV 750MG/RTV 1	25		0.03		0.03	0.02	0.05	
C _{MAX}	ug/mL	ZDV WITH TPV 500MG/RTV 10	13	29		0.78		0.76	0.49	1.20
		ZDV WITHOUT TPV 500MG/RTV 1	29		2.12		1.96	1.18	3.28	
	ug/mL	ZDV WITH TPV 750MG/RTV 20	13	25		0.74		0.81	0.59	1.10
		ZDV WITHOUT TPV 750MG/RTV 1	25		2.10		1.83	1.16	2.89	

Table 2. Summary of the pharmacokinetic parameters of GZDV with and without TPV/RTV and their geometric means with 90% confidence intervals

PK PARAMETER	LAB UNIT	TREATMENT	DAY	N	Mini-mum	Med-ian	Maxi-mum	Geometric		
								Mean	Range Lower Limit	Range Upper Limit
AUC 0-12h	h*ug/mL	qZDV WITH TPV 500MG/RTV 1	13	29		16.10		15.00	12.13	18.56
		qZDV WITHOUT TPV 500MG/RT 1	29		16.33		14.75	12.06	18.04	
	h*ug/mL	qZDV WITH TPV 750MG/RTV 2	13	25		15.85		15.77	12.76	19.60
		qZDV WITHOUT TPV 750MG/RT 1	25		13.85		14.46	11.64	17.97	
C6h	ug/mL	qZDV WITH TPV 500MG/RTV 1	13	29		0.24		0.25	0.15	0.41
		qZDV WITHOUT TPV 500MG/RT 1	29		0.16		0.17	0.11	0.25	
	ug/mL	qZDV WITH TPV 750MG/RTV 2	13	25		0.34		0.31	0.20	0.48
		qZDV WITHOUT TPV 750MG/RT 1	25		0.16		0.16	0.09	0.30	
C _{MAX}	ug/mL	qZDV WITH TPV 500MG/RTV 1	13	29		7.87		7.68	6.26	9.41
		qZDV WITHOUT TPV 500MG/RT 1	29		9.51		9.40	6.74	13.12	
	ug/mL	qZDV WITH TPV 750MG/RTV 2	13	25		7.76		7.60	5.98	9.65
		qZDV WITHOUT TPV 750MG/RT 1	25		8.93		9.31	7.05	12.29	

Table 3. Summary of the steady-state pharmacokinetic parameters of TPV with and without ZDV and their geometric means with 90% confidence intervals

PK PARAMETER	LAB UNIT	TREATMENT	DAY	N	Mini-mum	Med-ian	Maxi-mum	Geometric			
								Mean	Range Lower Limit	Range Upper Limit	
AUC 0-12h	umol	TPV 500MG WITH ZDV	13	29		814.77		850.76	567.53	1275.33	
		TPV 500MG WITHOUT ZDV	12	29		1009.41		1032.20	703.86	1513.70	
	umol	TPV 750MG WITH ZDV	13	26		1920.32		1974.87	1400.49	2784.82	
		TPV 750MG WITHOUT ZDV	12	25		1988.79		1940.76	1287.02	2928.58	
	C12h	umol	TPV 500MG WITH ZDV	13	29	/	24.66	/	23.76	12.36	45.66
			TPV 500MG WITHOUT ZDV	12	29		35.41		30.92	15.66	61.06
umol		TPV 750MG WITH ZDV	13	25		90.95		89.69	48.67	165.28	
		TPV 750MG WITHOUT ZDV	12	25		79.67		83.76	37.20	188.62	
C _{MAX}	umol	TPV 500MG WITH ZDV	13	29		130.26		130.81	92.22	185.64	
		TPV 500MG WITHOUT ZDV	12	29		153.60		150.66	110.37	205.65	
	umol	TPV 750MG WITH ZDV	13	25		258.98		261.39	205.15	333.05	
		TPV 750MG WITHOUT ZDV	12	25		278.12		255.04	190.77	343.63	

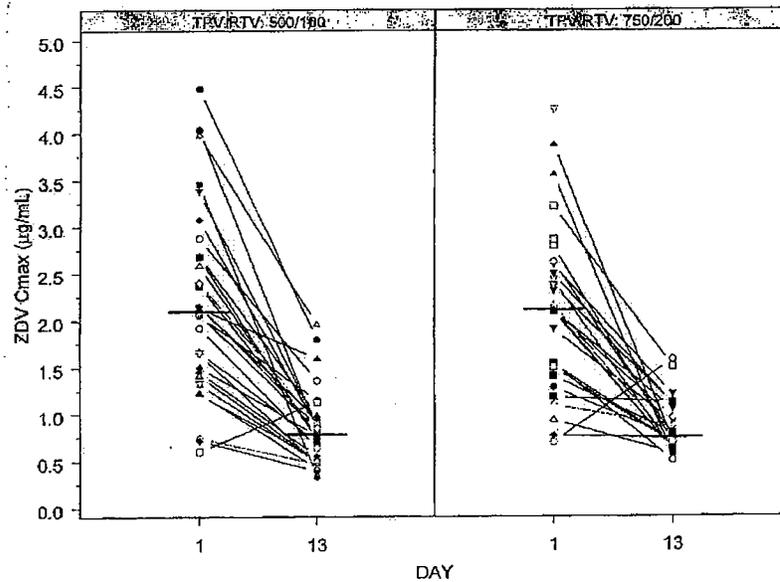
Table 4. Summary of the steady-state pharmacokinetic parameters of RTV with and without ZDV and their geometric means with 90% confidence intervals

PK PARAMETER	LAB UNIT	TREATMENT	DAY	N	Mini-mum	Med-ian	Maxi-mum	Geometric		
								Mean	Range Lower Limit	Range Upper Limit
AUC 0-12h	h*ug/mL	RTV 100MG WITH ZDV	13	29		3.39		3.32	2.03	5.44
		RTV 100MG WITHOUT ZDV	12	29		5.45		3.94	1.96	7.90
	h*ug/mL	RTV 200MG WITH ZDV	13	24		11.54		11.40	6.95	18.70
		RTV 200MG WITHOUT ZDV	12	24		14.38		13.52	8.15	22.40
C12h	ug/mL	RTV 100MG WITH ZDV	13	29	/	0.02	/	0.02	0.01	0.04
		RTV 100MG WITHOUT ZDV	12	29		0.03		0.02	0.01	0.05
	ug/mL	RTV 200MG WITH ZDV	13	24		0.10		0.12	0.05	0.29
		RTV 200MG WITHOUT ZDV	12	24		0.11		0.12	0.05	0.31
C _{MAX}	ug/mL	RTV 100MG WITH ZDV	13	29		0.96		1.01	0.63	1.64
		RTV 100MG WITHOUT ZDV	12	29		1.33		1.14	0.61	2.14
	ug/mL	RTV 200MG WITH ZDV	13	24		3.05		2.96	1.88	4.65
		RTV 200MG WITHOUT ZDV	12	24		3.15		3.08	1.83	5.18

Table 5. Summary of geometric mean ratios and 90% confidence intervals for pharmacokinetic parameters for the coadministration of TPV/RTV with ZDV

		TPV 500/RTV 100 mg			TPV 750 mg /RTV 200 mg		
		N	Ratio	90% CI	N	Ratio	90% CI
ZDV	C_{max}	29	0.39	0.33-0.45	25	0.44	0.36-0.54
	C_{p6h}	29	0.89	0.81-0.99	25	1.25	1.08-1.44
	AUC_{0-12h}	29	0.57	0.52-0.63	25	0.67	0.62-0.73
GZDV	C_{max}	29	0.82	0.74-0.90	25	0.82	0.73-0.92
	C_{p6h}	29	1.52	1.34-1.71	25	1.94	1.62-2.31
	AUC_{0-12h}	29	1.02	0.97-1.06	25	1.09	1.05-1.14
TPV	C_{max}	29	0.87	0.80-0.94	25	1.02	0.94-1.10
	C_{p12h}	29	0.77	0.68-0.87	25	1.07	0.86-1.34
	AUC_{0-12h}	29	0.82	0.76-0.89	25	1.02	0.92-1.13
RTV	C_{max}	29	0.89	0.77-1.03	25	1.17	0.82-1.68
	C_{p12h}	29	0.91	0.72-1.15	22	0.92	0.76-1.11
	AUC_{0-12h}	29	0.84	0.73-0.98	25	1.09	0.69-1.72

Figure 1. ZDV C_{max} , C_{p6h} and AUC_{0-12h} with and without TPV/RTV by subjects (Solid line represents median value)



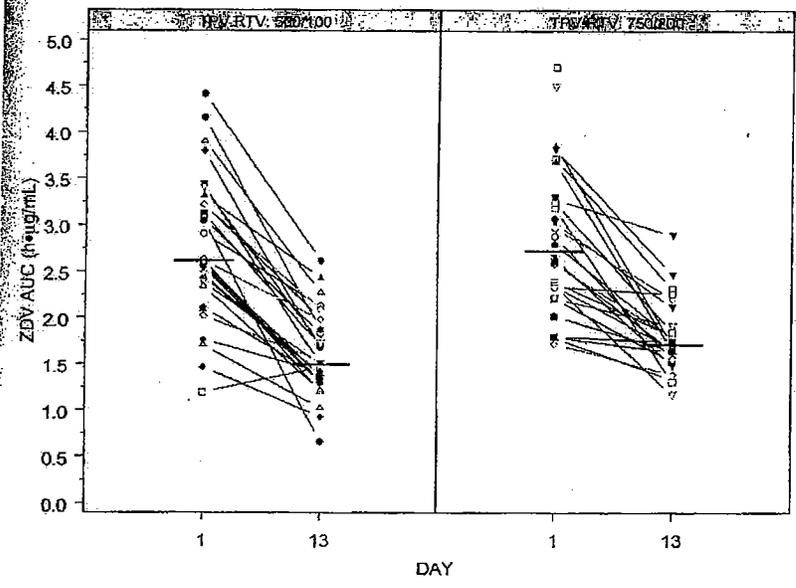
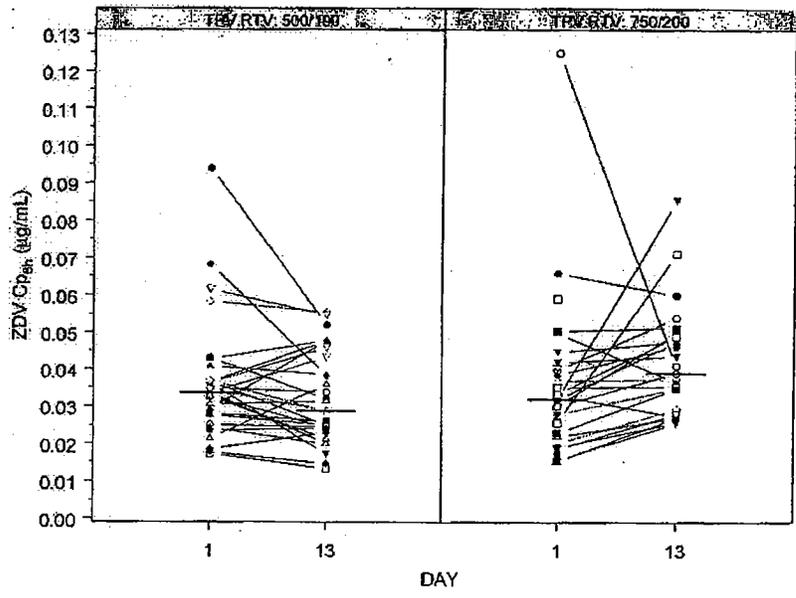
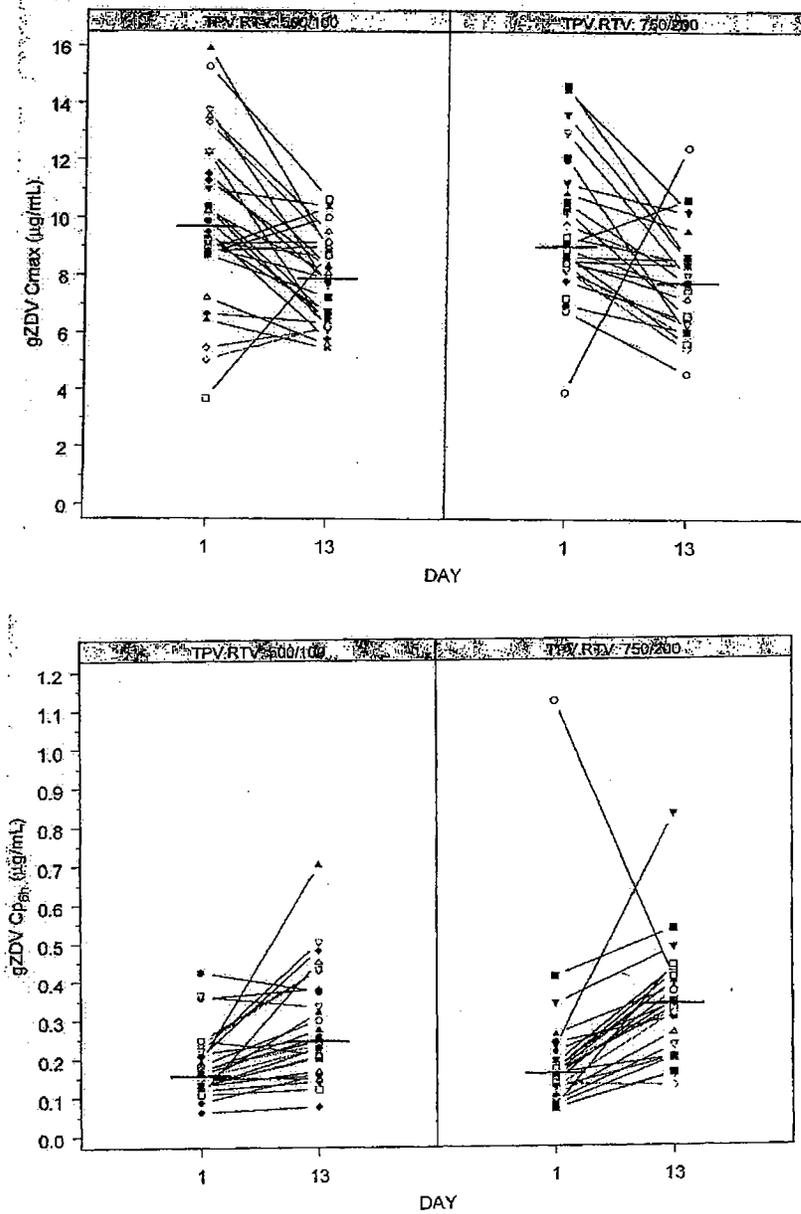


Figure 2. GZDV C_{max} , C_{p6h} and AUC_{0-12h} with and without TPV/RTV by subjects (Solid line represents median value)



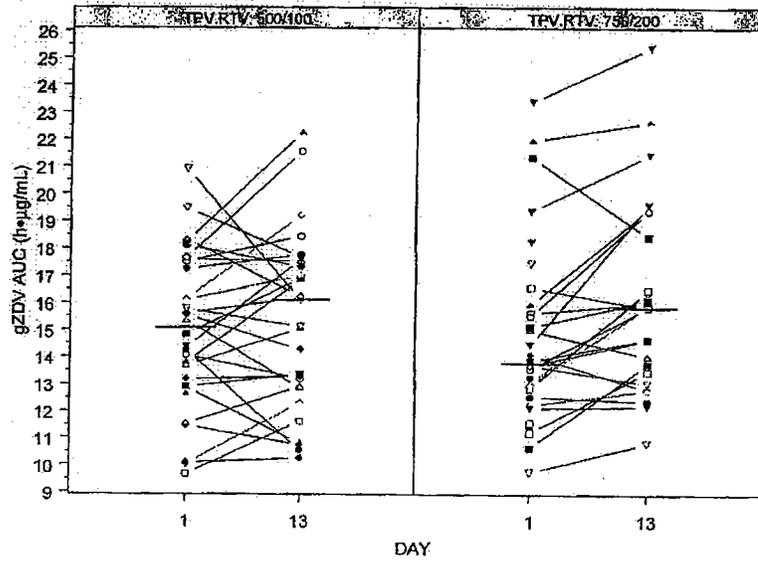
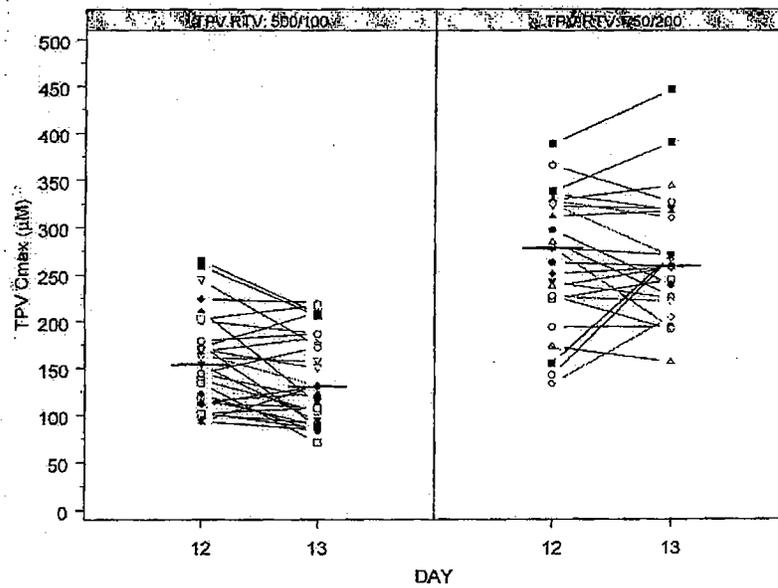


Figure 3. TPV C_{max} , C_{p12h} and AUC_{0-12h} with and without ZDV by subjects (Solid line represents median value)



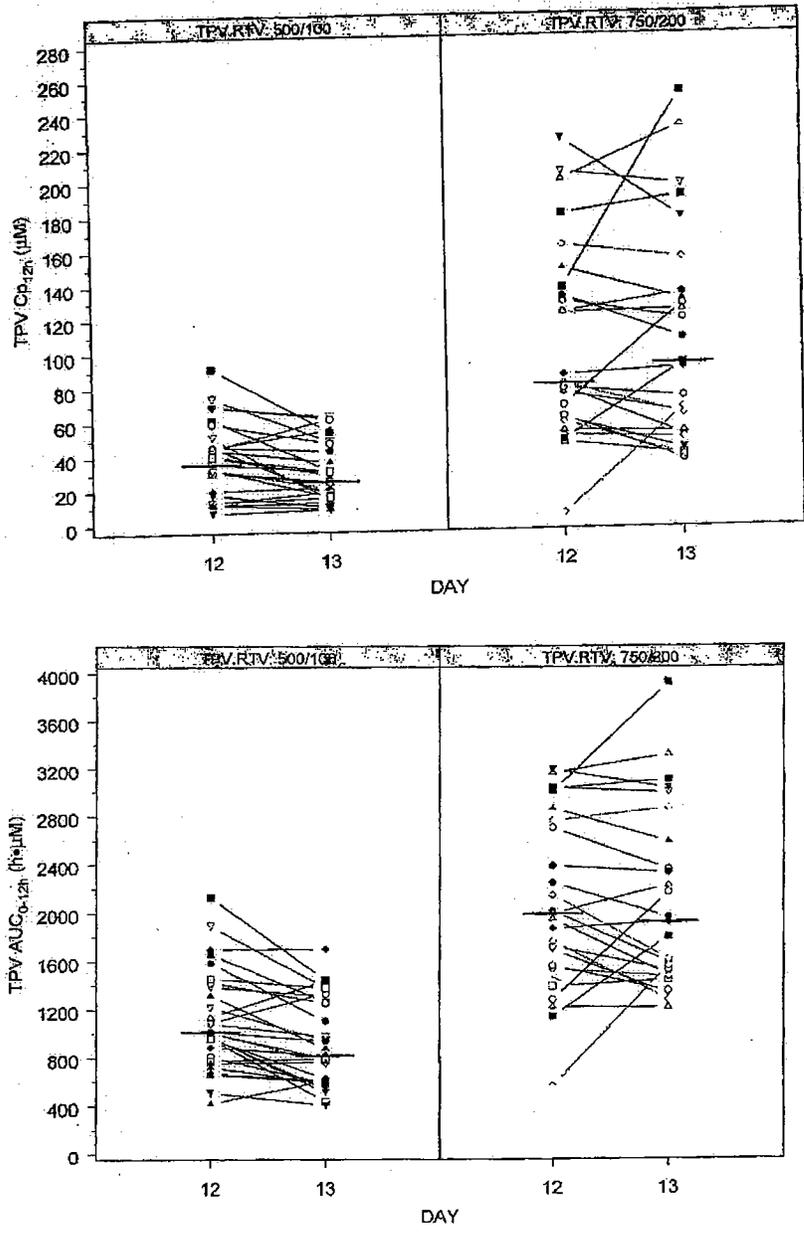
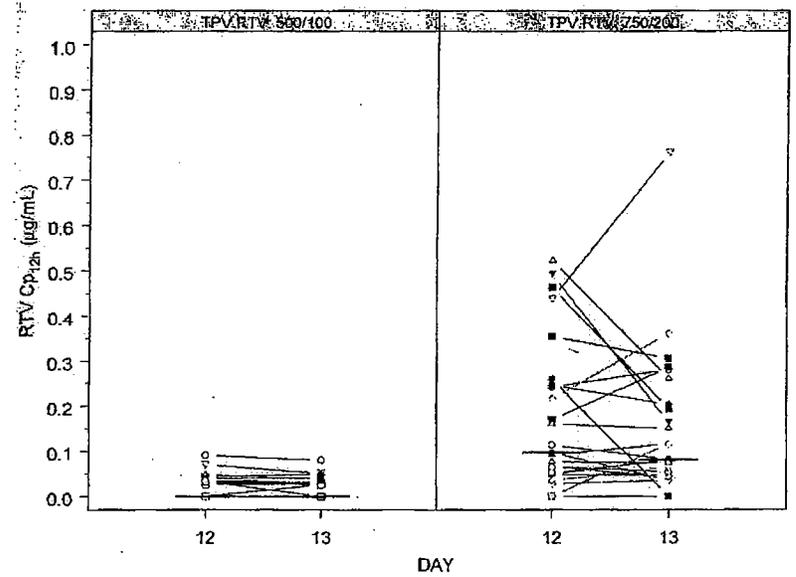
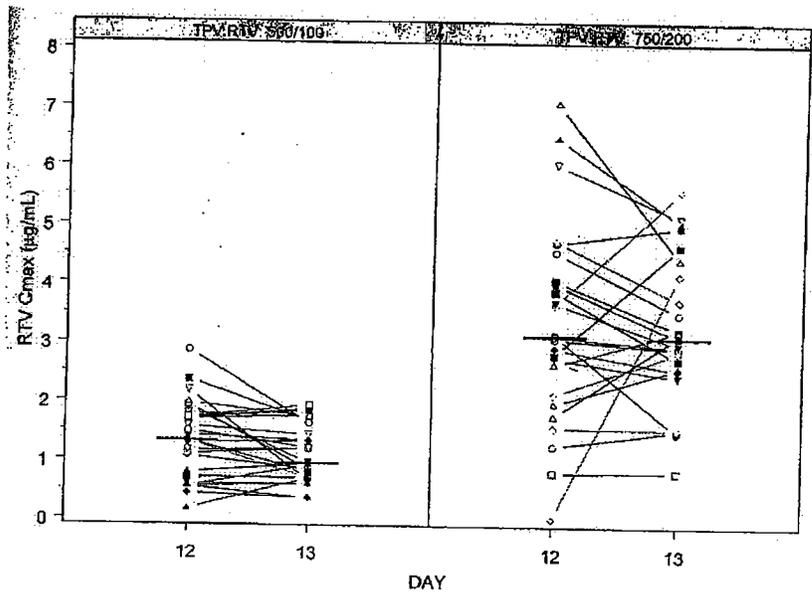
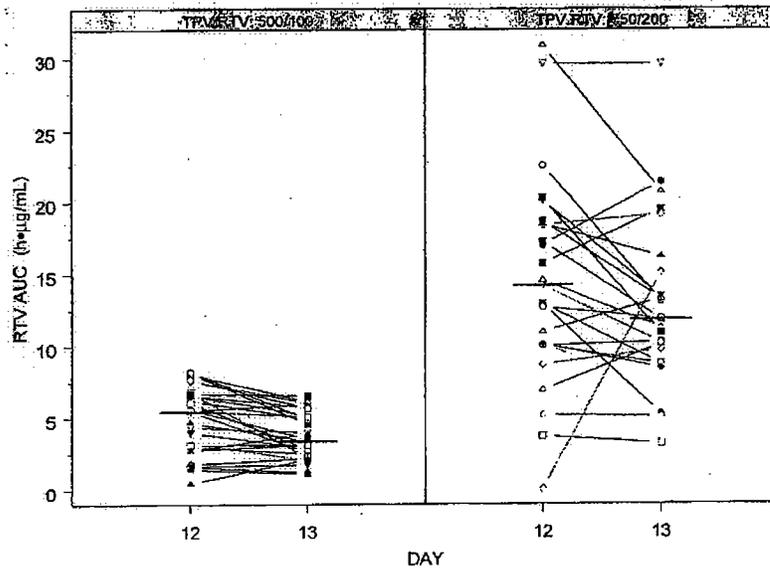


Figure 4. RTV C_{max} , C_{p12h} and AUC_{0-12h} with and without ZDV by subjects (Solid line represents median value)





SAFETY RESULTS: In general, consistent with other TPV trials, GI events were the most frequently observed AEs. There were no SAEs in the study (See details in Medical officer's review).

CONCLUSIONS AND DISCUSSION: The interaction of tipranavir with zidovudine was initially studied in Study 1182.6 where TPV was found to decrease ZDV AUC and C_{max} by 47% and 68%, respectively. This study confirmed that coadministration of TPV/RTV with ZDV markedly decreased ZDV exposure, i.e., AUC ↓43% at TPV 500 mg/RTV 100 mg dose and AUC ↓33% at TPV 750 mg/RTV 200 mg dose. However, zidovudine glucuronide exposure (C_{max} and AUC) was not affected by the coadministration of TPV/RTV. Tipranavir exposure (C_{max} , C_{p12h} and AUC_{0-12h}) decreased about 13-23% when coadministered with ZDV at TPV/RTV 500 mg/100 mg group, while tipranavir exposure decreased slightly 2-7% when coadministered with ZDV at TPV/RTV 750 mg/200 mg group. Ritonavir PK was not affected by coadministration of ZDV.

Zidovudine is renally eliminated with greater than 70% unchanged drug and the remainder is excreted as the glucuronide metabolite, GZDV. Ritonavir is reported to have interaction with zidovudine likely due to interaction with the glucuronyl transferase. Ritonavir is an UGT inducer and UGT is involved in the metabolism of zidovudine. Other possible mechanism is that TPV and/or RTV induce transporters involved in the renal excretion of ZDV and GZDV.

At the proposed clinical dose, 500 mg TPV/200 mg RTV, when co-administered with 300 mg ZDV, ZDV plasma exposure is expected to have about 30-40% decrease based on the data from this study. The clinical consequence of this interaction is not clear. The PK of either TPV or RTV is unlikely to have changes at the dose level of 500 mg/200 mg when coadministered with ZDV.

1182.41

TITLE: A single-center, open-label, randomized, parallel, multiple dose comparison of the effect of tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg, administered daily on three non-consecutive days and twice daily for 7 days, on the pharmacokinetic characteristics of efavirenz 600 mg a day in healthy adult volunteers

OBJECTIVES: To characterize the effect of two dose combinations of tipranavir/ritonavir (tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg) on the pharmacokinetics of efavirenz (EVZ) 600 mg

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, two-dose, parallel group study in healthy adult volunteers to investigate the pharmacokinetic interaction between tipranavir/ritonavir and efavirenz. A total of 68 subjects entered the study and were randomized into two TPV/RTV dose groups by 1:1 ratio. Subjects were scheduled to take both TPV and RTV for 10 days and EFV for 17 days.

Day 1: EFV 600 mg, single dose

Day 3: TPV 500 mg/RTV 100 mg or TPV 750 mg/RTV 200 mg single dose

Day 4: No drug

Day 5: TPV 500 mg/RTV 100 mg or TPV 750 mg/RTV 200 mg single dose plus EFV 600 mg single dose

Day 6: No drug

Days 7-13: EFV 600 mg QD

Day 14: TPV 500 mg/RTV 100 mg or TPV 750 mg/RTV 200 mg single dose plus EFV 600 mg QD

Days 15-21: 500 mg/RTV 100 mg or TPV 750 mg/RTV 200 mg BID plus EFV 600 mg QD

Day 22: No drug

The overall demographic characteristics of 20 subjects were as following: Male (66.2 %) and female (33.8%); White (63.2%), Black (30.9%) and Asian (5.9).

INVESTIGATOR AND STUDY LOCATION: [

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FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Sustiva: 200 mg capsules

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of EFV concentrations on Days 1, 5, 13, 14 and 21 and of TPV/RTV concentrations on Days 3, 5, 14 and 21 prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 post dose. Additional samples for trough concentration were taken for EFV on Days 12 and 20 and for TPV/RTV on Day 20.

ASSAY: Plasma samples were analyzed for TPV and ritonavir using a validated high performance liquid chromatography [method. The calibration curve ranged from ~ ng/mL to ~ ng/mL. EFV concentrations were determined by a validated high performance liquid chromatography [method. The calibration curve ranged from ~ µg/mL to ~ µg/mL.

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

PHARMACOKINETIC RESULTS:

Table 1. Geometric means of the single-dose and steady-state pharmacokinetic parameters of EFV, alone and in combination with single-dose and steady-state TPV/RTV

Day	n	EFV in TPV/RTV 500/100 mg group			n	EFV in TPV/RTV 750/200 mg group		
		C _{p24h} (μmol)	C _{max} (μmol)	AUC _{0-24h} (μmol*h)		C _{p24h} (μmol)	C _{max} (μmol)	AUC _{0-24h} (μmol*h)
1	33	2.10	5.82	132.51	32	2.31	6.26	164.46
5	33	2.40	8.63	155.92	32	2.49	8.64	161.34
13	28	4.63	10.37	154.84	28	4.38	10.44	148.05
14	28	4.82	12.27	172.36	28	4.66	12.73	170.88
21	24	4.44	10.73	151.94	22	3.93	10.92	143.07

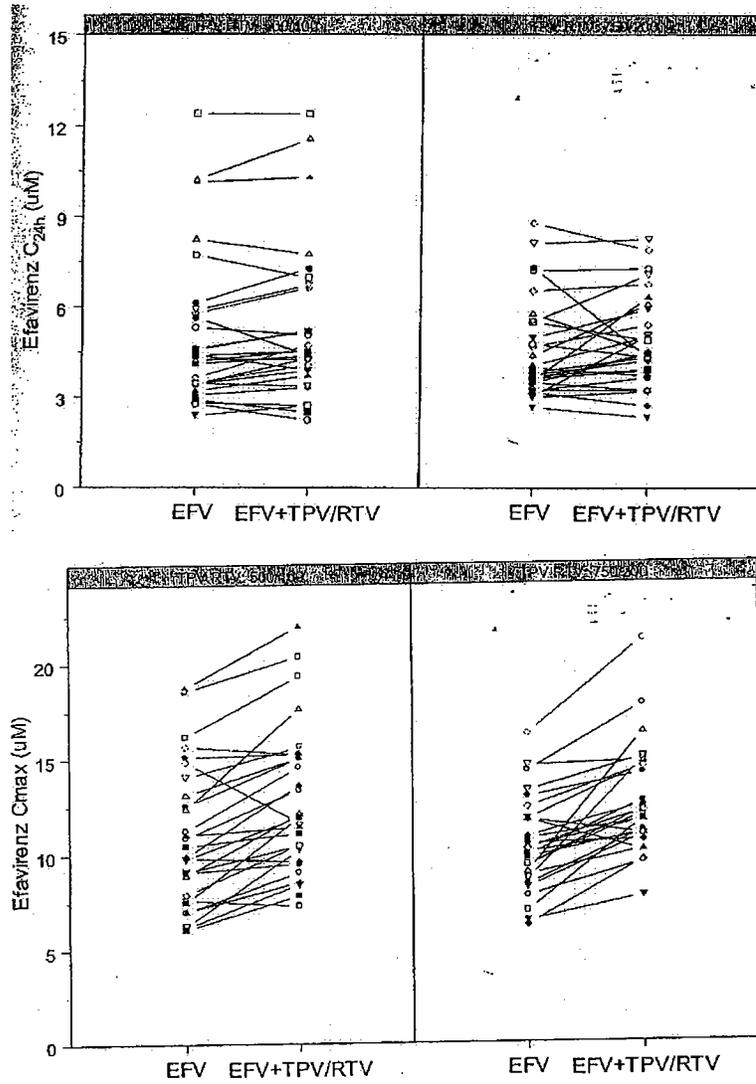
Table 2. Summary of geometric mean ratios and 90% confidence intervals for single-dose and steady-state pharmacokinetic parameters of EFV in combination with single-dose and steady-state TPV/RTV

Drug Name (Substrate)	PK Parameter	TPV 500 mg/RTV 100 mg				TPV 750 mg/RTV 200 mg				
		90% CI				90% CI				
		Number Subjects	Ratio	Lower	Upper	Number Subjects	Ratio	Lower	Upper	
Day 1 (EFV (sd) single dose) vs. Day 5 (EFV, TPV/RTV sd)										
Efavirenz	AUC	30	1.19	1.05	1.34	26	1.08	0.98	1.20	
	C _{max}	30	1.48	1.35	1.62	26	1.30	1.18	1.44	
	C _{24h}	30	1.14	1.03	1.27	26	1.08	0.96	1.21	
	AUC ¹	30	1.04	0.91	1.18	26	0.92	0.81	1.05	
	C _{max} ¹	30	1.37	1.24	1.50	26	1.19	1.08	1.32	
	C _{24h} ¹	30	1.01	0.90	1.12	26	0.95	0.84	1.07	
	Day 13 (EFV at (ss) steady state) vs. Day 14 (EFV at ss with sd TPV/RTV)									
	AUC	28	1.11	1.08	1.15	28	1.15	1.11	1.20	
	C _{max}	28	1.18	1.12	1.25	28	1.22	1.15	1.29	
C _{24h}	28	1.04	1.00	1.08	28	1.07	0.99	1.14		
Day 13 (EFV at ss) vs. Day 21 (EFV at ss and TPV/RTV at ss)										
AUC	24	1.04	0.97	1.12	22	1.00	0.93	1.09		
C _{max}	24	1.09	0.99	1.19	22	1.12	0.98	1.28		
C _{24h}	24	1.02	0.92	1.12	22	0.94	0.84	1.04		

¹Day 5 AUC, C_{max} and C_{24h} corrected for carryover efavirenz concentrations from Day 1

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Figure 1. Effect of single-dose TPV/RTV 500/100 mg or 750/200 mg (Day 14) on the steady-state EFV pharmacokinetic parameters (Day 13) (C_{p24h} , C_{max} and AUC_{0-24h})



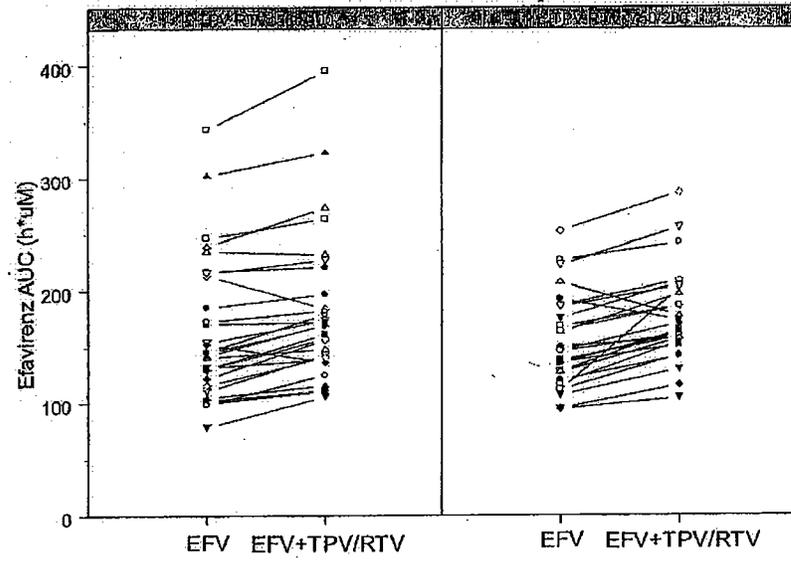


Figure 2. Median steady-state plasma concentration vs. time profile of EFV alone (Day 13) and in combination with steady-state TPV/RTV 500/100 mg or 750/200 mg BID (Day 21)

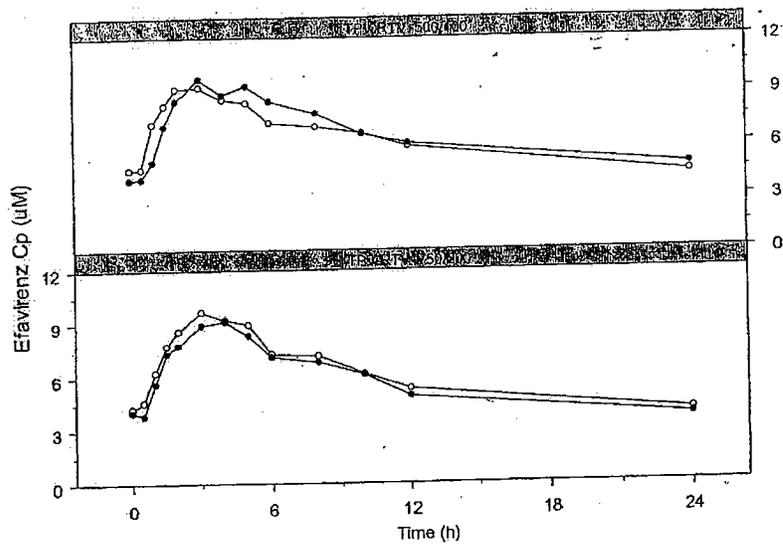


Table 3. Geometric means of the single-dose and steady-state pharmacokinetic parameters of TPV and RTV in combination with single-dose and steady-state EFV

Tipranavir							
TPV/RTV 500/100 mg				TPV/RTV 750/200 mg			
Day	C _{p12h} (µmol)	C _{max} (µmol)	AUC _{0-12h} (µmol*h)	C _{p12h} (µmol)	C _{max} (µmol)	AUC _{0-12h} (µmol*h)	
3	18.32	71.65	619.20	35.52	111.24	1069.84	
5	16.00	66.14	559.83	31.86	101.63	991.24	
14	4.55	42.30	265.40	22.47	79.27	736.24	
21	7.71	92.59	511.61	44.69	182.60	1351.76	

Ritonavir							
TPV/RTV 500/100 mg				TPV/RTV 750/200 mg			
Day	C _{p12h} (µg/mL)	C _{max} (µg/mL)	AUC _{0-12h} (µg/mL*h)	C _{p12h} (µg/mL)	C _{max} (µg/mL)	AUC _{0-12h} (µg/mL*h)	
3	0.04	0.45	2.63	0.13	1.05	6.49	
5	0.02	0.28	1.60	0.09	0.99	5.84	
14	0.00	0.12	0.78	0.05	0.45	2.67	
21	0.01	0.25	0.76	0.04	0.88	4.21	

Table 4. Summary of geometric mean ratios and 90% confidence intervals for single-dose and steady-state pharmacokinetic parameters of TPV/RTV in combination with single-dose and steady-state EFV

Drug Name (Substrate)	PK Parameter	TPV 500 mg/RTV 100 mg				TPV 750 mg/RTV 200 mg			
		Number		90% CI		Number		90% CI	
		Subjects	Ratio	Lower	Upper	Subjects	Ratio	Lower	Upper
Tipranavir	AUC	Day 3 (TPV/RTV (sd) single dose) vs. Day 5 (TPV/RTV and EFV sd dose)							
		24	0.92	0.81	1.04	26	0.93	0.79	1.10
		24	0.93	0.82	1.06	26	0.91	0.81	1.03
	C _{max}	Day 3 (TPV/RTV sd) vs. Day 14 (TPV/RTV sd and EFV at (ss) steady state)							
		21	0.43	0.35	0.52	25	0.66	0.56	0.79
		21	0.61	0.51	0.72	25	0.69	0.58	0.83
	C _{12h}	Day 3 (TPV/RTV sd) vs. Day 21 (TPV/RTV and EFV at ss)							
		21	0.23	0.16	0.33	25	0.64	0.52	0.79
		19	0.86	0.71	1.05	19	1.30	1.11	1.52
	AUC	Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)							
		19	1.35	1.14	1.60	19	1.62	1.42	1.84
		19	0.39	0.24	0.61	19	1.38	0.95	1.99
	C _{max}	Day 3 (TPV/RTV sd) vs. Day 5 (TPV/RTV and EFV sd dose)							
		18	1.94	1.57	2.40	19	1.78	1.54	2.07
		18	2.17	1.75	2.69	19	2.14	1.81	2.54
C _{12h}	Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)								
	18	1.71	1.10	2.67	19	1.92	1.47	2.51	
	19	0.86	0.71	1.05	19	1.30	1.11	1.52	
Ritonavir	AUC	Day 3 (TPV/RTV sd) vs. Day 5 (TPV/RTV and EFV sd dose)							
		22	0.59	0.44	0.78	21	0.88	0.63	1.22
		22	0.60	0.46	0.77	21	0.88	0.68	1.14
	C _{max}	Day 3 (TPV/RTV sd) vs. Day 14 (TPV/RTV sd and EFV at ss)							
		22	0.57	0.34	0.96	21	0.74	0.45	1.22
		12	0.24	0.14	0.42	25	0.43	0.31	0.60
	C _{12h}	Day 3 (TPV/RTV sd) vs. Day 21 (TPV/RTV and EFV at ss)							
		12	0.32	0.22	0.47	25	0.44	0.34	0.57
		12	0.07	0.01	0.36	25	0.44	0.27	0.72
	AUC	Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)							
		16	0.49	0.27	0.86	19	0.90	0.58	1.40
		16	0.67	0.39	1.13	19	1.02	0.71	1.47
	C _{max}	Day 3 (TPV/RTV sd) vs. Day 5 (TPV/RTV and EFV sd dose)							
		16	0.21	0.09	0.48	19	0.51	0.25	1.03
		7	1.53	0.63	3.71	20	1.84	1.41	2.39
C _{12h}	Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)								
	7	1.49	0.97	2.29	20	2.23	1.73	2.87	
	7	5.15	0.17	160.10	20	0.92	0.57	1.47	

Table 5. Median ratios (90% CIs) of steady-state pharmacokinetic parameters of TPV and RTV after administration of 500/100 or 750/200 mg BID alone (data from historic studies) and in combination with steady-state EFV 600 mg QD

Regimen	C _{max} (μM)	AUC (μM•h)	C _{min} (μM)
TPV/r 500/100 mg BID & Efavirenz 600 mg QD (n=24) ³	0.79 (0.69 – 0.89)	0.69 (0.57 – 0.83)	0.58 (0.36 – 0.86)
TPV/r 750/200 mg BID & Efavirenz 600 mg QD (n=21) ³	0.97 (0.85 – 1.09)	1.01 (0.85 – 1.18)	0.97 (0.69 – 1.28)

SAFETY RESULTS: In general, both doses of TPV/RTV were moderately well tolerated in this trial. No new or unexpected safety issues were reported in the study.

CONCLUSIONS AND DISCUSSION: Efavirenz is metabolized extensively by cytochrome P450 3A4 and 2B6. EFV is also an inducer and inhibitor of CYP3A enzyme and can decrease the concentrations of drugs that primarily depend upon CYP3A metabolism. Both tipranavir and ritonavir are substrates as well as inducers of CYP3A. Ritonavir is also a potent inhibitor of CYP3A. Ritonavir increases the half-life and trough levels of TPV when used together. Because TPV/RTV is recommended together, the pharmacokinetic interaction of this combination with other HIV drugs is important to understand. This study demonstrated that both single-dose and steady-state TPV/r (500/100 mg or 750/200 mg) did not substantially affect the steady-state AUC_{0-12h}, C_{max} and C_{p24h} of EFV. Steady-state EFV markedly decreased single-dose TPV AUC (500/100, -57%; 750/200, -34%), C_{max} (500/100, -39%; 750/200, -31%) and C_{p12h} (500/100, -77%; 750/200, -36%) and single-dose RTV AUC (500/100, -76%; 750/200, -57%), C_{max} (500/100, -68%; 750/200, -56%) and C_{p12h} (500/100, -93%; 750/200, -56%). Steady-state efavirenz decreased steady-state TPV AUC 31%, C_{max} 21% and C_{p12h} 42% at the 500 mg/100 mg regimen, respectively, based on the cross study comparison (Studies 1182.5, 1182.22, 1182.37 and 1182.46). However, steady-state efavirenz had little effect on steady-state TPV AUC, C_{max} and C_{p12h} at the tipranavir/ritonavir 750 mg/200 mg regimen by the cross study comparison (Studies 1182.5, 1182.22, 1182.37, 1182.46 and 1182.55).

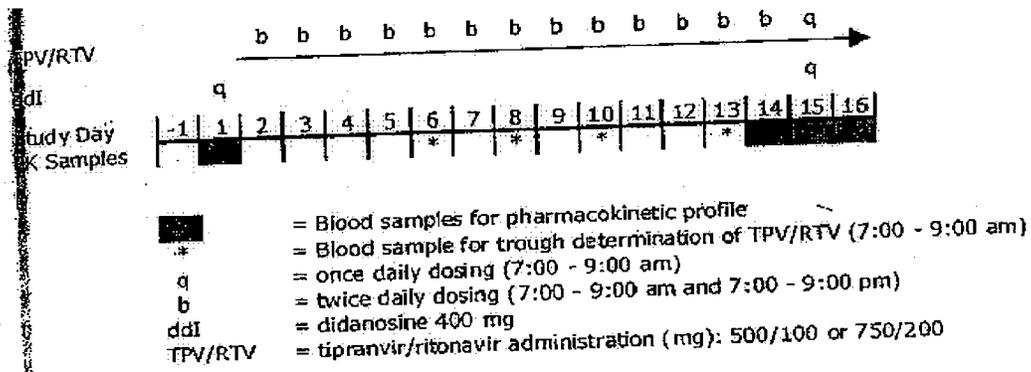
The change of pharmacokinetic parameters of TPV was less pronounced in the RTV 200 mg group, suggesting that inhibition of CYP3A by the 200 mg RTV partially counteracted the effects of CYP3A induction by EFV. It is anticipated the effect of EFV on TPV/RTV 500/200 mg would be less than or similar to that of EFV on TPV/RTV 750/200 mg. A dose adjustment of TPV/RTV will not be needed in the presence of efavirenz.

1182.42

TITLE: An open-label, randomized, parallel group study of the drug-drug pharmacokinetic interaction of steady state tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg, both bid for 13.5 days with single dose didanosine 400 mg (delayed release capsule EC beadlets) in healthy volunteers

OBJECTIVES: To characterize the effect of two dose combinations of tipranavir/ritonavir (tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg twice a day) on the single-dose pharmacokinetics of ddi as well as the effects of single-dose ddi on the pharmacokinetics of TPV/RTV in healthy volunteers

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, parallel group study. A total of 23 healthy subjects were enrolled and treated (11 in 500 mg/100 mg TPV/RTV and 12 in 750 mg /200 mg TPV/RTV dose group). The scheme of the study design is shown below:



All morning doses of medication were taken after an overnight fast. Breakfast was consumed one hour after morning dose. No meal was permitted one hour before or after evening dose.

Due to adverse events, 5 of the 11 subjects in 500 mg/100 mg TPV/RTV dose groups and 1 of the 12 in 750 mg /200 mg TPV/RTV dose group completed the treatment (Please refer to Medical Officer's review).

The overall demographic characteristics of 23 subjects were as following: Male (78.3%) and female (21.7%); White (100%).

INVESTIGATOR AND STUDY LOCATION: []

]

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Videx EC: 400 mg delayed release capsule EC beadlets

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of ddi concentrations on Days 1 and 15 prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 post dose, and for assay of TPV concentrations on Days 14 and 15 prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose.

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

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max} , C_{p12h} and AUC_{0-12h} were provided for TPV/RTV (with and without ddl) and geometric means and coefficients of variation for C_{max} , C_{p6h} and AUC_{0-12h} were provided for ddl (with and without TPV/RTV). The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

PHARMACOKINETIC RESULTS:

Table 1. Summary of the single-dose pharmacokinetic parameters of ddl with and without TPV/RTV

TPV/RTV (mg/bid)	N	Day 1 Mean (SD)			N	Day 15 Mean (SD)		
		C_{max} (µg/mL)	C_{p6h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)		C_{max} (µg/mL)	C_{p6h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)
500/100	11	1.308 (0.728)	0.090 (0.074)	2.770 (1.237)	5	1.130 (0.608)	0.139 (0.023)	2.401 (0.955)
750/200	12	1.470 (0.671)	0.129 (0.103)	3.224 (1.372)	1	1.145	0.170	3.183

Table 2. Summary of the steady-state pharmacokinetic parameters of TPV with and without ddl

TPV/RTV (mg/bid)	N	Day 14 Mean (SD)			N	Day 15 Mean (SD)		
		C_{max} (µmol/mL)	C_{p12h} (µmol/mL)	AUC_{0-12h} (hr-µmol/mL)		C_{max} (µmol/mL)	C_{p12h} (µmol/mL)	AUC_{0-12h} (hr-µmol/mL)
500/100	5	98.61 (26.39)	12.73 (6.37)	559.56 (117.29)	5	129.61 (29.99)	9.57 (5.81)	597.94 (77.89)
750/200	1	227.65	35.90	1520.57	1	202.50	31.15	1365.00

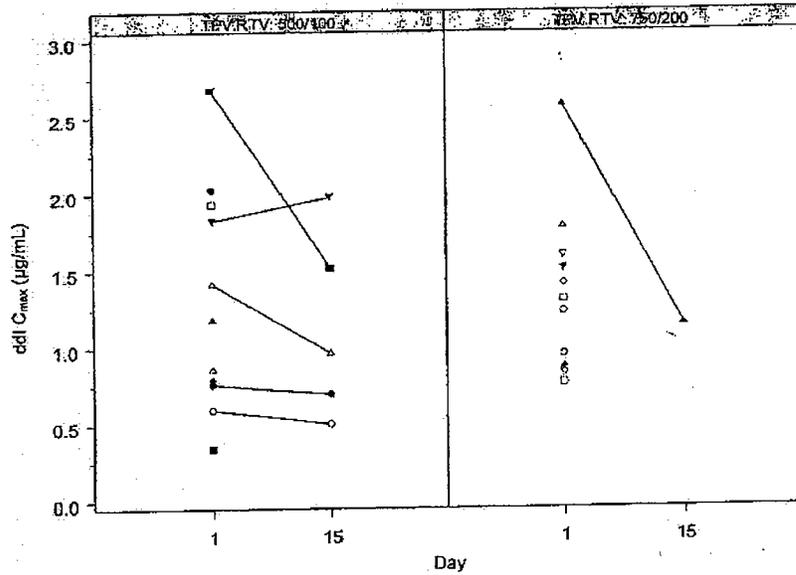
Table3 . Summary of the steady-state pharmacokinetic parameters of RTV with and without ddl

TPV/RTV (mg/bid)	N	Day 14 Mean (SD)			N	Day 15 Mean (SD)		
		C_{max} (µg/mL)	C_{p12h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)		C_{max} (µg/mL)	C_{p12h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)
500/100	5	0.47 (0.23)	0.00 (0.00)	1.71 (1.12)	5	0.52 (0.35)	0.00 (0.00)	1.78 (1.13)
750/200	1	0.62	0.00	2.24	1	0.90	0.00	3.70

Table 4. Summary of geometric mean ratios and 90% confidence intervals for pharmacokinetic parameters for the coadministration of TPV/RTV with ddl

		TPV 500/RTV 100 mg			TPV 750 mg /RTV 200 mg		
		N	Ratio	90% CI	N	Ratio	90% CI
ddl	C_{max}	5	0.90	0.72-1.11	-	-	-
	C_{p6h}	5	0.80	0.63-1.02	-	-	-
	AUC_{0-12h}	5	1.17	0.62-2.20	-	-	-
TPV	C_{max}	5	1.32	1.09-1.60	-	-	-
	C_{p12h}	5	0.66	0.31-1.43	-	-	-
	AUC_{0-12h}	5	1.08	0.82-1.42	-	-	-
RTV	C_{max}	5	0.86	0.26-2.81	-	-	-
	C_{p12h}	5	-	-	-	-	-
	AUC_{0-12h}	5	0.78	0.20-3.05	-	-	-

Figure 1. ddl C_{max} , C_{p6h} and AUC_{0-12h} with (Day 15) and without TPV/RTV (Day 1) by subjects



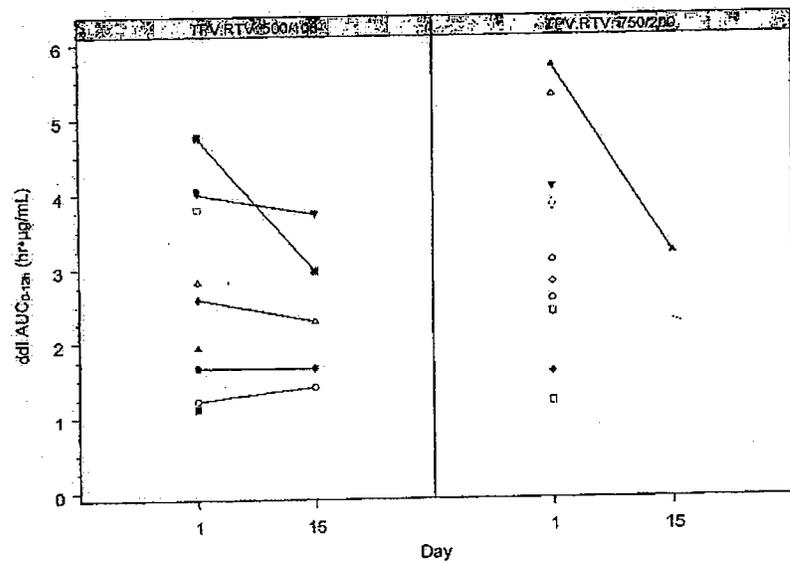
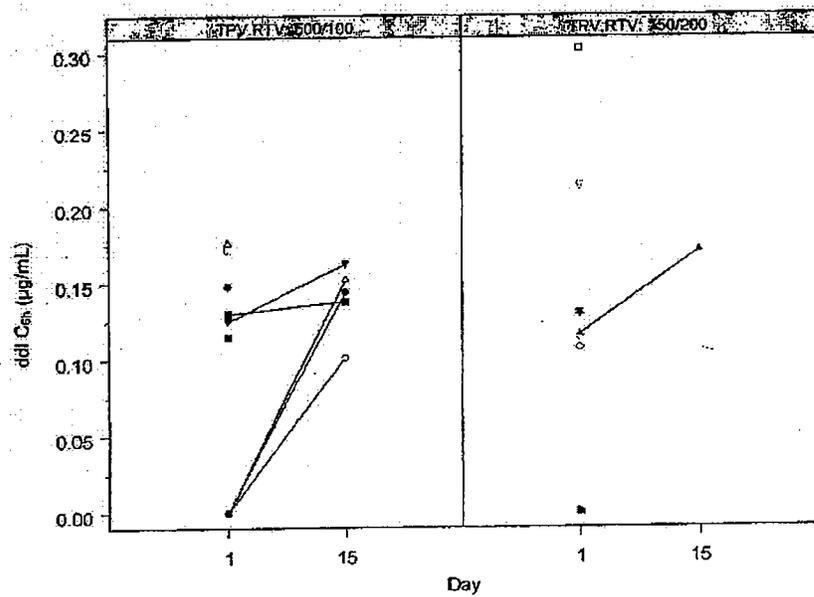
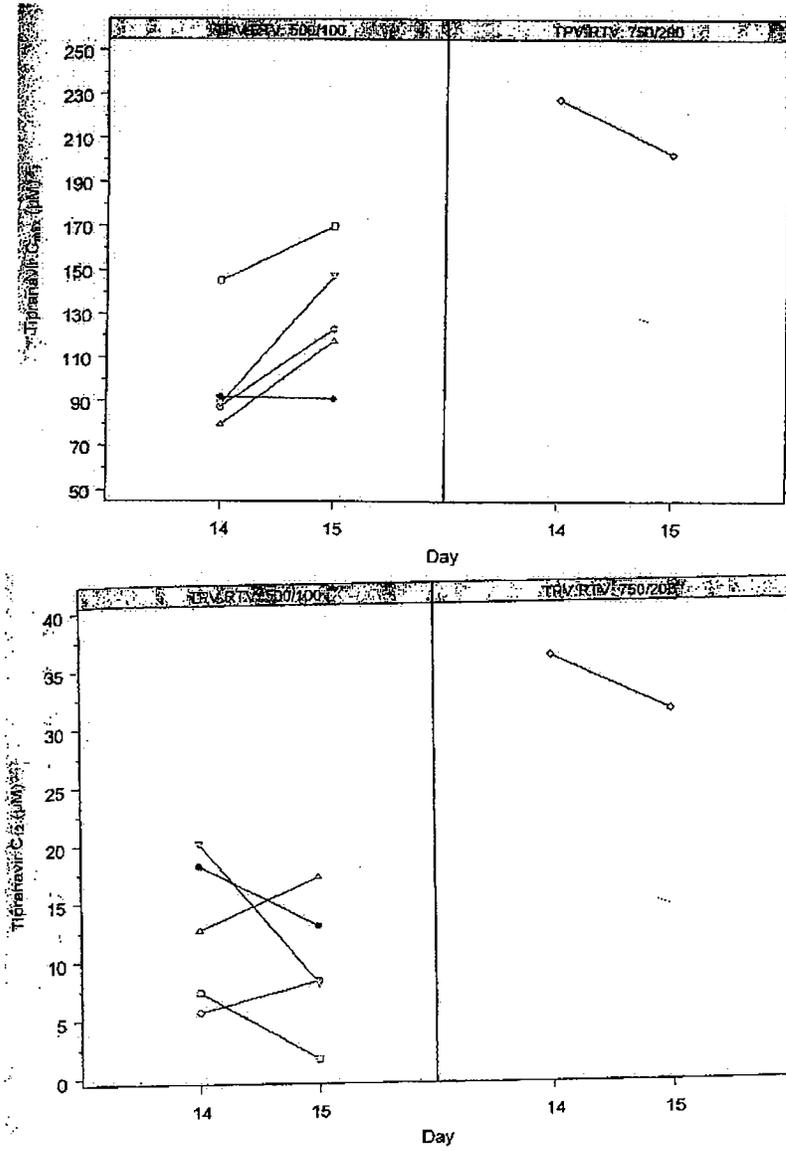
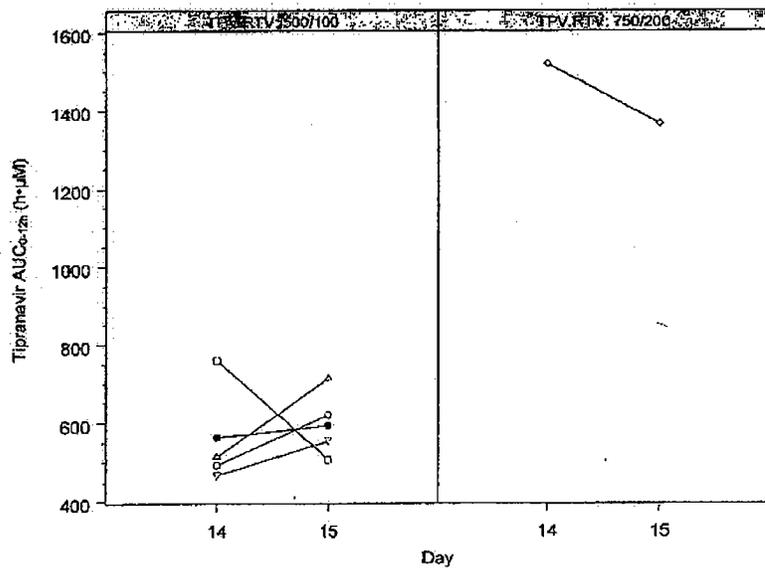


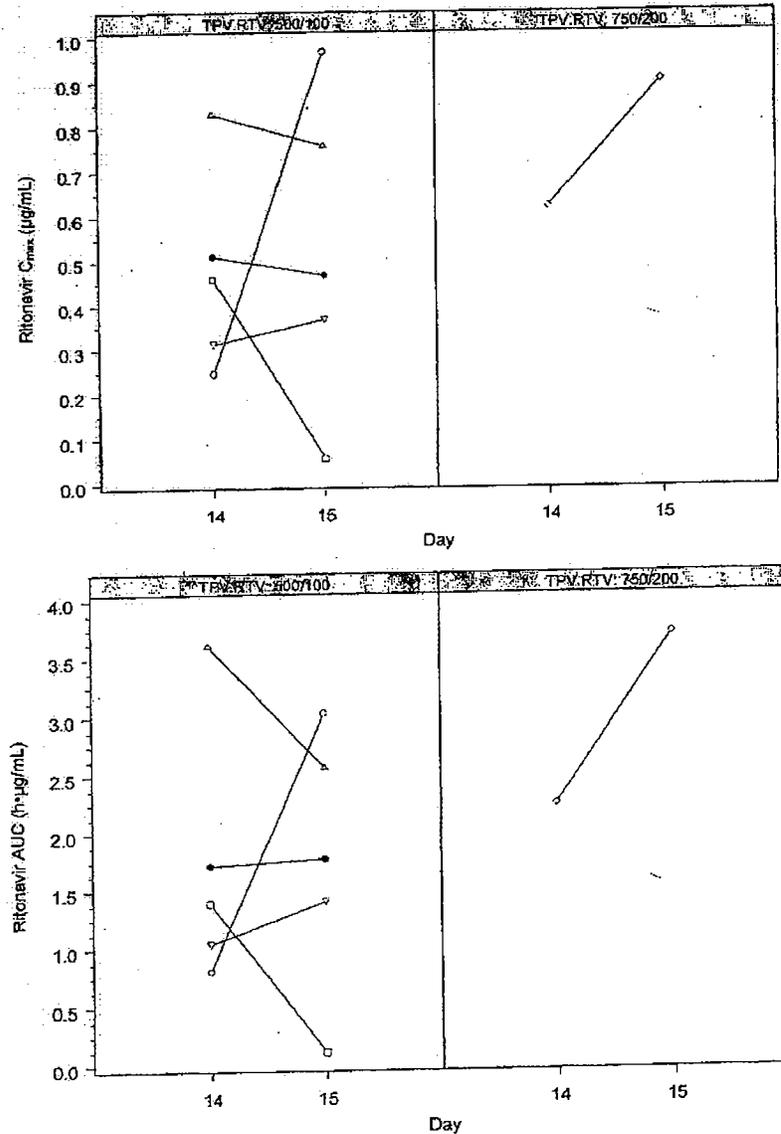
Figure 2. TPV C_{max} , C_{p12h} and AUC_{0-12h} with and without ddl by subjects





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Figure 3. RTV C_{max} and AUC_{0-12h} with and without ddl by subjects



SAFETY RESULTS: Please refer to Medical Officer's review.

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

changed when coadministered with ddl but with wide 90% CIs. The changes of RTV C_{p12h} could not be evaluated as concentrations were below limit of quantitation for all subjects on Study Days 14 and 15. Thus this study failed to provide a definitive characterization of the interaction between ddl and TPV/RTV due to inadequate number of subjects completed the study for data analysis. Further study may be needed to fully characterize the extent of the interaction between ddl and TPV/RTV at the proposed dose level, 500 mg/200 mg.

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1182.44

TITLE: A single-center, open-label study in healthy volunteers to determine the effects of steady-state TPV/r (500 mg/200 mg) on the single-dose pharmacokinetics of rifabutin 150 mg, and the effects of single-dose rifabutin (150 mg) on the steady-state pharmacokinetics of TPV 500 mg (co-administered with RTV 200 mg)

OBJECTIVES: To determine the effects of steady-state TPV/r (500 mg/200 mg) on the single-dose pharmacokinetics of rifabutin (RFB) 150 mg, and the effects of single-dose rifabutin (150 mg) on the steady-state pharmacokinetics of TPV 500 mg (co-administered with RTV 200 mg)

SUBJECTS AND STUDY DESIGN: This was an open-label study conducted in healthy adult subjects. 110 subjects were screened for the study and 24 subjects entered the study. Briefly, subjects received:

Days 1: RFB (150 mg) at 8 AM
Day 8-20 TPV/r (500 mg/200 mg) BID
Day 15: RFB (150 mg) at 8 AM

Medicines were allowed to be taken with food, except on pharmacokinetic sampling days.

The overall demographic characteristics of 23 subjects were as following: Male (83.3%) and female (16.7%); White (91.7%), Black (8.3%), and Hispanic (8.3%).

INVESTIGATOR AND STUDY LOCATION: [

]

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Mycobutin: 150 mg capsules

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of RFB and its metabolite, 25-O-desacetyl-RFB concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120 and 144 post dose on Days 1-7 and 15-21. Blood samples were collected for assay of TPV concentrations prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 post dose on Days 14 and 15.

ASSAY: Plasma samples were analyzed for TPV by [using a validated high performance liquid chromatography [method. The calibration curve ranged from [ng/mL to [ng/mL. RFB and 25-O-desacetyl-RFB concentrations were performed by [using HPLC, [method.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max} , C_{p12} and $AUC_{0-\infty}$ (or AUC_{0-12h}) were provided for RFB and its metabolite, 25-O-desacetyl-RFB with and without TPV/RTV, and for tipranavir co-administered with RTV with RFB. The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

PHARMACOKINETIC RESULTS:

Table 1. Summary of RFB pharmacokinetics on study Day 1 (alone) and study Day 15 (RFB + TPV/r)

PK Parameter	Day	Mean	SD	Min	Median	Max	Geo. Mean	Harm. Mean
C _{max} (ng/mL)	1	180.32	91.60		156.50		162.03	
	15	283.80	73.45		283.00		275.53	
C _{p12h} (ng/mL)	1	50.75	23.32		48.95		46.71	
	15	103.26	27.72		99.25		100.06	
AUC _{0-∞} (h•ng/mL)	1	2443	1241		2157		2217	
	15	6630	1683		6206		6441	
T _{max} (h)	1	3.6	1.0		3.0		3.5	
	15	4.3	1.0		4.0		4.1	
λ _z (h ⁻¹)	1	0.02034	0.01525		0.01340		0.01679	
	15	0.01098	0.00287		0.00975		0.01064	
t _{1/2} (h)	1	47.1	20.6		51.8		41.3	34.1
	15	67.0	15.9		71.2		65.1	63.2
T _{last} (h)	1	115.2	28.7		120.0		110.9	
	15	144.0	0.0		144.0		144.0	
C _{p last} (ng/mL)	1	2.93	1.19		2.55		2.78	
	15	11.05	3.40		10.70		10.50	
C _{I/F} (L/h)	1	73.7	31.6		69.6		67.7	
	15	24.0	5.7		24.2		23.3	
V (L)	1	4442	1882		4368		4028	
	15	2276	591		2318		2188	

Note: n = 20 subjects; Geo. Mean = geometric mean; Harm. Mean = harmonic mean

Table 2. Summary of 25-O-desacetyl-RFB pharmacokinetics on study Day 1 (alone) and study Day 15 (RFB + TPV/r)

PK Parameter	Day	Mean	SD	Min	Median	Max	Geo. Mean	Harm. Mean
C_{max} (ng/mL)	1	20.68	9.29		20.40		18.72	
	15	62.17	18.88		56.10		59.83	
C_{p12h} (ng/mL)	1	6.09	3.35		4.91		5.40	
	15	43.70	11.80		43.80		42.24	
$AUC_{0-\infty}$ (h•ng/mL)	1	210	122		175		182	
	15	3878	957		3716		3775	
T_{max} (h)	1	3.7	1.0		3.0		3.6	
	15	5.9	1.2		6.0		5.8	
λ_z (h ⁻¹)	1	0.11489	0.04292		0.11301		0.10719	
	15	0.01112	0.00302		0.01007		0.01080	
$t_{1/2}$ (h)	1	6.9	2.8		6.1		6.5	6.0
	15	65.9	14.2		68.9		64.2	62.3
T_{last} (h)	1	19.8	8.9		24.0		18.2	
	15	144.0	0.0		144.0		144.0	
C_{plast} (ng/mL)	1	3.40	0.95		3.28		3.27	
	15	8.71	2.62		8.45		8.32	

Note: n = 20 subjects; Geo. Mean = geometric mean; Harm. Mean = harmonic mean

Table 3. Summary of geometric mean ratios and 90% confidence intervals for RFB and 25-O-desacetyl-RFB AUC , C_{max} and C_{p12h} when single-dose RFB was co-administered with steady-state TPV/r

PK Parameter	n	% Change	Ratio	90% CI
RFB(parent)				
$AUC_{0-\infty}$ (h•ng/mL)	20	190	2.90	(2.59, 3.26)
C_{max} (ng/mL)	20	70	1.70	(1.49, 1.94)
C_{p12h} (ng/mL)	20	114	2.14	(1.90, 2.41)
25-O-desacetyl-RFB (metabolite)				
$AUC_{0-\infty}$ (h•ng/mL)	20	1971	20.71	(17.66, 24.28)
C_{max} (ng/mL)	20	220	3.20	(2.78, 3.68)
C_{p12h} (ng/mL)	20	683	7.83	(6.70, 9.14)
RFB + 25-O-desacetyl-RFB (parent + metabolite)				
$AUC_{0-\infty}$ (h• μ M)	20	333	4.33	(3.86, 4.86)
C_{max} (μ M)	20	86	1.86	(1.63, 2.12)
C_{p12h} (μ M)	20	176	2.76	(2.44, 3.12)

Note: Subjects 2002, 2009, 2015 and 2020 omitted

Table 4. Summary of TPV pharmacokinetics on study Day 14 (alone) and study Day 15 (RFB + TPV/r)

PK Parameter	Day	Mean	SD	Min	Median	Max	Geo. Mean	Harm. Mean
C _{p12h} (µM)	14	40.03	19.04		38.81		35.15	
	15	45.06	19.72		41.41		40.95	
C _{max} (µM)	14	145.25	37.81		141.13		140.64	
	15	145.31	43.96		143.68		139.69	
AUC _{0-12h} (µM)	14	1001	302		980		955	
	15	991	286		996		953	
T _{max} (h)	14	2.9	0.6		3.0		2.8	
	15	2.7	0.8		3.0		2.6	
λ _z (h ⁻¹)	14	0.1567	0.0528		0.1525		0.1486	
	15	0.1322	0.0457		0.1198		0.1253	
t _{1/2} (h)	14	4.9	1.6		4.5		4.7	4.4
	15	5.8	1.9		5.8		5.5	5.2
Cl/F (L/h)	14	0.91	0.31		0.85		0.87	
	15	0.91	0.27		0.83		0.87	
V (L)	14	6.01	1.46		6.08		5.85	
	15	7.14	1.57		7.33		6.95	

Note: n = 21 subjects; Geo. Mean = geometric mean; Harm. Mean = harmonic mean

Table 5. Summary of geometric mean ratios and 90% confidence intervals for TPV AUC, C_{max} and C_{p12h} when steady-state TPV/r was coadministered with RFB

PK Parameter	n	% Change	Ratio	90% CI
AUC _{0-12h} (h•µM)	21	0	1.00	(0.96, 1.04)
C _{max} (µM)	21	-1	0.99	(0.93, 1.07)
C _{p12h} (µM)	21	16	1.16	(1.07, 1.27)

Note: Subjects 2002, 2009, 2015 omitted

Figure 1. Effect of steady-state TPV/r on RFB and 25-O-desacetyl-RFB pharmacokinetic parameters (C_{p12h} , C_{max} and $AUC_{0-\infty}$)

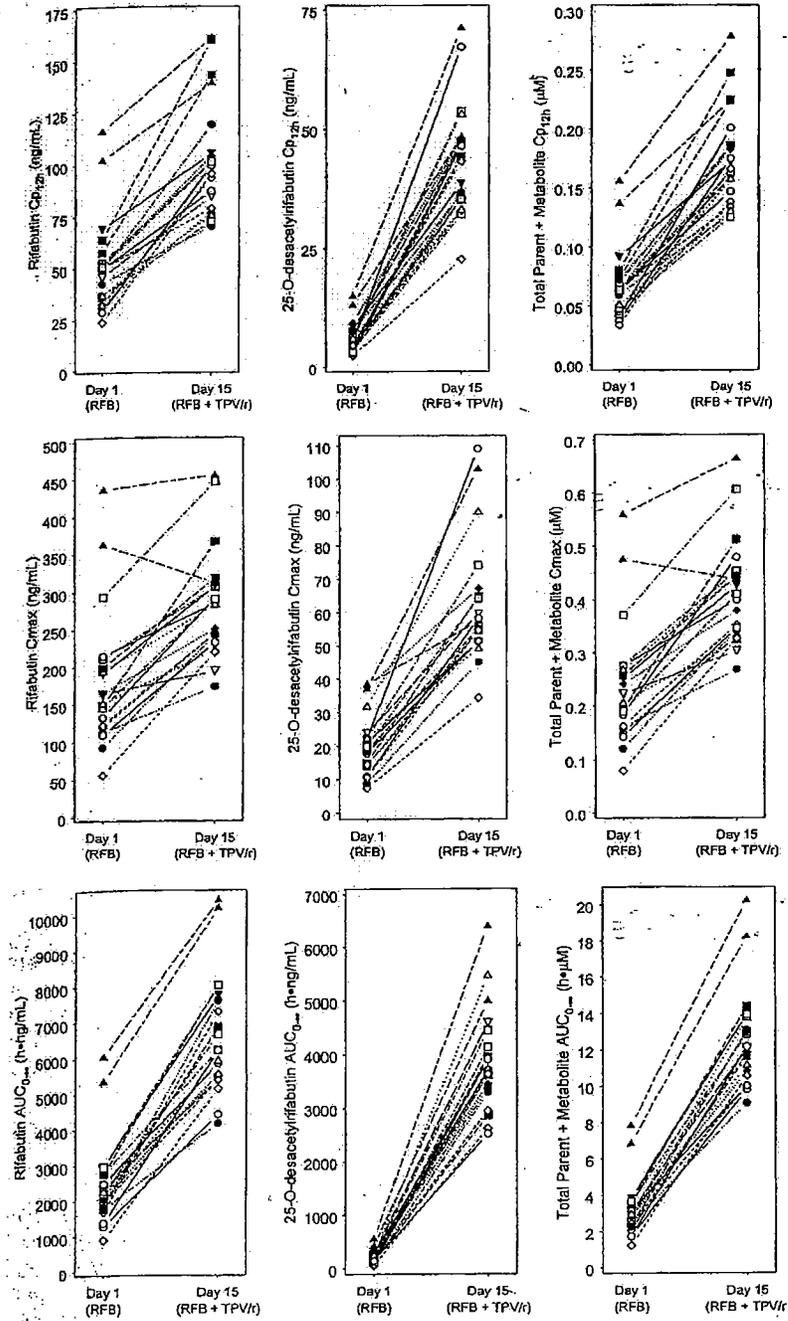
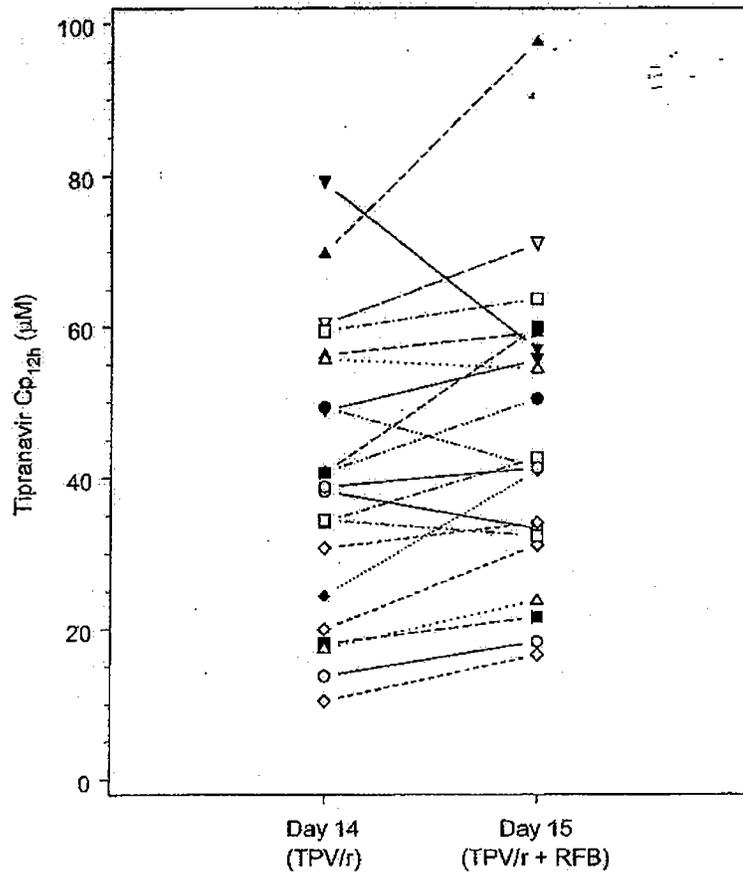
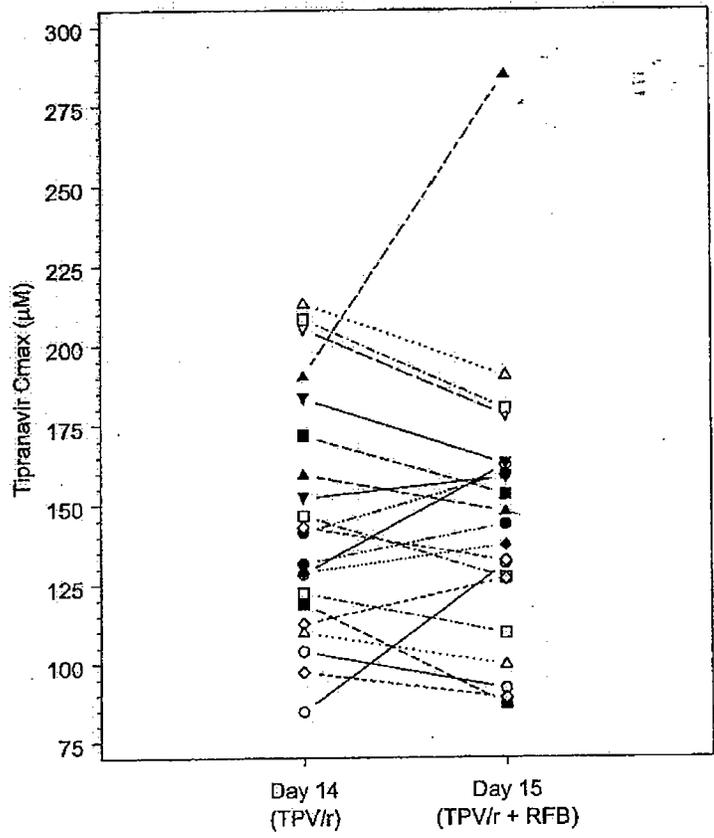


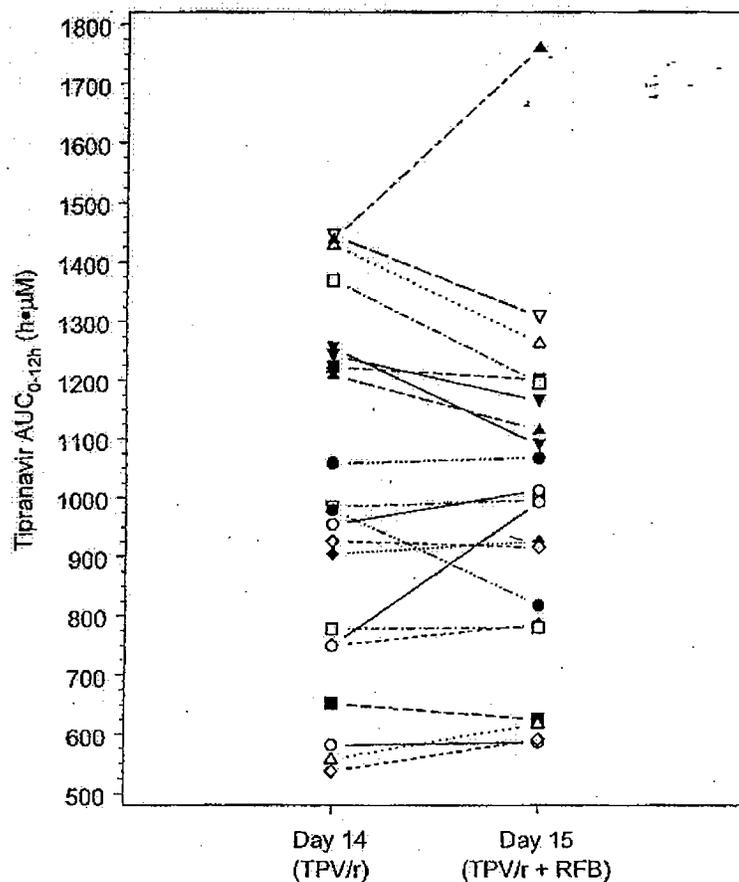
Figure 2. Effect of single-dose RFB on TPV pharmacokinetic parameters (C_{p12h} , C_{max} and AUC_{0-12h})



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SAFETY RESULTS:

Consistent with previous TPV trials, GI-related AEs were the most frequently reported AEs in the study. There were no deaths or serious adverse events reported in the study (See details in Medical Officer's review).

CONCLUSIONS AND DISCUSSION:

A single 150 mg dose of RFB increased the TPV C_{p12} at steady-state by 16% while no effect on AUC and C_{max} . However, the steady-state TPV increased a single dose RFB's AUC, C_{max} and C_{p12} by 2.9-fold, 1.7-fold and 2.1-fold, respectively. This change may attribute to inhibition of CYP3A4 mediated metabolism of RFB by ritonavir. Modification of the RFB dosing in combination with TPV/r is required. However, the effect of multiple dose of RFB on the steady-state PK of TPV/r was not studied. The concern is that RFB is also a CYP3A and P-gp inducer and the multiple dose of RFB might shift the balance of induction and inhibition towards more induction side thus reduce the TPV exposure.

1182.45

TITLE: Relative bioavailability of 500/200 mg of tipranavir/ritonavir pediatric solution compared to 500/200 mg of tipranavir/ritonavir capsules following oral administration and bioavailability of 500/200 mg tipranavir/ritonavir pediatric solution under the influence of food in healthy female and male subjects. An open-label, randomized, single-dose, three-way crossover trial

OBJECTIVES: To determine the relative bioavailability of 500/200 mg of tipranavir/ritonavir oral solution compared to 500/200 mg of tipranavir/ritonavir capsules following oral administration and to determine the food effect on the bioavailability of 500/200 mg tipranavir/ritonavir oral solution

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, single-dose, three-way crossover study conducted in healthy adult subjects. There were three treatments for each subject: Treatment 1: TPV/RTV 500/200 oral solution (fasted), Treatment 2: TPV/RTV 500/200 oral solution (fed, high fat breakfast) and Treatment 3: TPV/RTV 500/200 capsules (fasted). 57 subjects were enrolled for the study and 30 subjects entered the study. There were seven days between treatments. 30 subjects were randomized to one of the six treatment sequences in a balanced ratio.

For Treatment 2, the dose was taken within 30 minutes after high-fat breakfast.

The overall demographic characteristics of 30 subjects were as following: Male (60%) and female (40%); White (100%).

INVESTIGATOR AND STUDY LOCATION: []

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation, oral solution, 100 mg/mL. Norvir: 100 mg soft elastic capsules, oral solution 80 mg/mL.

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of TPV and RTV concentrations prior to the dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 1, 24, 48 and 72 hours post dose.

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

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

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PHARMACOKINETIC RESULTS:

Table 1. Summary of the pharmacokinetic parameters of TPV for subjects receiving TPV/RTV 500/200 mg capsule, oral solution fasted and in fed state (N=30)

AUC _{0-∞} (hr-ng/mL)	Capsule (fasted)	Oral Solution (fasted)	Oral Solution (fed)
Mean	451000	623000	591000
SD	93900	149000	145000
Geometric mean	442000	606000	574000
CV% of geometric mean	21.4	24.8	24.8
C_{max} (ng/mL)	Capsule (fasted)	Oral Solution (fasted)	Oral Solution (fed)
Mean	52100	76800	54100
SD	12100	13600	10600
Geometric mean	50700	75600	53100
CV% of geometric mean	24.2	18.0	20.0

Table 2. Summary of the pharmacokinetic parameters of RTV for subjects receiving TPV/RTV 500/200 mg capsule, oral solution fasted and in fed state

AUC _{0-∞} (hr-ng/mL)	Capsule (fasted)	Oral Solution (fasted)	Oral Solution (fed)
Mean	13300	14800	14200
SD	5160	5580	6280
Geometric mean	12400	13800	13300
CV% of geometric mean	37.9	39.7	37.5
C_{max} (ng/mL)	Capsule (fasted)	Oral Solution (fasted)	Oral Solution (fed)
Mean	2610	3120	2060
SD	1000	1300	642
Geometric mean	2430	2890	1970
CV% of geometric mean	40.8	40.7	31.1

Table 3. Summary of geometric mean ratios and 90% confidence intervals

TPV	AUC	C _{max}	Comparison
	0.73 (0.70, 0.77)	0.67 (0.62, 0.71)	Capsule (fasted) vs. Oral solution (fasted)
	0.95 (0.90, 1.00)	0.71 (0.67, 0.76)	Oral solution (fed) vs. Oral solution (fasted)
	1.30 (1.23, 1.36)	1.07 (1.00, 1.14)	Oral solution (fed) vs. Capsule (fasted)
RTV	AUC	C_{max}	Comparison
	0.92 (0.83, 1.02)	0.86 (0.76, 0.97)	Capsule (fasted) vs. Oral solution (fasted)
	0.96 (0.87, 1.07)	0.70 (0.62, 0.79)	Oral solution (fed) vs. Oral solution (fasted)
	1.05 (0.94, 1.16)	0.81 (0.72, 0.92)	Oral solution (fed) vs. Capsule (fasted)

Figure 1. Comparison of plasma tipranavir pharmacokinetic parameters for subjects receiving TPV/RTV 500/200 mg capsule, oral solution fasted and in fed state

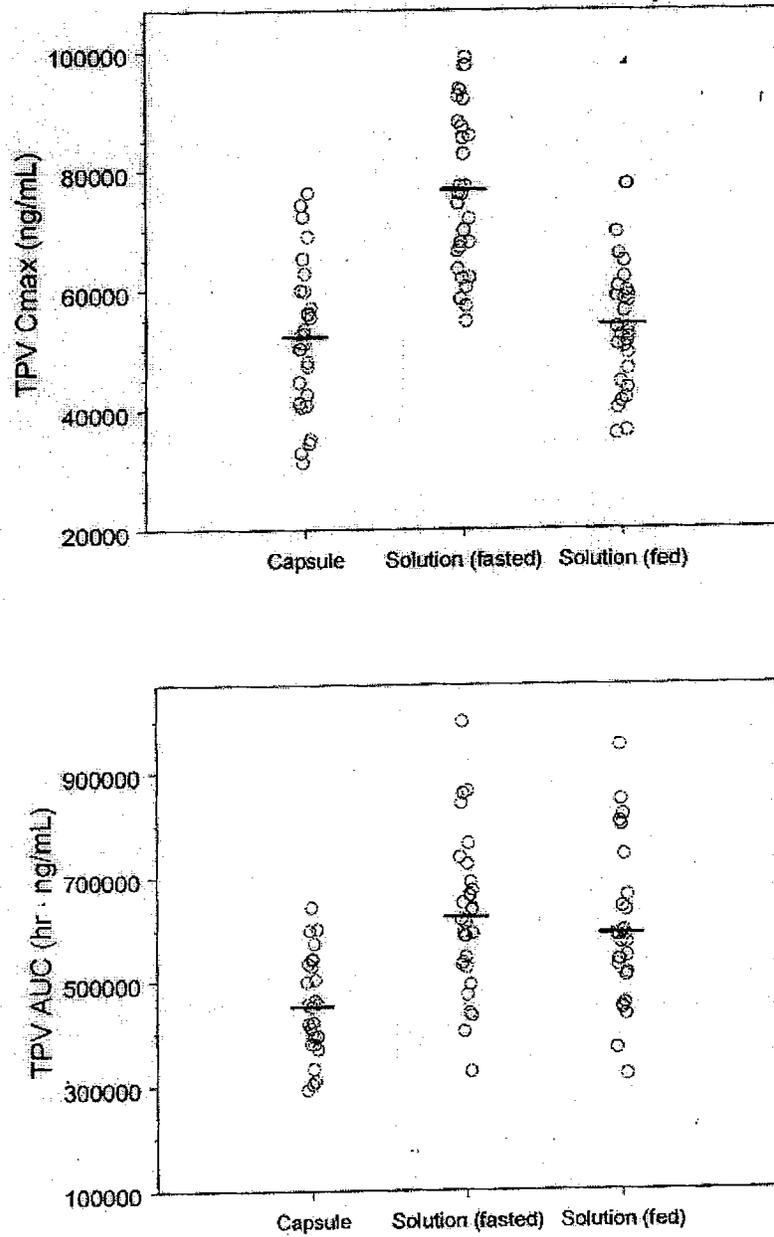
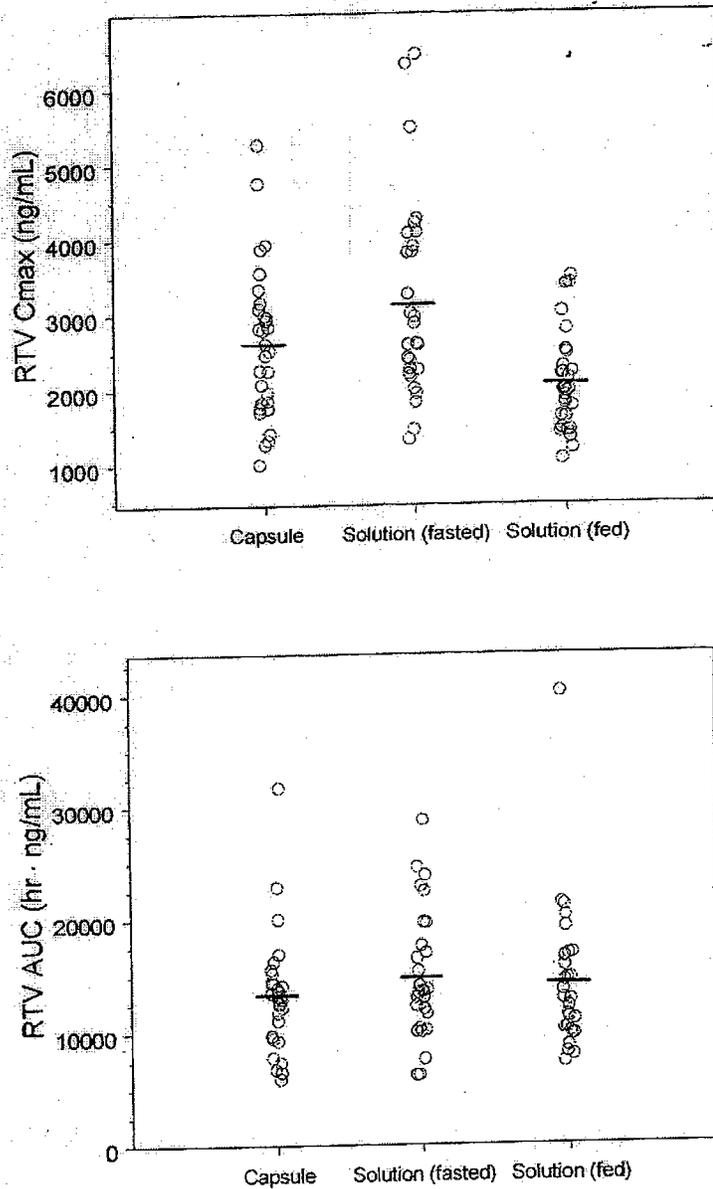


Figure 2. Comparison of plasma ritonavir pharmacokinetic parameters for subjects receiving TPV/RTV 500/200 mg capsule, oral solution fasted and in fed state



SAFETY RESULTS: Neither unexpected nor severe safety issues were reported in the study (See details in Medical Officer's review).

CONCLUSIONS AND DISCUSSION: Comparing the results following TPV solution administered under fed and fasted conditions, the effect of high fat meal was minimal on AUC (geometric mean ratio: 0.95 with 90% CI: 0.90, 1.00) but significant on C_{max}, about 30% decrease (geometric mean ratio: 0.71 with 90% CI: 0.67, 0.76). Comparing the results following TPV capsule and solution administered under the fasted condition, geometric mean ratios with 90% CIs for AUC and C_{max} were 0.73 (0.70, 0.77), 0.67

(0.62, 0.71), respectively, demonstrating that TPV solution is about 30% more bioavailable than TPV capsule and that these two formulations are not bioequivalent (with ritonavir co-administration) under the fasted condition.

Comparing the results following TPV solution administered under the fed condition to TPV capsule under the fasted condition, geometric mean ratios with 90% CIs for AUC and C_{max} were 1.30 (1.23, 1.36), 1.07 (1.00, 1.14), respectively. Considering the AUC_{0-12h} and C_{max} of TPV capsule increased 31% and 16%, respectively, with a high-fat meal, the calculated geometric mean ratios for AUC and C_{max} comparing the TPV solution to TPV capsule administered under the fed condition are 0.91 and 0.90, respectively.

The relative bioavailability study design (single dose) does not provide definitive results, as discussed below.

TPV is a dual substrate of CYP3A and P-gp. The steady state concentrations of TPV depend on the net effect (induction or inhibition) on CYP3A and P-gp. The capsule and solution formulations have different excipients that may have different effects on CYP3A and P-gp (The capsule formulation has Cremophor EL and solution formulation has vitamin E polyethylene glycol succinate). Thus, it is difficult to predict relative bioavailability of these two formulations at steady-state from single-dose data given the complex enzyme/transporter interactions during absorption. It is necessary to evaluate the relative bioavailability of the two formulations at steady-state.

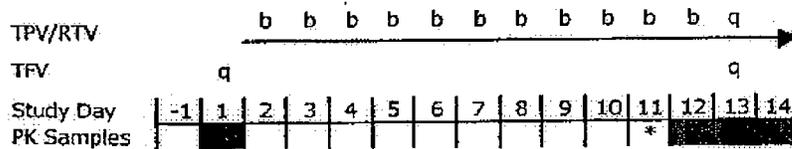
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TITLE: A single-center, open-label, randomized, parallel, multiple dose comparison of the effect of tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg twice a day for 11.5 days on the pharmacokinetic characteristics of tenofovir disoproxil fumarate 300 mg in healthy volunteers

OBJECTIVES: To characterize the effect of two dose combinations of tipranavir/ritonavir (tipranavir 500 mg and ritonavir 100 mg or tipranavir 750 mg and ritonavir 200 mg twice a day) on the pharmacokinetics of tenofovir disoproxil fumarate as well as the effects of tenofovir disoproxil fumarate on the pharmacokinetics of TPV/RTV in healthy volunteers

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, parallel, multiple dose study. A total of 49 healthy subjects were evenly randomized to either 500 mg/100 mg TPV/RTV or 750 mg /200 mg TPV/RTV dose group. 47 subjects completed the study. The scheme of the study design is shown below:



- = Blood samples for pharmacokinetic profile
- * = Blood sample for trough determination of TPV/RTV (7:00 - 8:00 pm)
- q = once daily dosing (7:00 - 8:00 am)
- b = twice daily dosing (7:00 - 8:00 am and 7:00 - 8:00 pm)
- TFV = tenofovir disoproxil fumarate, 300 mg
- TPV/RTV = tipranavir/ritonavir administration, 500 mg/100 mg and 750 mg/200 mg

Standard medium fat meals (500-682 Kcal, 23-25% calories from fat) were given at the time of or after drug administration on PK sampling days (Days 1, 12 and 13).

The overall demographic characteristics of 49 subjects were as following: Male (53.1%) and female (46.9%); White (100%).

INVESTIGATOR AND STUDY LOCATION: []

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

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

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

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max} , C_{p12h} and AUC_{0-12h} were provided for TPV/RTV (with and without tenofovir) and geometric means and coefficients of variation for C_{max} , C_{p12h} and AUC_{0-24h} were provided for tenofovir disoproxil fumarate (with and without TPV/RTV). The geometric mean ratios with 90% confidence intervals were calculated between comparison groups.

PHARMACOKINETIC RESULTS:

Table 1. Summary of the single dose pharmacokinetic parameters of TFV with and without TPV/RTV

TPV/RTV (mg/bid)	N	Day 1 Geometric means (CV%)			Day 13 Geometric means (CV%)		
		C_{max} (ng/mL)	C_{p12h} (ng/mL)	AUC_{0-24h} (hr-ng/mL)	C_{max} (ng/mL)	C_{p12h} (ng/mL)	AUC_{0-24h} (hr-ng/mL)
500/100	24	291 (34.5)	50.8 (23.6)	1606.54 (17.7)	219 (20.1)	54.2 (26.3)	1575.48 (20.0)
750/200	23	318 (38.4)	53.0 (31.9)	1685.08 (28.0)	196 (32.9)	59.6 (21.3)	1696.29 (19.4)

Table 2. Summary of the steady-state pharmacokinetic parameters of TPV with and without TFV

TPV/RTV (mg/bid)	N	Day 12 Geometric means (CV%)			Day 13 Geometric means (CV%)		
		C_{max} (μ M)	C_{p12h} (μ M)	AUC_{0-12h} (hr- μ M)	C_{max} (μ M)	C_{p12h} (μ M)	AUC_{0-12h} (hr- μ M)
500/100	24	84.15 (39.0)	13.91 (87.9)	547.9 (44.8)	71.89 (35.4)	11.14 (74.4)	460.0 (41.1)
750/200	23	143.40 (35.7)	35.21 (85.4)	1002.8 (45.5)	128.50 (31.6)	32.29 (81.6)	925.0 (43.4)

Table 3. Summary of the steady-state pharmacokinetic parameters of RTV with and without TFV

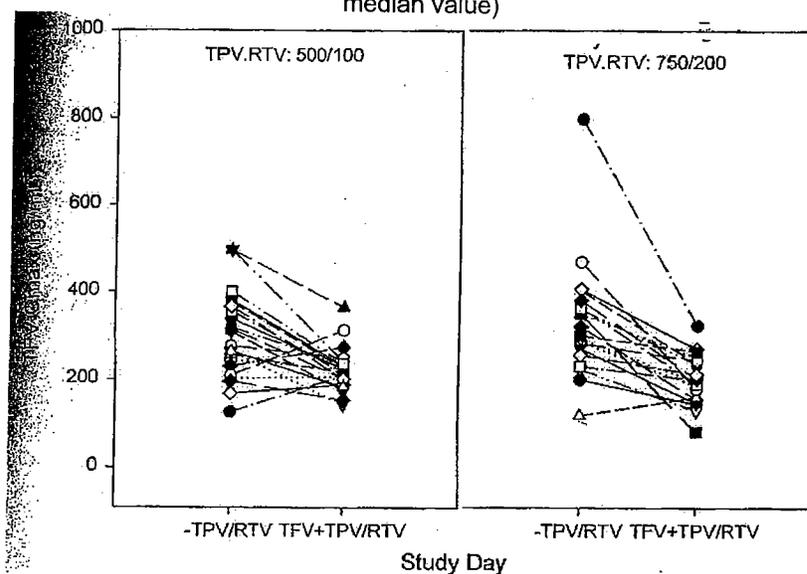
TPV/RTV (mg/bid)	N	Day 12 Geometric means (CV%)			Day 13 Geometric means (CV%)		
		C_{max} (μ g/mL)	C_{p12h} (μ g/mL)	AUC_{0-12h} (hr- μ g/mL)	C_{max} (μ g/mL)	C_{p12h} (μ g/mL)	AUC_{0-12h} (hr- μ g/mL)
500/100	24	0.569 (88.4)	0.0354 (27.9)	2.08 (80.6)	0.369 (75.5)	0.0363 (42.5)	1.50 (78.6)
750/200	23	1.717 (72.2)	0.0904 (98.5)	6.962 (78.8)	1.667 (60.9)	0.1006 (100.7)	7.256 (71.4)

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Table 4. Summary of geometric mean ratios and 90% confidence intervals for pharmacokinetic parameters for the coadministration of TPV/RTV with TFV

		TPV/RTV 500/100		TPV/RTV 750/200	
		Ratio	90% CI	Ratio	90% CI
TFV	C_{max}	0.77	0.68-0.87	0.62	0.54-0.71
	C_{p12h}	1.07	0.98-1.17	1.14	1.01-1.27
	AUC_{0-24h}	0.98	0.91-1.05	1.02	0.94-1.10
TPV	C_{max}	0.83	0.74-0.94	0.89	0.84-0.96
	C_{p12h}	0.79	0.70-0.90	0.88	0.78-1.00
	AUC_{0-12h}	0.82	0.75-0.91	0.91	0.85-0.97
RTV	C_{max}	0.65	0.53-0.79	0.95	0.82-1.10
	C_{p12h}	0.87	0.68-1.12	1.14	0.84-1.53
	AUC_{0-12h}	0.73	0.62-0.86	1.02	0.88-1.18

Figure 1. TFV C_{max} , C_{p12h} and AUC_{0-24h} with and without TPV/RTV by subjects (Solid line represents median value)



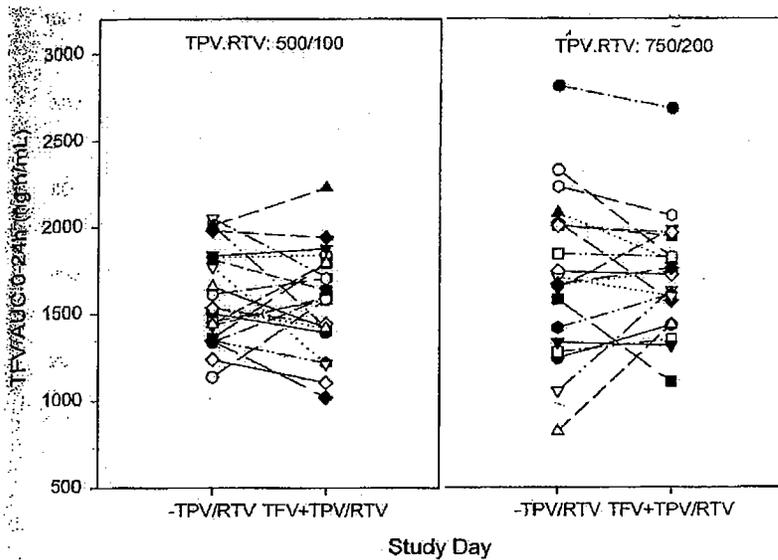
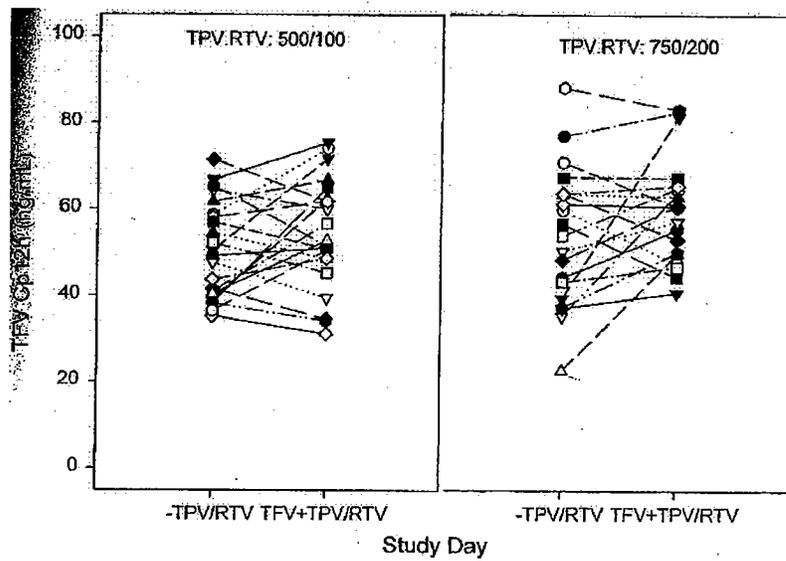
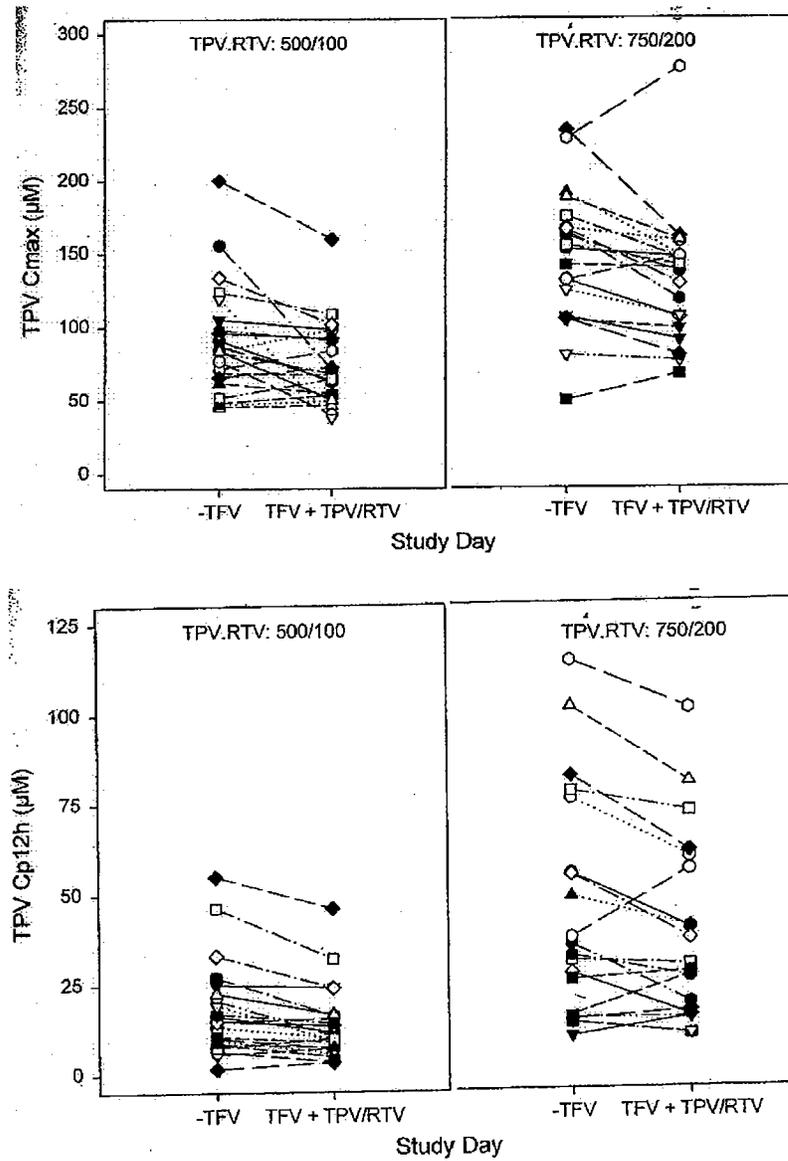


Figure 2. TPV C_{max} , C_{p12h} and AUC_{0-12h} with and without TFV by subjects (Solid line represents median value)



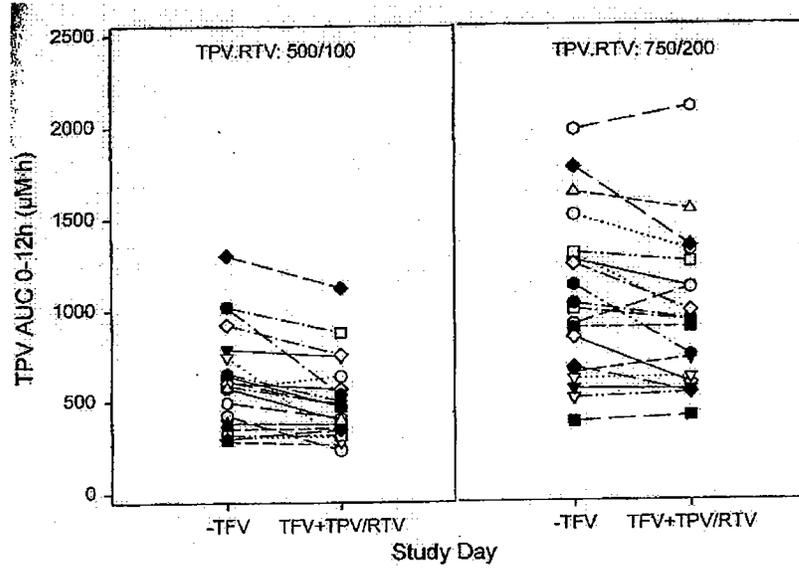
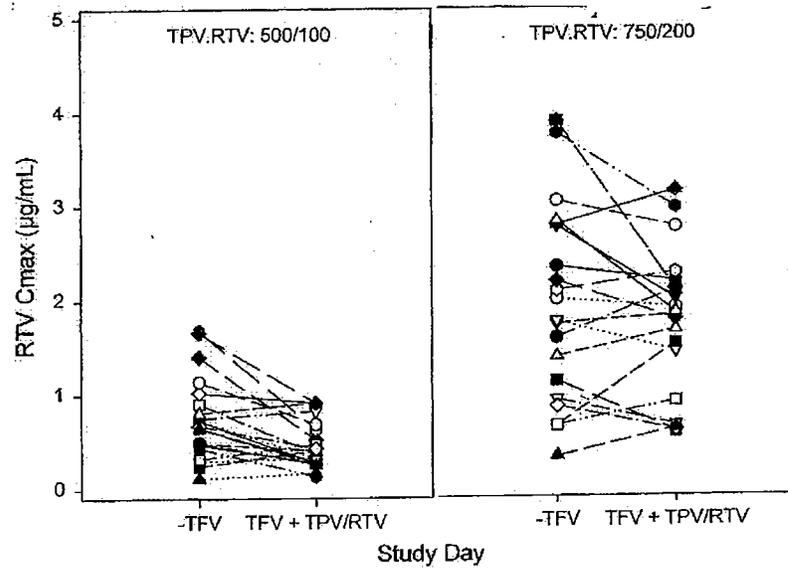
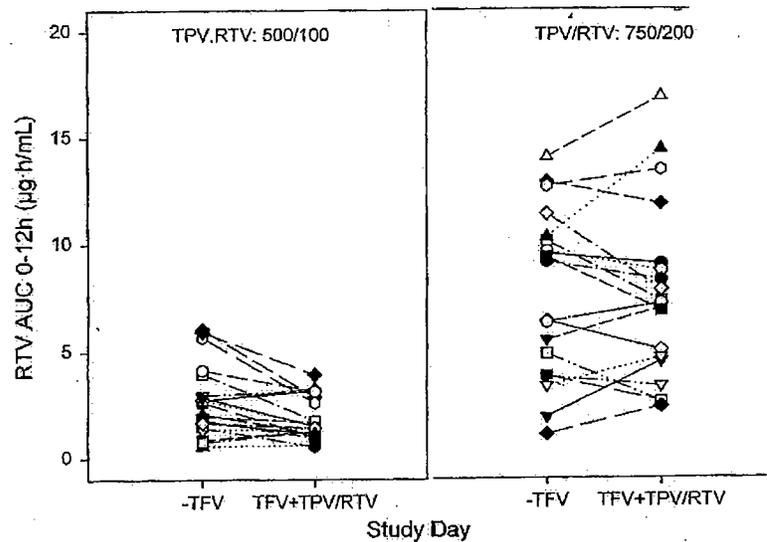
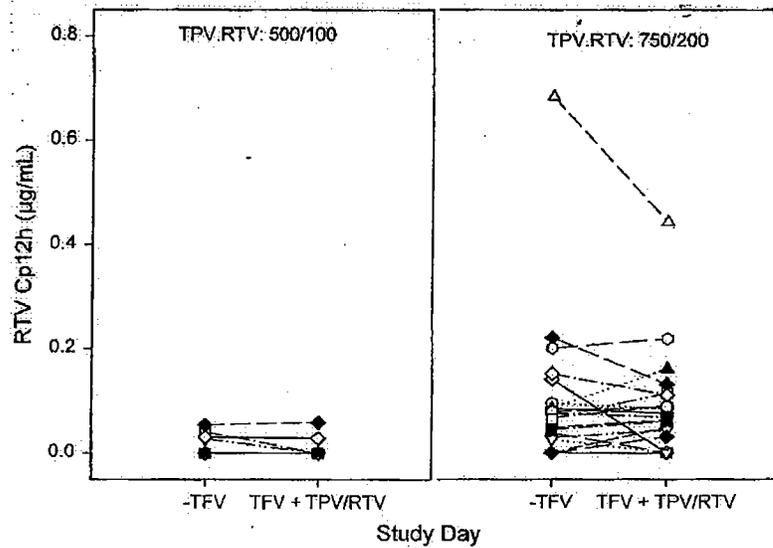


Figure 3. RTV C_{max}, C_{p12h} and AUC_{0-12h} with and without TFV by subjects (Solid line represents median value)





SAFETY RESULTS: In general, consistent with other TPV trials, GI events were the predominant observed AEs. There was no SAEs in the study (See details in Medical Officer's review).

CONCLUSIONS AND DISCUSSION:

This study demonstrated that the AUC and C_{p12h} of tenofovir disoproxil fumarate were not affected by the coadministration of TPV/RTV at two dose combinations. However, C_{max} of tenofovir disoproxil fumarate decreased about 23% in the presence of TPV/RTV 500mg/100 mg and 38% in the presence of TPV/RTV 750 mg/200 mg, respectively. It is generally believed that the antiviral activity of tenofovir disoproxil fumarate is associated with its AUC rather than its C_{max} thus the interaction between tenofovir disoproxil fumarate and TPV/RTV may not be clinically significant.

TPV exposures were decreased about 10 to 20% when coadministered with tenofovir disoproxil fumarate. However the 90% confidence intervals mostly reside within 80-120% boundaries.

TITLE: An open-label randomized, parallel-group pharmacokinetics trial of tipranavir/ritonavir, alone or in combination with RTV-boosted saquinavir (SQV), amprenavir (APV), or lopinavir (LPV), plus an optimized background regimen, in multiple antiretroviral (ARV) experienced patients

OBJECTIVES: The primary objective was to determine the change in C_{12h} from Week 2 (average of Day 7 and Day 14) to Week 4 (average of Day 21 and 28) for the RTV-boosted SQV, APV, and LPV regimens, after addition of TPV 500mg b.i.d. and RTV 100 mg b.i.d. on Day 14. The secondary objective was to determine the effects of TPV/r as compared with 3 dual boosted PI regimens in highly treatment-experienced HIV-1 infected patients.

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, parallel-group, multicenter study with 4 regimens. Briefly, ARV highly experienced HIV-1 patients who were excluded from RESIST 1 and RESIST 2 and had three or more mutations in protease codons 33, 82, 84 or 90 and with a viral load ≥ 1000 copies/mL were screened for this study. Qualifying patients (315) were evenly randomized to receive one of four treatment arms:

1. TPV/r (500 mg/200 mg b.i.d.) plus an optimized non-PI background regimen (OBR) from baseline
2. LPV/r (400 mg/100 mg b.i.d.) plus OBR from baseline with TPV/r (500 mg/100 mg b.i.d.) added at Week 2
3. APV/r (600 mg/100 mg b.i.d.) plus OBR from baseline with TPV/r (500 mg/100 mg b.i.d.) added at Week 2
4. SQV/r (1000 mg/100 mg b.i.d.) plus OBR from baseline with TPV/r (500 mg/100 mg b.i.d.) added at Week 2

Trough concentrations (C_{12h}) were determined for each PI on Days 7, 14, 21, and 28 after baseline. The primary PK endpoints were analyzed at Week 4. Safety and efficacy (e.g., viral load) were analyzed until Week 24.

Of the 315 treated patients, 273 completed the study. The overall demographic characteristics of 315 subjects were as following: Male (93.3%) and female (6.7%); White (76.2%), Black (7.3%) and Missing (16.5%).

Medications could be taken with or without food. Intake with food was recommended to reduce the potential for GI adverse events.

INVESTIGATOR AND STUDY LOCATION: Multicenter trial with 100 participating centers worldwide

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Invirase or Fortovase: 200 mg soft gel capsules. Agenerase: 150 mg capsules. Kaletra: 133.3 mg/33.3 mg capsules. Kaletra dose increased to 533 mg/133 mg if in combination with efavirenz or nevirapine.

PHARMACOKINETIC SAMPLE COLLECTION: Plasma samples for trough PI concentrations were collected on Days 7, 14, 21 and 28. In addition, selected sites participated in an optional intensive PK sub-study at Weeks 2 and 4 when full 12 hour PK samplings were conducted at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose.

ASSAY: Plasma samples were analyzed for TPV, RTV, APV, LPV and SQV by [] using a validated high performance liquid chromatography [] method. The calibration curves ranged from — ng/mL to — ng/mL for TPV, — ng/mL to — ng/mL for APV, — ng/mL to — ng/mL for SQV, — ng/mL to — ng/mL for LPV, and — ng/mL to — ng/mL for RTV.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental PK analysis was conducted using WinNonlin (v.3.1, Pharsight). The primary endpoints were C_{12h} for PIs at Week 2 (average of Day 7 and Day 14) and at Week 4 (average of Day 21 and 28). AUC_{12h} , C_{max} and C_{12h} of PIs at Weeks 2 and 4 were calculated from the intensive PK sub-study.

PHARMACOKINETIC RESULTS:

Table 1. Geometric mean ratio with 90% confidence intervals of PK parameters of lopinavir, saquinavir and amprenavir with and without co-administration of tipranavir

Substrate Drug	AUC Ratio (Intensive PK)	C_{max} Ratio (Intensive PK)	C_{12h} Ratio (Intensive PK)	C_{12h} Ratio (TDM PK)
Lopinavir	0.45 (0.32, 0.63) n=21	0.53 (0.40, 0.69) n=21	0.30 (0.17, 0.51) n=21	0.48 (0.40, 0.58) n=69
Saquinavir	0.24 (0.19, 0.32) n=20	0.30 (0.23, 0.40) n=20	0.18 (0.13, 0.26) n=20	0.20 (0.16, 0.25) n=68
Amprenavir	0.56 (0.49, 0.64) n=16	0.61 (0.51, 0.73) n=16	0.45 (0.38, 0.53) n=16	0.44 (0.39, 0.49) n=74

Table 2. Geometric mean with 90% confidence intervals of C_{12h} of lopinavir, saquinavir and amprenavir with and without co-administration of tipranavir

Drug	n	C_{12h} geometric mean values ($\mu\text{g} / \text{mL}$) ¹	
		Before addition of TPV/r	After addition of TPV/r
Lopinavir	69	5.34 (4.79, 5.96)	2.59 (2.11, 3.18)
Saquinavir	68	0.46 (0.36, 0.58)	0.093 (0.076, 0.114)
Amprenavir	74	1.83 (1.67, 2.01)	0.80 (0.71, 0.90)

¹ Trough values were included in the calculation of each geometric mean if they were obtained within 8-16 hours of previous dose. Weeks 1 and 2 were combined to compare to Weeks 3 and 4 combined.

The sponsor reported a total of about 20% of protocol deviations related to PK trough sampling in the study. However, these values were excluded in the trough concentration evaluation.

Table 3. Geometric mean of AUC_{12h}, C_{max} and C_{12h} of lopinavir, saquinavir and amprenavir with (Week 4) and without (Week 2) co-administration of tipranavir

Drug	n	AUC ($\mu\text{g}\cdot\text{h} / \text{mL}$)		C _{max} ($\mu\text{g} / \text{mL}$)		C _{12h} ($\mu\text{g} / \text{mL}$)	
		Week 2	Week 4	Week 2	Week 4	Week 2	Week 4
Lopinavir	21	88.6	39.7	9.99	5.26	5.83	1.72
Saquinavir	20	11.7	2.85	1.90	0.57	0.39	0.07
Amprenavir	16	30.3	17.0	5.68	3.46	1.64	0.73

Table 4. Geometric mean of AUC_{12h}, C_{max} and C_{12h} of tipranavir alone and in the presence of a boosted-PI

Treatment (90% CL)	n	TPV AUC ¹ ($\mu\text{g}\cdot\text{h} / \text{mL}$)	TPV C _{max} ($\mu\text{g} / \text{mL}$)	TPV C _{12h} ($\mu\text{g} / \text{mL}$)	TPV C _{12h} TDM ² ($\mu\text{g} / \text{mL}$)
TPV/r alone (2 weeks)	30	409 (368, 455)	56 (51, 62)	17 (14, 21)	20 (18, 23) n=61
TPV/r alone (4 weeks)	29	410 (365, 461)	56 (51, 62)	17 (14, 21)	23 (20, 25) n=61
TPV/r + LPV/r (4 weeks)	20	558 (432, 720)	68 (55, 85)	31 (22, 43)	29 (25, 35) n=72
TPV/r + SQV/r (4 weeks)	18	384 (318, 464)	50 (42, 60)	17 (13, 22)	17 (15, 19) n=71
TPV/r + APV/r (4 weeks)	16	607 (529, 696)	78 (70, 87)	29 (23, 35)	23 (20, 25) n=75

¹ Values are shown as geometric means of each treatment group.

² Therapeutic Drug Monitoring

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Table 5. Geometric mean of AUC_{12h}, C_{max} and C_{12h} of ritonavir with tipranavir and with dual PIs

	RTV	n	RTV AUC ¹ (µg·h / mL)	RTV C _{max} (µg / mL)	RTV C _{12h} (µg / mL)
2 Weeks					
TPV/r	200 mg	30	5.32 (4.56, 6.20)	1.04 (0.88, 1.23)	0.11 (0.08, 0.15)
LPV/r	100 mg	20	4.12 (3.39, 5.02)	0.59 (0.47, 0.74)	0.24 (0.19, 0.30)
SQV/r	100 mg	21	9.16 (7.07, 11.88)	1.32 (1.01, 1.73)	0.35 (0.26, 0.47)
APV/r	100 mg	20	2.67 (2.15, 3.30)	0.44 (0.35, 0.56)	0.14 (0.12, 0.16)
4 Weeks					
TPV/r	200 mg	30	4.70 (3.87, 5.70)	0.95 (0.79, 1.14)	0.11 (0.08, 0.15)
TPV/LPV/r	200 mg	20	5.31 (3.64, 7.73)	0.92 (0.61, 1.38)	0.21 (0.13, 0.32)
TPV/SQV/r	200 mg	19	6.88 (5.13, 9.23)	1.27 (0.95, 1.69)	0.13 (0.09, 0.18)
TPV/APV/r	200 mg	17	3.43 (2.64, 4.46)	0.75 (0.60, 0.93)	0.09 (0.06, 0.13)

¹ Values are shown as geometric means of each treatment group.

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Table 6. Geometric mean with 90% confidence intervals of C_{12h} of ritonavir with tipranavir and with dual PIs

	n	RTV C_{12h} ($\mu\text{g} / \text{mL}$)		Ratio of RTV C_{12h} Weeks 3 & 4 to Weeks 1 & 2
		Weeks 1 and 2 with RTV 100 mg	Weeks 3 and 4 with RTV 200 mg and TPV	RTV Dose ratio = 2 and TPV introduced
Lopinavir	69	0.28 (0.25, 0.31)	0.33 (0.27, 0.39)	1.18 (1.00, 1.38)
Saquinavir	68	0.42 (0.37, 0.48)	0.21 (0.18, 0.25)	0.50 (0.44, 0.58)
Amprenavir	74	0.22 (0.19, 0.24)	0.19 (0.16, 0.22)	0.88 (0.76, 1.02)
		Weeks 1 and 2 with RTV 200 mg	Weeks 3 and 4 with RTV 200 mg	RTV Dose ratio = 1 and TPV unchanged
Tipranavir	61	0.17 (0.14, 0.20)	0.20 (0.16, 0.23)	1.15 (0.99, 1.33)

Figure 1. Lopinavir C_{12h} alone and with TPV/r

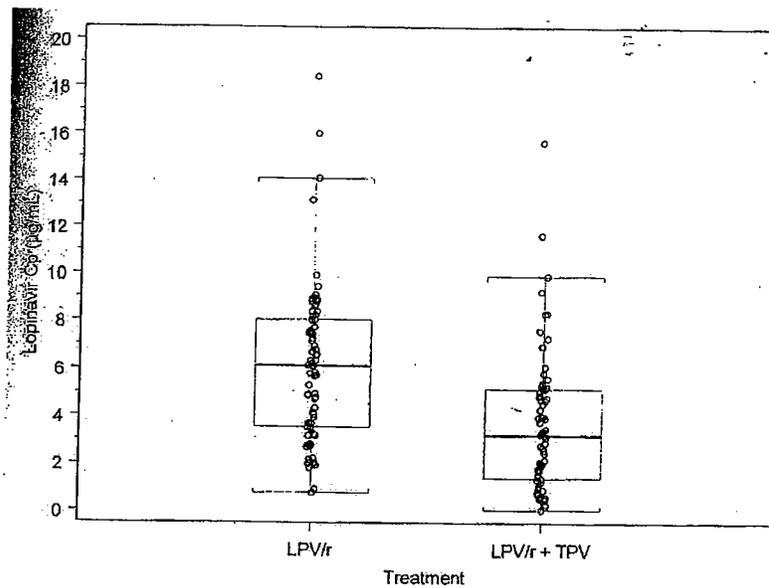


Figure 2. Amprenavir C_{12h} alone and with TPV/r

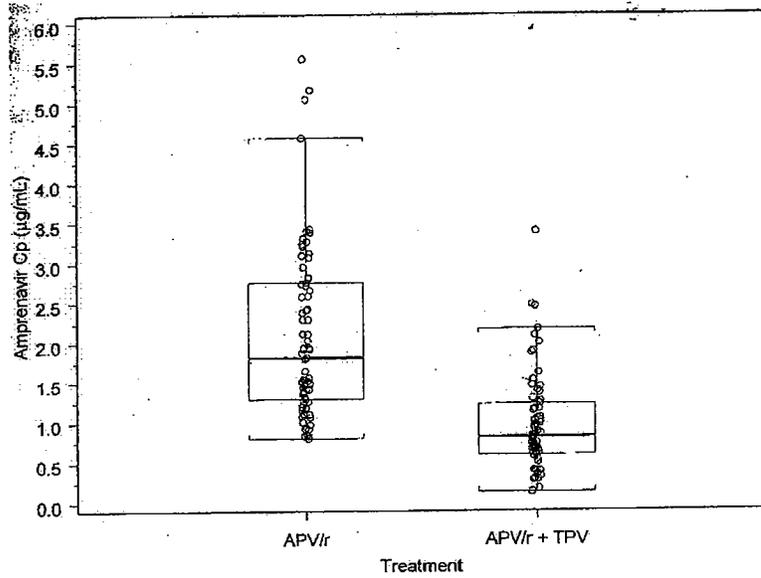
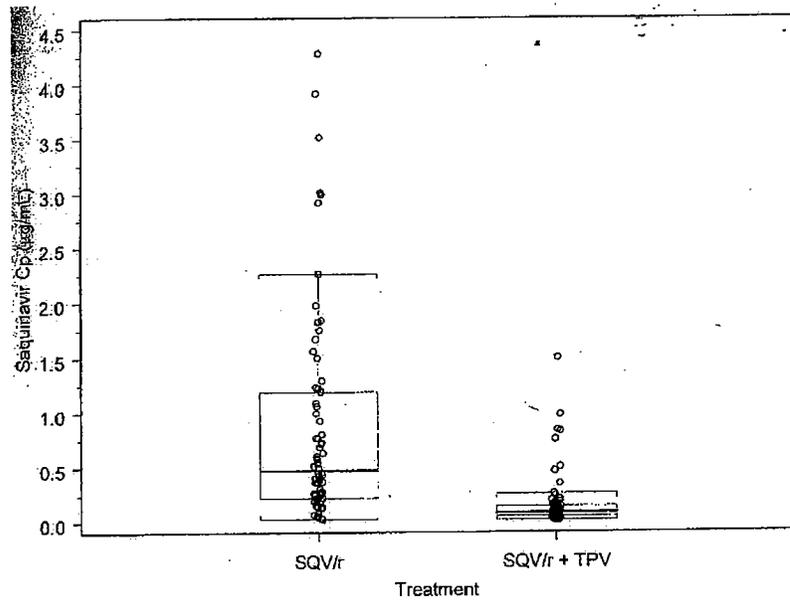


Figure 3. Saquinavir C_{12h} alone and with TPV/r



SAFETY RESULTS:

Please see Medical Office's review.

EFFICACY RESULTS:

Please see Medical Office's review.

CONCLUSIONS AND DISCUSSION:

Study 1182.51 was a preliminary PK study to investigate the potential drug interactions between TPV/r and the other ritonavir boosted-PIs and to provide initial clinical data for this dual PI approach. All four arms received the same total dose of RTV after Week 4, i.e., 200 mg b.i.d. The co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased LPV, SQV, or APV steady-state trough plasma concentrations by 52%, 80% and 56%, respectively. This data were also consistent with the results of the intensive PK sub-study where co-administration of TPV/r at 500 mg/200 mg b.i.d. decreased LPV, SQV, or APV steady-state trough plasma concentrations by 70%, 82% and 55%, respectively, AUC by 55%, 76% and 44%, respectively, and C_{max} by 47%, 70% and 39%, respectively. TPV exposure increased slightly in the dual-boosted groups co-administered with APV/r and LOP/r, but decreased slightly when co-administered with SQV/r. RTV trough plasma concentration were similar in APV/r and LPV/r groups with the addition of TPV/r. However RTV trough plasma concentrations in the SQV/r group decreased by 50% with the addition of TPV/r. This decrease in RTV concentration might account for the most dramatic reduction in SQV exposure with the addition of TPV/r. However, the mechanism underlying the TPV/r-PI/r interaction is not apparent. Possible explanation is that tipranavir is also a potent P-gp inducer and the low dose of ritonavir cannot compensate the P-gp induction effect caused by tipranavir. All the PIs studied in this trial are known dual substrates of CYP3A and P-gp and subject to high intestinal first-pass effect. Thus the net interplay between intestinal CYP3A and P-gp may have caused lower systemic exposure of these PIs when co-administered with tipranavir at the steady-state. The interaction may also be due to changes in protein binding. It is possible that free concentrations of the PIs did not change as much as the total concentrations.

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TITLE: Double-blinded, randomized, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/RTV) in multiple antiretroviral drug-experienced subjects

OBJECTIVES: To determine an optimal dose combination of tipranavir and ritonavir that will be used in subsequent Phase III trials.

SUBJECTS AND STUDY DESIGN: This was a double-blinded, randomized, parallel group, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/RTV) in multiple antiretroviral drug-experienced subjects. The doses were 500mg/100 mg, 500mg/200mg and 750mg/200 mg TPV/RTV BID. The primary efficacy endpoint was viral load reduction after two weeks of TPV/RTV therapy, and the primary safety endpoints were proportions of patients reporting moderate or severe diarrhea, any grade of vomiting, and any serious adverse events during the first 4 weeks of TPV/RTV therapy.

The patient population of this study was treatment experienced in each of three classes of ARVs. They had received at least 3 months of NRTIs, NNRTIs, and \geq two PIs, had a viral load of \geq 1000 copies/mL, and a genotype indicating at least one primary PI resistance mutation, including 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M with not more than one of 82L/T, 84V, or 90M.

216 subjects entered the study. Following genotypic screening, subjects were randomized to one of the three blinded regimens, discontinued from their current PI and administered TPV/RTV therapy for two weeks while remaining on their other ARV medications (functional monotherapy). After two weeks, each patient's background ARV medications were optimized. The patients remained on blinded TPV/RTV and optimized ARV therapy until the interim analysis identified the optimal TPV/RTV regimen.

The overall demographic characteristics of 216 subjects were as following: Male (84.3%) and female (15.7%); White (76.4%), Black (23.1%) and Asian (0.5%).

Dose selection for this study was based on the results from four previous clinical trials (1182.2, 1182.3, 1182.4, and 1182.5) of TPV doses ranging from 250 mg to 1250 mg and TPV doses of 100 mg or 200 mg.

INVESTIGATOR AND STUDY LOCATION: Multicenter

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

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of TPV trough concentrations on Days 7 and 14 on all 216 subjects. A population PK sub-study at selected sites at Week 2 (Day 14) was performed (23 in the TPV/r 500/100 group, 24 in the TPV/r 500/200 group and 22 in the 750/200 group). For the sub-study, in addition to the morning trough sample, three blood samples were collected per subject after administration of TPV/RTV on Day 14. A sampling strategy was used to distribute the collection of concentration-time data over an interval that covered most of the absorption and elimination phases of drugs.

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

PHARMACOKINETIC DATA ANALYSIS: NONMEM (version 5, [] was used to evaluate the population pharmacokinetics of TPV in the study patient population.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP: The relationship between reductions in HIV RNA viral load and TPV trough plasma concentrations for the three treatment groups was assessed by comparing change in viral load on Day 14 relative to viral load at baseline with TPV trough concentrations collected on Day 14.

PHARMACOKINETIC RESULTS:

Table 1. Summary Tipranavir Plasma Trough Concentrations on Study Days 7 and 14

TPV/r (mg)	Statistic	Tipranavir Cp 8 - 16 Hours Post-dose		Tipranavir Cp 11.5 - 12.5 Hours Post-dose	
		Study Day		Study Day	
		7	14	7	14
500/100	N (patients)	61	64	17	22
	Geo. Mean (μM)	18.80	20.29	18.41	20.99
	Median (μM)	22.71	21.02	20.20	19.68
	Min - Max (μM)	[]			
	N < 20 μM	27	29	7	11
	N \geq 20 μM	34	35	10	11
	% < 20 μM	44	45	41	50
500/200	N (patients)	64	65	32	29
	Geo. Mean (μM)	31.85	27.49	29.33	25.14
	Median (μM)	31.41	29.42	27.19	31.01
	Min - Max (μM)	[]			
	N < 20 μM	17	15	10	5
	N \geq 20 μM	47	50	22	24
	% < 20 μM	27	23	31	17
750/200	N (patients)	59	62	29	22
	Geo. Mean (μM)	42.50	33.06	44.07	42.11
	Median (μM)	52.25	42.28	51.10	48.50
	Min - Max (μM)	[]			
	N < 20 μM	10	14	4	4
	N \geq 20 μM	49	48	25	18
	% < 20 μM	17	23	14	18

Table 2. Summary Tipranavir Pharmacokinetic Parameters Derived from NONMEM Population Modeling

	TPV/r (mg)		
	Median (min - max)		
	500/100	500/200	750/200
N	69	72	69
$C_{P_{0h,12h}}$ (μM)	23.75 ^a	33.75 ^a	51.24 ^a
	21.80	33.92	44.51
	[]
C_{max} (h)	50.96	61.81	87.24
	[]
T_{max} (h)	2.55	2.60	2.60
	[]
AUC_{0-12h} ($h \cdot \mu M$)	451.70	598.05	817.02
	[]
K_a (h^{-1})	0.7495	0.7493	0.7527
	[]
K_e (h^{-1})	0.1047	0.0811	0.0827
	[]
CL (L/h)	1.84	1.39	1.52
	[]
V (L)	17.83	18.26	18.25
	[]
$t_{1/2}$ (h)	6.62	8.55	8.38
	[]

^a Geometric mean.

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Figure 1. Tipranavir Plasma Trough Concentrations on Study Days 7 and 14

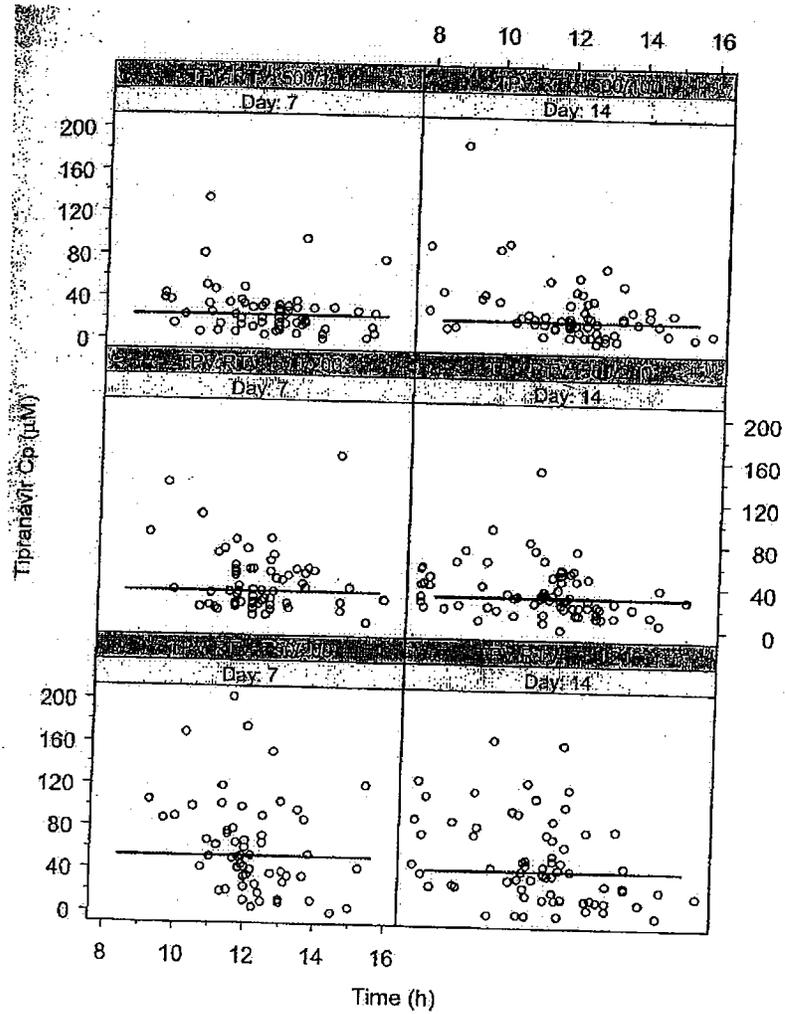


Figure 2. Tipranavir Plasma Trough Concentrations on Study Days 7 and 14 and Tipranavir Plasma Concentrations for a subset of Patients Sampled over 12-hour Period after TPV/r administration on Day 14

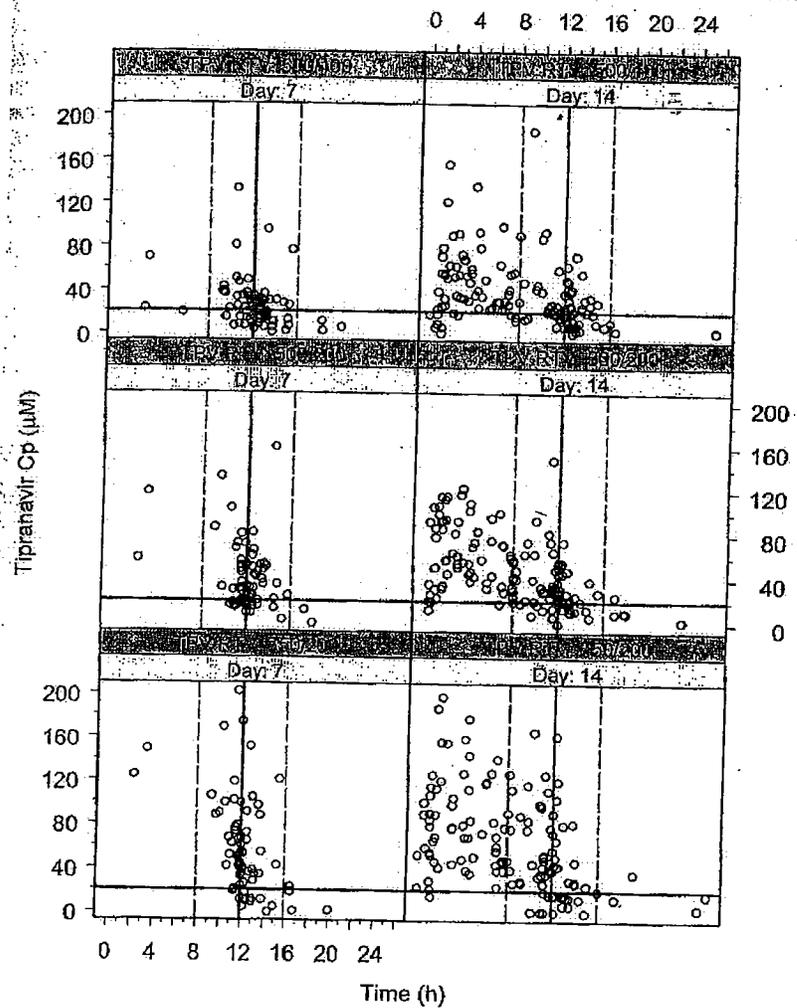


Figure 3. Ritonavir Plasma Trough Concentrations on Study Days 7 and 14 and Ritonavir Plasma Concentrations for a subset of Patients Sampled over 12-hour Period after TPV/r administration on Day 14

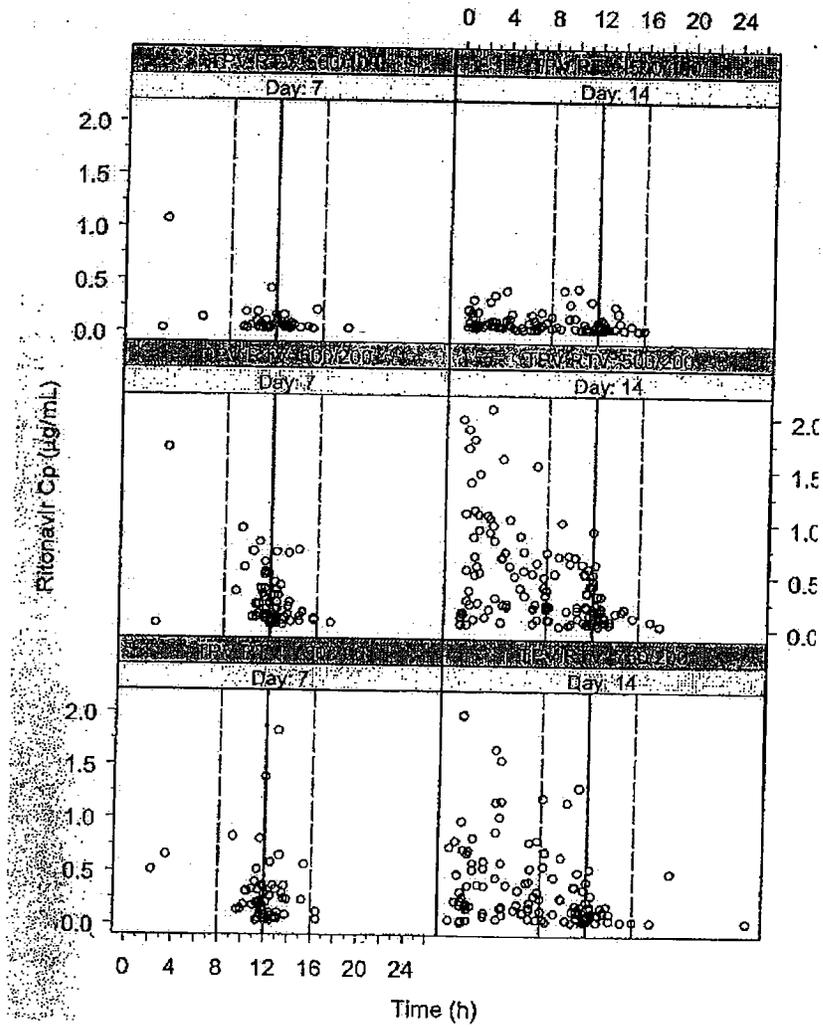
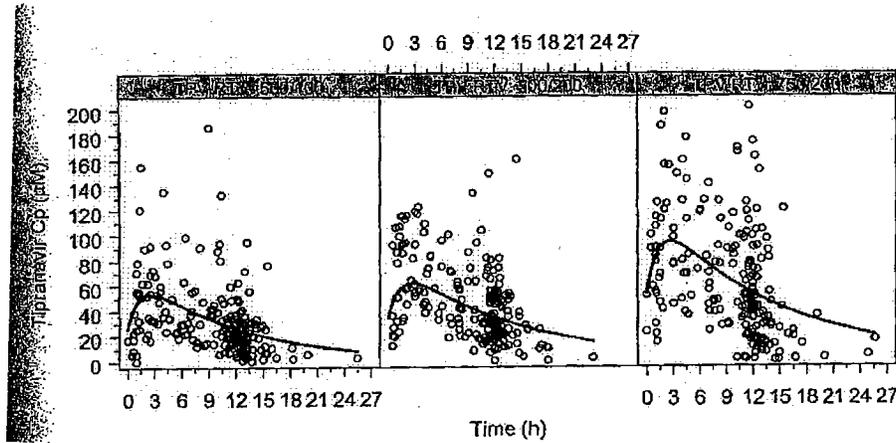


Figure 4. Observed (circles) and NONMEM Model-predicted Tipranavir Plasma Concentrations (lines) for the Population



PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP ANALYSIS:

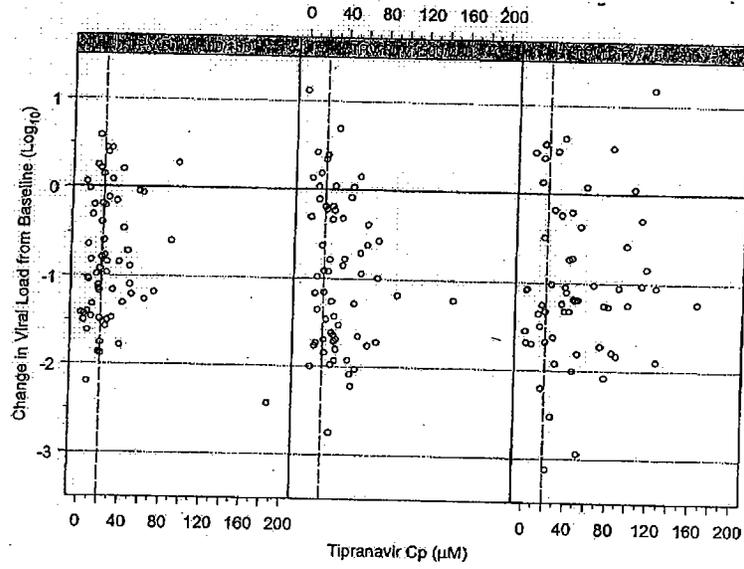
Table 3. Relationship of Change in Viral Load from Baseline to Day 14 and Tipranavir Trough Plasma Concentration

Change in Viral Load (Log ₁₀)	TPV/r dose											
	500/100				500/200				750/200			
	TPV Cp (µM)				TPV Cp (µM)				TPV Cp (µM)			
	<20		>20		<20		>20		<20		>20	
	N	ΔVL	N	ΔVL	N	ΔVL	N	ΔVL	N	ΔVL	N	ΔVL
>0 to 1.18	4	0.23	7	0.28	5	0.19	6	0.24	4	0.43	6	0.50
-1 to 0	9	-0.40	15	-0.60	5	-0.62	17	-0.57	1	-0.49	9	-0.37
-2 to -1	15	-1.42	12	-1.39	5	-1.73	21	-1.65	10	-1.42	24	-1.24
<-2	1	-2.20	1	-2.42	0	-	4	-2.15	1	-2.20	5	-2.52

Note: The 20 µM cutoff was proposed by the applicant.

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Figure 5. Relationship of Change in Viral Load from Baseline to Day 14 and Tipranavir Trough Plasma Concentration



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Table 4. Summary of Day 14 TPV C_{trough}, Fold-wild Type and Inhibitory Quotient by TPV/r dose

TPV/r (mg)	Statistic	TPV C _{min} (µM)	Fold-Wild Type	Inhibitory Quotient ^a
500/100	n	54	54	54
	Mean	28.549	4.54	117.957
	SD	28.808	14.45	138.247
	Min	[]
	Median	20.968	1.10	68.281
	Max	[]
	Geo Mean	19.545	1.51	59.336
500/200	n	55	55	55
	Mean	36.493	3.73	153.091
	SD	26.061	13.35	175.908
	Min	[]
	Median	29.138	1.40	101.043
	Max	[]
	Geo Mean	26.846	1.54	80.158
750/200	n	52	52	52
	Mean	51.358	1.68	240.975
	SD	41.429	1.74	256.861
	Min	[]
	Median	42.284	1.00	132.253
	Max	[]
	Geo Mean	30.241	1.23	113.168

EFFICACY RESULTS:

All three dose combinations studied were effective in reducing plasma HIV-1 RNA counts after 2 weeks of TPV/r therapy. However, the TPV/r 500/100 dose was inferior to other doses. This dose did not sustain viral load reduction to 24 weeks. The antiviral activity of TPV/r 500/200 and TPV/r 750/200 doses was comparable and sustained at least 0.5 log₁₀ at 24 weeks (See Dr. Zheng's Pharmacometric review and the Medical Officer's review).

SAFETY RESULTS:

The safety results demonstrated a strong dose relationship. An increasing incidence of severe adverse events, discontinuations as a result of adverse events were observed with increasing dose. TPV/r 750/200 dose was the least well tolerated of the three (See Dr. Zheng's Pharmacometric review and the Medical Officer's review).

CONCLUSIONS AND DISCUSSION:

Tipranavir pharmacokinetic data demonstrated the two highest doses (750/200 and 500/200) adequately achieved the preclinical target TPV trough concentration of 20 μM . There was decreased variability in the drug concentration curves for the TPV/r 500/200 dose compared to either 500/100 or 750/200 doses probably due to the balance of CYP3A induction and inhibition by tipranavir and ritonavir, respectively. Combining efficacy, tolerability and PK data, TPV/r 500/200 dose seems to be the appropriate choice for further study in Phase III clinical trials. However, a number of subjects may not achieve adequate concentrations at this dose (See a detailed exposure-response discussion in Dr. Zheng's Pharmacometric review).

The population pharmacokinetic portion of the report will be reviewed in a separate PPK study report.

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1182.55

TITLE: The pharmacodynamic/pharmacokinetic interaction of tipranavir and ritonavir with loperamide in healthy volunteers

OBJECTIVES: The objective of the study was to determine if the co-administration of loperamide (LOP) with tipranavir (TPV), ritonavir (RTV), or TPV plus RTV (TPV/r) caused a clinically significant change in the respiratory response to carbon dioxide (CO₂), defined as a 10% decrease in the area under the pharmacodynamic effect/time curve or at least a 25% decrease in at least one pharmacodynamic time point.

SUBJECTS AND STUDY DESIGN: This was a phase I, randomized, open-label and parallel-group drug interaction study conducted in healthy adult subjects. 128 subjects were screened for the study and 24 subjects entered the study. Briefly, all 24 subjects received LOP (16 mg) alone on Day 1 (9 AM). Subjects were then randomly assigned to Group I (TPV 750 mg BID) and Group II (RTV 200 mg BID). Days 2 and 3: no study drugs were administered. Days 4-8 and Day 9 at 8 AM: Group I received treatment with 5.5 days of TPV 750 mg BID, and Group II received treatment with 5.5 days of RTV 200 mg BID. Day 9: After the TPV or RTV dose at 8 AM, LOP (16 mg) was re-administered (at 9 AM). Days 10 and 11: no study drugs were administered. Day 12 through the morning of Day 22: Group I and II subjects received 10.5 days of TPV 750 mg/RTV 200 mg BID starting on 8 AM on Day 12. Day 22: after the TPV/r dose at 8 AM, LOP (16 mg) was taken by subjects in both Groups I and II at 9 AM.

Study drugs could be taken with a light snack except on PK sampling days. Subjects were required to fast for 12 hours before administration of the morning dose of study drug on the serial PK sampling days (Days 1, 9, 21 and 22). Subjects fasted for an additional 4h after dosing on these days.

The overall demographic characteristics of 24 subjects were as following: Male (58.3%) and female (41.7%); White (79.2%), Black (16.7%) and Asians (4.2%).

INVESTIGATOR AND STUDY LOCATION: []

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Imodium: 2 mg caplets.

PHARMACODYNAMIC ENDPOINTS: The primary endpoints for assessing the respiratory response to LOP alone and after administration of TPV, RTV, and TPV/r were: 1. The maximum decrease in the mean percentage baseline CO₂ response slope (observed at one of the examination time points during the 6-hour re-breathing test); 2. The 0-to-6 hour AUC (AUC_{0-6h}) for the percentage baseline CO₂ response slope profile. The secondary endpoint was papillary response to LOP after administration of TPV, RTV or TPV/r, as measured by the ratio between the diameter of the pupil and the iris. The pharmacodynamic measurements were conducted on Days 1, 9, and 22.

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were collected for assay of LOP concentrations during each period prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 9, 11, 12, 24, 36, 48 and 60 hours post dose on Days 1-3, Days 9-11 and Days 22-24. Blood samples were collected for assay of TPV and/or RTV concentrations during each period prior to the dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 13, 24, 36, 48 and 60 hours post dose on Days 9-11, Day 21 (up to 12 hours postdose) and Days 22-24. Additional trough samples were collected on Days 3, 6, 9, 12, and 13 prior to the morning dose (at time 0).

ASSAY: Samples were analyzed for TPV and RTV concentrations by [] using a validated high performance liquid chromatography [] method. The calibration curve ranged from — ng/mL to — ng/mL. Loperamide and N-demethyl-

loperamide concentrations were performed by \square using HPLC — method. The calibration curve ranged from — pg/mL to — ng/mL.

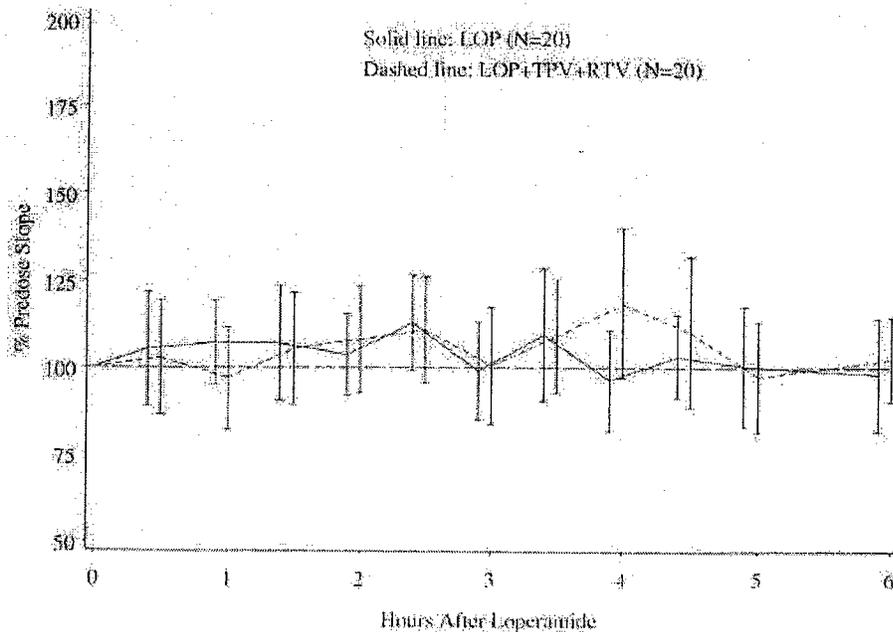
PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max} , C_{min} and AUC_{τ} were provided for loperamide and N-demethyl-loperamide (with and without TPV and /or RTV), and tipranavir and RTV (with and without LOP). The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACODYNAMIC RESULTS:

Table 1. Comparison of Mean AUC_{0-6h} for the Percentage CO_2 Response Slope

Mean AUC_{0-6h} for the Percentage CO_2 Response Slope		P-value	Geometric Mean Ratio (90% CI)
LOP Alone (Day 1) (n=20)	LOP+TPV/r (Day 22) (n=20)	0.8444	101.6% (87.1%, 116.0%)
622.39 (31.329)	633.036 (38.578)		
LOP Alone (Day 1) (n=10)	LOP+TPV (Day 9) (n=10)	0.838	99% (82.4%, 117.9%)
623.593 (48.513)	633.617 (59.519)		
LOP Alone (Day 1) (n=9)	LOP+RTV (Day 9) (n=9)	0.207	112% (94.7%, 132.6%)
608.515 (45.135)	687.774 (59.259)		

Figure 1. Mean Percentage Baseline Ventilatory Slope (± 2 SEM) for LOP Alone (Day 1) Compared with LOP+TPV/r (Day 22)

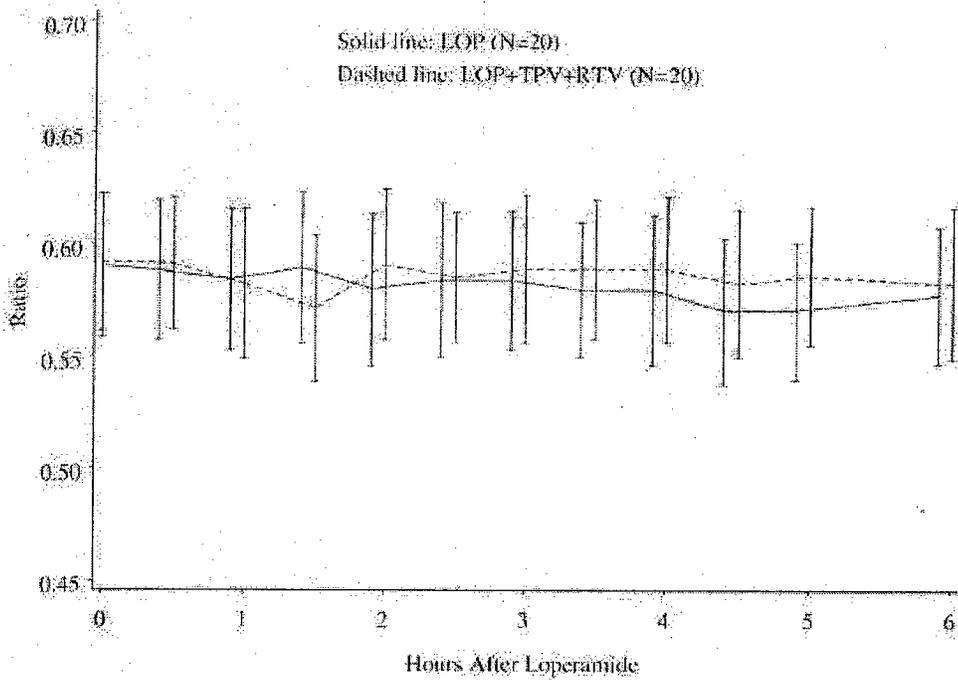


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Table 2. Baseline Pupillary Response Mean \pm SEM Prior to LOP Treatment on Day 1 (LOP Alone), Days 9 (LOP + TPV or RTV) and Day 22 (LOP + TPV/r)

Mean Pupil-to-Iris Diameter Ratio (\pm SEM)		
LOP (Day 1) (n=20)	LOP+TPV/r (Day 22) (n=20)	P -value
0.591 (0.016)	0.592 (0.015)	0.927
LOP (Day 1) (n=10)	LOP+TPV (Day 9) (n=10)	
0.574 (0.029)	0.561 (0.027)	0.160
LOP (Day 1) (n=9)	LOP+RTV (Day 9) (n=9)	
0.612 (0.015)	0.609 (0.016)	1.000

Figure 2. Mean Pupil-to-Iris Diameter ratio (± 2 SEM) Over 6 Hours of Testing with LOP Alone (Day 1) and LOP + TPV/r (Day 22)



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PHARMACOKINETIC RESULTS:

Table 3. Summary of Single Dose LOP Pharmacokinetics in the Absence and Presence of Steady-State TPV, RTV or TPV/r

LOP PK Parameter ¹	LOP alone (Day 1) ²	LOP + TPV (Day 9) ³	LOP + RTV (Day 9) ⁴	LOP + TPV/r (Day 22) ²
t _{max} (h)	4.6	3.2	6.1	7.2
C _{max} (ng/mL)	3.2	1.4	5.5	1.2
(pmol/mL)	6.6	2.8	11.4	2.6
AUC _{0-∞} (h•ng/mL)	58.3	22.0	121.1	28.8
(h•pmol/mL)	122.1	46.1	253.9	60.3
CL/F (L/h)	275	728	132	556
V (L)	6951	19961	4113	11394
Lambda z (h ⁻¹)	0.03952	0.03645	0.03213	0.04883
t _{1/2} (h)	17.5	19.0	21.6	14.2
	17.1 ⁵	18.4 ⁵	20.7 ⁵	14.0 ⁵

¹ Geometric mean.

² n=24.

³ n=12.

⁴ n=11.

⁵ Harmonic mean.

Table 4. Summary of Geometric Mean Ratios and 90% Confidence Intervals for Single Dose LOP Pharmacokinetic Parameters in the Absence vs. Presence of Steady-State TPV, RTV or TPV/r

Comparison	n	LOP AUC _{0-∞} (h•pmol/mL)			LOP C _{max} (pmol/mL)		
		% Change	Geom Mean Ratio	90% CI	% Change	Geom Mean Ratio	90% CI
Effect of TPV or RTV on LOP PK							
TPV subgroup: Day 1 vs. Day 9 (+TPV)	12	-63	0.37	(0.27, 0.51)	-58	0.42	(0.29, 0.62)
RTV subgroup: Day 1 vs. Day 9 (+RTV)	11	121	2.21	(1.53, 3.19)	83	1.83	(1.23, 2.73)
Effect of TPV/r on LOP PK							
Day 1 vs. Day 22 (+TPV/r)	24	-51	0.49	(0.40, 0.61)	-61	0.39	(0.31, 0.48)
Day 1 vs. Day 22 (TPV subgroup)	12	-55	0.45	(0.35, 0.59)	-64	0.36	(0.28, 0.46)
Day 1 vs. Day 22 (RTV subgroup)	12	-46	0.54	(0.38, 0.76)	-58	0.42	(0.28, 0.62)

Table 5. Summary of N-demethyl-loperamide after a Single Dose of LOP in the Absence and Presence of Steady-State TPV, RTV or TPV/r

N-demethyl-loperamide PK Parameter ¹	LOP alone (Day 1) ²	LOP + TPV (Day 9) ³	LOP + RTV (Day 9) ⁴	LOP + TPV/r (Day 22) ²
t _{max} (h)	6.8	6.6	9.9	12.9
C _{max} (ng/mL)	5.5	1.9	5.3	1.1
(pmol/mL)	11.8	4.1	11.4	2.4
AUC _{0-∞} (h•ng/mL)	227.4	64.4	309.8	51.9
(h•pmol/mL)	491.1	139.1	669.0	112.0
Lambda z (h ⁻¹)	0.02115	0.02312	0.01499	0.02563
t _{1/2} (h)	32.8	30.0	46.3	27.0
	32.0 ⁵	29.3 ⁵	42.0 ⁵	26.3 ⁵

¹ Geometric mean.

² n=24.

³ n=12.

⁴ n=11.

⁵ Harmonic mean.

Table 6. Summary of Geometric Mean Ratios and 90% Confidence Intervals for N-demethyl-loperamide Pharmacokinetic Parameters after a Single Dose LOP in the Absence vs. Presence of Steady-State TPV, RTV or TPV/r

Comparison	n	AUC _{0-∞} (h•pmol/mL)			C _{max} (pmol/mL)		
		% Change	Geom Mean Ratio	90% CI	% Change	Geom Mean Ratio	90% CI
Effect of TPV or RTV on N-demethyl-loperamide PK							
TPV subgroup: Day 1 vs. Day 9 (+TPV)	12	-72	0.28	(0.23, 0.33)	-66	0.34	(0.27, 0.43)
RTV subgroup: Day 1 vs. Day 9 (+RTV)	11	44	1.44	(1.00, 2.09)	-1	0.99	(0.78, 1.25)
Effect of TPV/r on N-demethyl-loperamide PK							
Day 1 vs. Day 22 (+TPV/r)	24	-77	0.23	(0.19, 0.27)	-79	0.21	(0.17, 0.25)
Day 1 vs. Day 22 (TPV subgroup)	12	-78	0.22	(0.18, 0.26)	-81	0.19	(0.15, 0.24)
Day 1 vs. Day 22 (RTV subgroup)	12	-76	0.24	(0.18, 0.33)	-78	0.22	(0.15, 0.32)

Figure 3. Comparison of Loperamide C_{max} after a Single Dose of Loperamide on Days 1, 9 and 22

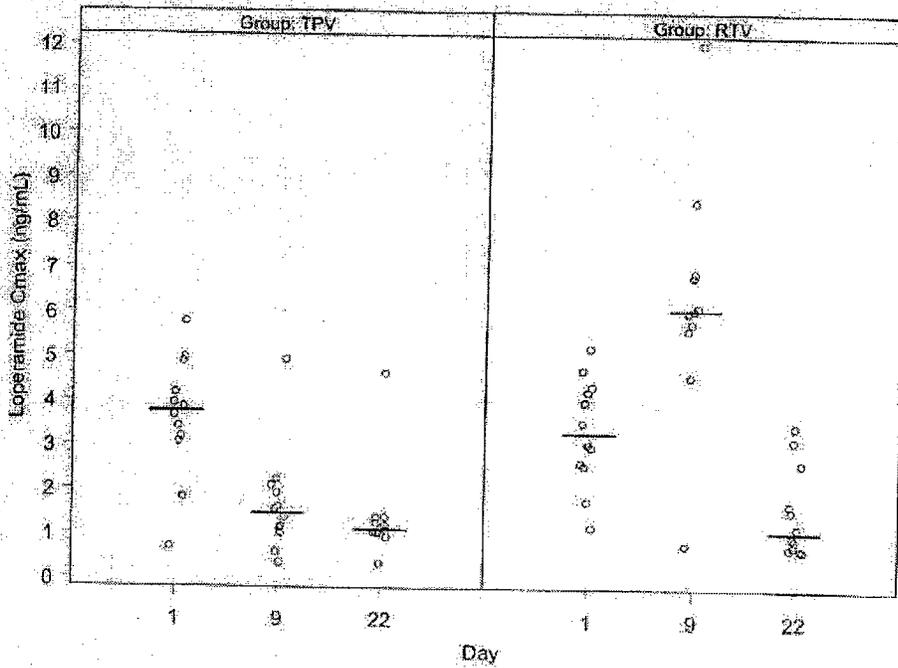


Figure 4. Comparison of Loperamide $AUC_{0-\infty}$ after a Single Dose of Loperamide on Days 1, 9 and 22

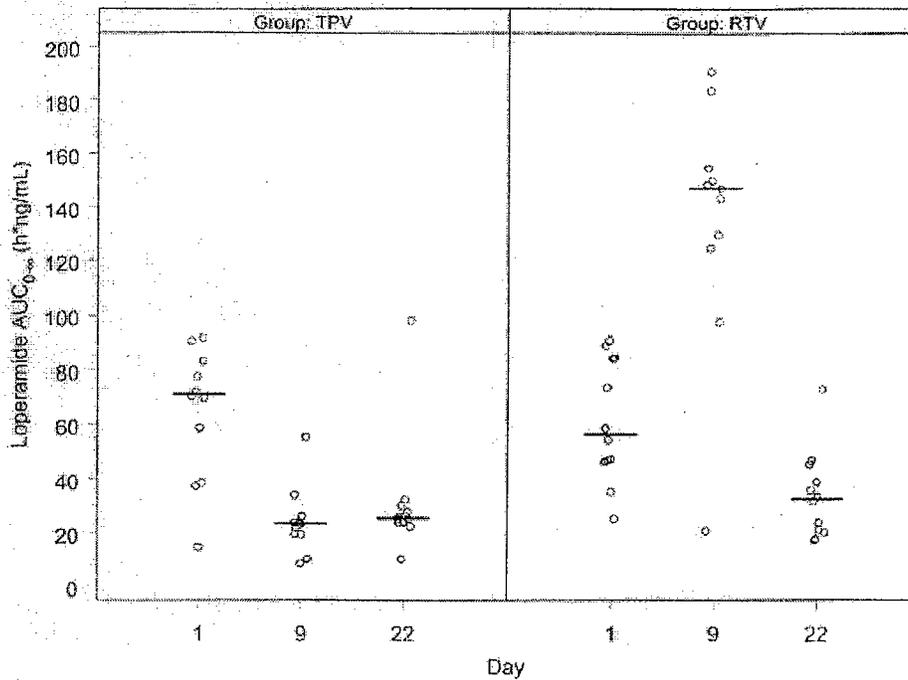
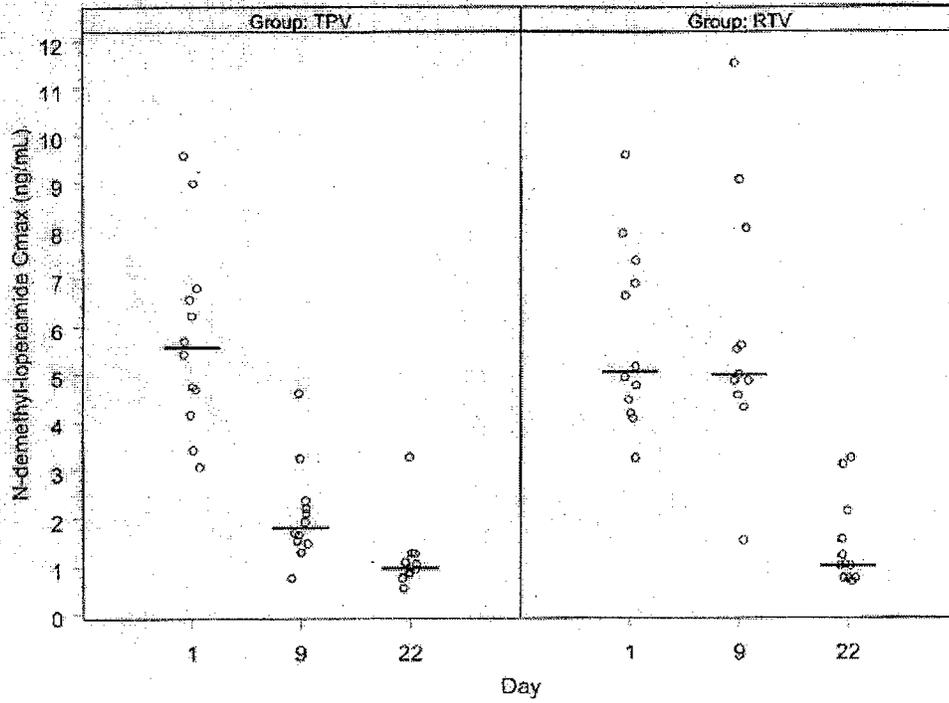


Figure 5. Comparison of N-demethyl-loperamide C_{max} after a Single Dose of Loperamide on Days 1, 9 and 22



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Figure 6. Comparison of N-demethyl-loperamide $AUC_{0-\infty}$ after a Single Dose of Loperamide on Days 1, 9 and 22

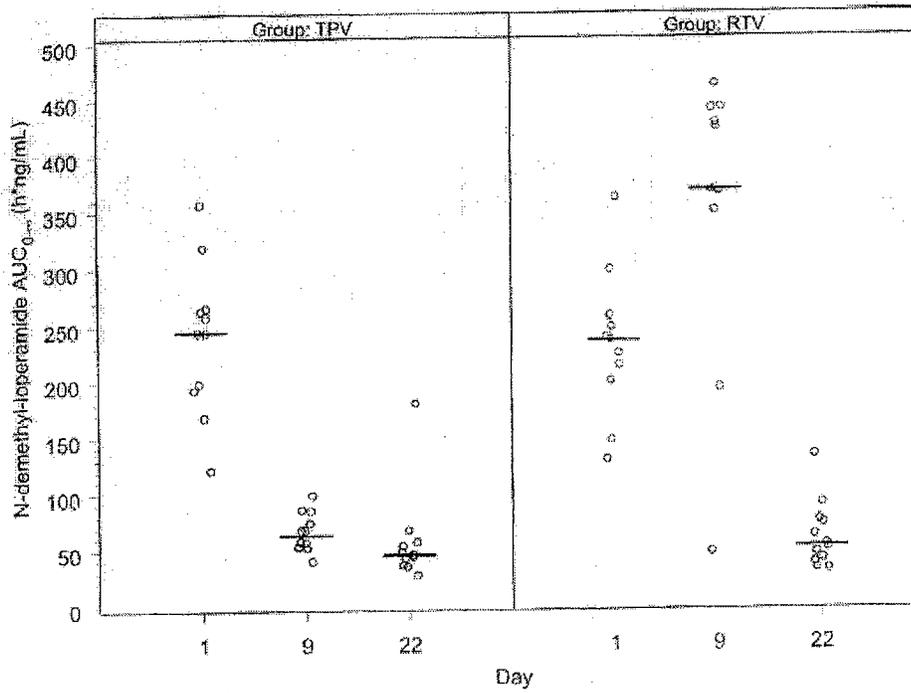


Table 7. Summary of TPV and RTV Steady-State Pharmacokinetics (Coadministered as TPV/r) in the Absence and Presence of Single –dose LOP

Pharmacokinetic Parameter ¹	TPV		RTV	
	TPV/r Alone (Day 21)	TPV/r + LOP ² (Day 22)	TPV/r Alone (Day 21)	TPV/r + LOP ² (Day 22)
t_{max} (h)	2.9	2.6	3.5	3.1
C_{max} ³	154.2	159.4	1.6	1.1
Cp_{12h} ²	37.8	28.0	0.045	0.031
AUC_{0-12h} ³	1040	1022	6.02	4.69
CL/F (L/h)	1.20	1.22	53.2	42.6
V (L)	7.7	6.9	89.4	130.9
$\lambda_{1/2}$ (h ⁻¹)	0.1545	0.1771	0.3718	0.3253
$t_{1/2}$ (h)	4.5	3.9	1.9	2.1
	4.2 ⁴	3.6 ⁴	1.8 ⁴	2.0 ⁴

¹ n = 24 subjects

² TPV, μ M; RTV, μ g/ml

³ TPV, h \cdot ng/ml; RTV, h \cdot pg/ml

⁴ Harmonic mean

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Table 8. Summary of Percentage Change (Day 21 to Day 22), Mean Ratios and 90% Confidence Interval for TPV and RTV Pharmacokinetic Parameters (Coadministered as TPV/r) in the Absence and Presence of Single –dose LOP

Parameter	n	TPV			RTV		
		% Change	Geom. Mean Ratio	90% CI	% Change	Geom. Mean Ratio	90% CI
Cp_{12h}	24	-26	0.74	(0.62, 0.88)	-30	0.70	(0.55, 0.87)
C_{max}	24	+3	1.03	(0.92, 1.17)	-28	0.72	(0.50, 1.04)
AUC_{0-12h}	24	-2	0.98	(0.86, 1.12)	-22	0.78	(0.59, 1.04)

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Figure 7. Effects of LOP on the TPV Pharmacokinetic Parameters C_{p12h} , C_{max} and AUC_{0-12h}

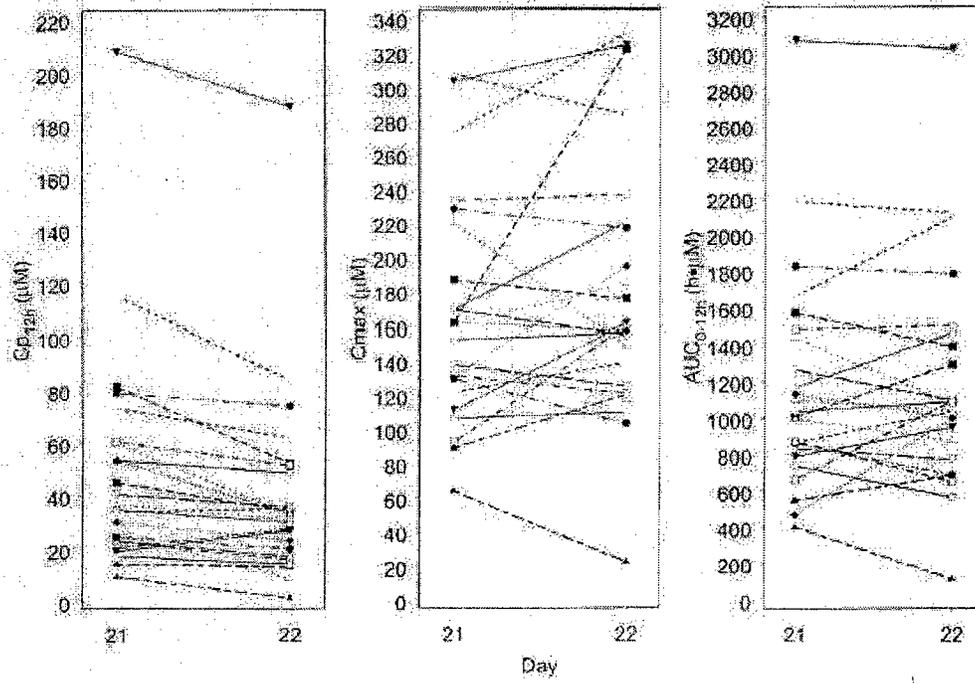
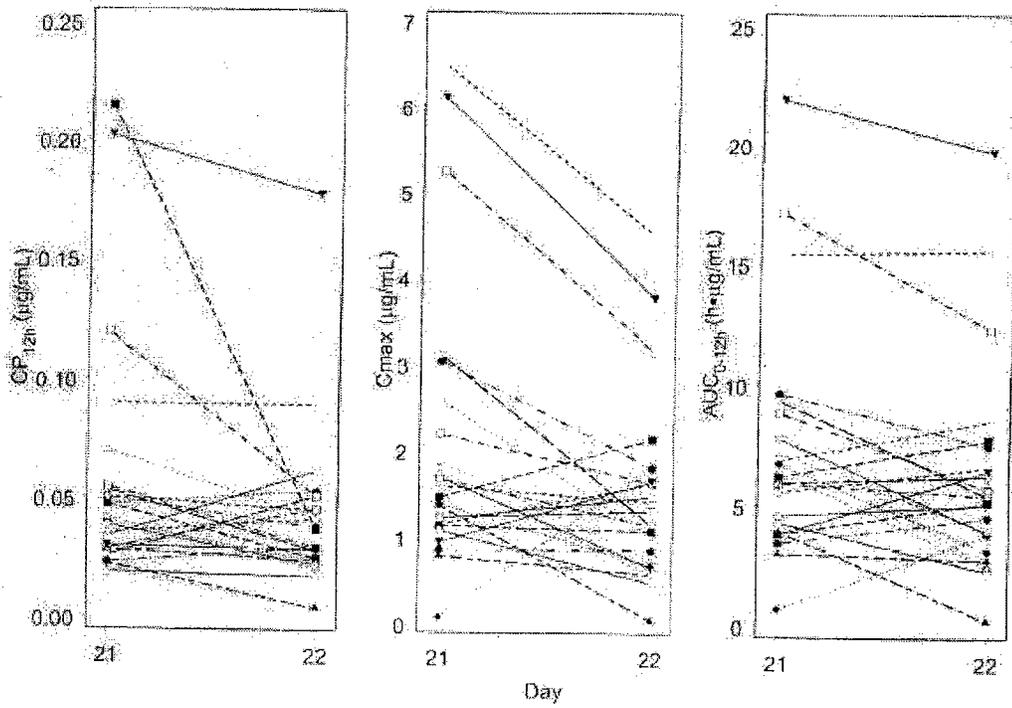


Figure 8. Effects of LOP on the RTV Pharmacokinetic Parameters C_{p12h} , C_{max} and AUC_{0-12h}



SAFETY RESULTS: No serious adverse events or deaths were reported during this study. No subjects had AEs leading to discontinuation of study treatment.

CONCLUSIONS AND DISCUSSION: The primary comparison of the pharmacodynamic response focused on the difference in response on Day 22 (combined effect of TPV/r with LOP) compared with the response on Day 1 (effect of LOP alone). Co-administration of LOP with TPV/r did not cause clinically relevant central CNS effects, as monitored by the respiratory responses of the AUC_{0-6h} for the percentage baseline CO_2 response profile or the difference between the LOP alone response profile and the LOP+TPV/r response profile (Geometric mean ratio and 90% CI: 101.6% (87.1%, 116.0%)). In addition, the papillary response (pupil-to-iris diameter ratio) results supported the observation that there were no CNS effects of coadministration of LOP+TPV/r.

The pharmacokinetic data demonstrated substantial changes in LOP exposure when LOP coadministered with TPV, RTV or TPV/r. Coadministration of LOP with steady-state TPV (Day 9) or TPV/r (Day 22) resulted in 63% and 51% decrease in LOP AUC, respectively, and 58% and 61% decrease in LOP C_{max} , respectively. However, coadministration of LOP with steady-state RTV (Day 9) resulted increases in AUC (121%) and C_{max} (83%). The effect of single-dose LOP on the steady-state pharmacokinetics of TPV in combination with ritonavir was less substantial but the clinical relevance is unknown. For TPV, only trough concentration was decreased 26% while C_{max} and AUC_{0-12h} remained unchanged. For RTV, trough concentration, C_{max} and AUC_{0-12h} were decreased by 30%, 28% and 22%, respectively. The exact mechanism of LOP and TPV interaction is unknown at the moment. Possible explanations include: 1. LOP is a known substrate of P-gp and P-gp plays a significant role in LOP's elimination. TPV may be a potent P-gp inducer and the presence of low dose of ritonavir could not compensate the induction effect, thus chronic administration of TPV or TPV/r reduced LOP's systemic exposure. 2. Physical and chemical-based formulation interaction of TPV, ritonavir and LOP resulted in decreased absorption of LOP. The dose of LOP used in this study was the maximum recommended daily dose, the clinical relevance of decrease in plasma exposure of LOP is unknown.

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DM-04-1070

TITLE: Nonlinear Mixed Effects Modeling of the Steady-State Pharmacokinetics of Tipranavir for Adult Healthy Volunteers and HIV+ Patients Receiving TPV/r 500 mg/200 mg bid

OBJECTIVES: To characterize the steady-state pharmacokinetics of tipranavir 500 mg bid coadministered with ritonavir 200 mg bid to adults. In addition, the effects of the demographic parameters HIV status, gender, race, age, and body weight on the population pharmacokinetic parameters of tipranavir were investigated.

SUBJECTS AND STUDY DESIGN: Tipranavir plasma concentrations collected after at least 6 days of multiple dosing with TPV/r 500 mg/200 mg bid were pooled from studies involving HIV positive patients with background antiretroviral therapy (BI Protocols 1182.51 and 1182.52), and healthy subjects (BI Protocols 1182.05, 1182.21, 1182.32 and 1182.44). The pooled study dataset was comprised of 79.1% male and 20.9% female; 85% white, 11% black, and 4% other race. The age of the study population ranged from 18 to 73 years (mean 41.7 ± 11.0) and body weight ranged from 47 to 123 kg (mean 75.3 ± 13.3). There were 64.2% HIV+ patients and 35.8% HIV-subjects. Nonlinear mixed effects modeling was performed on the pooled dataset using the computer program NONMEM. Tipranavir concentration-time data were fit to a one-compartment open model with first order absorption parameterized in terms of absorption rate constant (K_a), apparent oral clearance (CL), and volume of distribution (V). Univariate analysis was initially performed to determine the potential covariates, and intermediate and final models were built with covariates included or removed. For each analysis step comparing the nested models, the improvement in fit was mainly assessed by the change in the NONMEM minimum objective function value, and by the examination of scatterplots of observed versus predicted (population and individual) concentrations, and predicted concentration versus weighted residuals.

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

PHARMACOKINETIC SAMPLE COLLECTION: A total of 1866 tipranavir concentrations from 187 individuals were included in the analysis. These concentrations were obtained according to a fixed time sampling or a pseudorandom time sampling at the scheduled visits. These concentrations were fairly well distributed over the 12-hour dosing interval.

BI Protocol 1182.05: For this population pharmacokinetic analysis, the morning pre-dose sample from Study Day 25 and the steady-state PK profile from Study Day 25 were used (TPV/r 500 mg/200 mg). A total of 11 subjects (8 females, 3 males) contributed 132 plasma tipranavir concentrations (12 samples per subject: Day 25: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose) to the tipranavir plasma sample population. The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

BI Protocol 1182.21: For this population pharmacokinetic analysis, morning pre-dose samples from Study Day 19 and 20 and the steady-state PK profiles from Study Day 19 were used (TPV/r 500 mg/200 mg alone). A total of 23 subjects (12 females, 11 males) contributed 299 plasma tipranavir concentrations (13 samples per subject: Day 19: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose; Day 20, predose) to the tipranavir plasma sample population. The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

BI protocol 1182.32: For this population pharmacokinetic analysis, the steady-state morning predose sample and PK profile from Study Day 7 for the control subjects were used. A total of 9 subjects (1 female, 8 males) contributed 108 plasma tipranavir **concentrations (12 samples per**

subject: Day 7: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose) to the tipranavir plasma sample population. The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

BI Protocol 1182.44: For this population pharmacokinetic analysis, morning pre-dose samples from Study Day 14 and 15 and the steady-state PK profiles from Study Day 14 were used (TPV/r 500 mg/200 mg alone). A total of 24 subjects (4 females, 20 males) contributed 309 plasma tipranavir concentrations (13 samples per subject: Day 14: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose; Day 15, predose) to the tipranavir plasma sample population (Subjects 2002, 2009 and 2015 discontinued the study after the Study Day 14 12-h sample and no Study Day 15 pre-dose sample was available). The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

BI protocol 1182.51: For this population pharmacokinetic analysis only patients receiving TPV/r 500 mg/200 mg were included in the dataset. All patients had morning trough samples collected prior to drug administration on Study Days 7, 14, 21 and 28 while a subset of patients had post-dose PK profiles collected on Study Days 14, 28 and at Week 24/End of Trial (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose). A total of 48 patients (2 females, 46 males) contributed 808 plasma tipranavir concentrations to the tipranavir plasma sample population (1 patient contributed 1 PK profile + troughs; 8 patients contributed 2 PK profiles + troughs each; 13 patients contributed 3 PK profiles + troughs each; 2 patients contributed 2 troughs each; 3 patients contributed 3 troughs each; 21 patients contributed 4 troughs each). The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

BI Protocol 1182.52: For this population pharmacokinetic analysis only patients receiving TPV/r 500 mg/200 mg were included in this dataset. All patients had morning trough samples collected prior to drug administration on Study Days 7 and 14 and a subset of patients had a maximum of three post-dose samples collected according to the schedule listed below:

Month of Birth	Sample Collection Window (hours after TPV/r administration)		
	Sample 1	Sample 2	Sample 3
January	0.5 - 1	2 - 4	6 - 8
February	1 - 1.5	3 - 5	7 - 9
March	1.5 - 2	4 - 6	8 - 10
April	0.5 - 1	2 - 4	6 - 8
May	1 - 1.5	3 - 5	7 - 9
June	1.5 - 2	4 - 6	8 - 10
July	0.5 - 1	2 - 4	6 - 8
August	1 - 1.5	3 - 5	7 - 9
September	1.5 - 2	4 - 6	8 - 10
October	0.5 - 1	2 - 4	6 - 8
November	1 - 1.5	3 - 5	7 - 9
December	1.5 - 2	4 - 6	8 - 10

A total of 72 patients (12 females, 60 males) contributed 210 plasma tipranavir concentrations to the tipranavir plasma sample population (25 patients had pseudorandom post-dose sampling). The dates and clock-times of drug administrations and blood sample collections were recorded in the CRFs and used in the NONMEM analysis to describe the temporal component of the plasma tipranavir concentration-time relationship.

PLASMA BIOANALYTICAL ASSAY: Plasma concentrations of tipranavir were determined by a validated [] method at [] for BI Protocols 1182.05, 1182.21, 1182.32 and 1182.44 and a cross-validated method at [] for BI Protocols 1182.51 and 1182.52. The unit of measure for plasma tipranavir concentration was ng/mL. The limits of quantitation for the bioanalytical assay at [] were [] ng/mL (high range) and [] ng/mL (low range). For the bioanalytical assay at [] the limits of quantitation were [] ng/mL (BI 1182.51) and [] ng/mL (BI1182.52). The highest mean accuracy of QC samples was 13% and the highest precision of QC samples was []

POPULATION PHARMACOKINETIC ANALYSIS: The software package NONMEM® (Nonlinear Mixed Effects Model; Version V Level 2.1; double precision modules; [] was used for the population pharmacokinetic analysis.

NONMEM describes the observed concentration-time data in terms of:

1. A number of fixed effect parameters, θ , which may include the mean values of the relevant base pharmacokinetic model parameters, or a number of parameters which relate the structural model parameters to demographic and other covariates.
2. Two types of random effect parameters: (a) ω^2 : the variances of the interindividual variability (η) within the population, and (b) σ^2 : the variances of the residual intraindividual variability (ϵ) due to random fluctuations in an individual's parameter values, measurement error, model misspecification, and all sources of error not accounted for by the other parameters. The population or average values of the parameters, θ , the interindividual variances, ω^2 , and the residual variance, σ^2 , are estimated by NONMEM. Subject specific true values of η are obtained by NONMEM by including the first order conditional estimation (FOCE) option on the \$ESTIMATION record (METHOD=CONDITIONAL). The INTERACTION and REPEAT options also were included which take into account η - ϵ interaction and repeating the search with initial estimates that were the final estimates of the revised scaled transformed parameters from the first search rescaled to 0.1, respectively. These parameters are empirical Bayesian estimates of the individual's true parameters based on the population parameters and the individual's observed concentrations.

Tabulations, statistical and graphical summaries were produced with WinNonlin Professional v4.0 (Pharsight Corporation, Mountain View CA), SAS v8.02 (SAS Institute, Cary NC) and S-PLUS v6.2 (Insightful Corp., Seattle WA).

Pharmacokinetic Model Building: A one-compartment open model with first order absorption was evaluated as the base model. Individual subject pharmacokinetic parameters were described by the following equations:

$$Ka = \theta_{Ka} \cdot e^{\eta_1}$$

$$CL = \theta_{CL} \cdot e^{\eta_2}$$

$$V = \theta_V \cdot e^{\eta_3}$$

where Ka is the first order absorption rate constant, CL is the apparent oral clearance, V is the apparent volume of distribution, θ is the population mean estimate (or typical value) of the corresponding pharmacokinetic parameter, and η 's are the associated interindividual variability. NONMEM library subroutine ADVAN2 TRANS2 was used.

The intraindividual residual variability of tipranavir plasma concentration was estimated using a proportional error model, as described by the following equation:

$$Cp_{ij} = \tilde{Cp}_{ij} \cdot (1 + \varepsilon_{ij})$$

where Cp_{ij} is the observed value of the j^{th} plasma concentration of individual i ; \tilde{Cp}_{ij} is the predicted j^{th} plasma concentration of individual i ; and ε_{ij} is a random variable which represents the discrepancy between the observed and predicted j^{th} concentration.

The following criteria were considered to determine the best model:

1. The minimum objective function value (OFV) of the best model should be significantly smaller than the alternative model(s) based on the maximum likelihood ratio (MLR) test.

The MLR test was applied when the test models fulfilled the nested full/reduced model definition. A full model can be made equivalent to a reduced model by setting a parameter to a fixed value. The change in OFV between the two nested models is approximately χ^2 distributed with degree of freedom equal to the number of parameters which are set to a fixed value in the reduced model. A decrease of 3.84 units in the OFV was considered statistically significant ($p < 0.05$) for addition of one parameter during the development of the model.

2. The observed and predicted plasma concentrations were more randomly distributed across the line of unity for the preferred model.

3. The weighted residuals show less systematic distribution against covariates for the preferred model.

Evaluation of Potential Covariates: Following the determination of the base population pharmacokinetic model, potential covariates were examined to determine whether they improved the overall fit and reduced variability in the model. These covariates included gender, age, body weight, race and HIV status. Each covariate was added to the base model, and the resulting univariate model was then compared to the reduced model for significant improvement in fit. Covariates producing an improvement were then added to the base model as a group or as a single entity in a stepwise manner. Remaining covariates comprise the final model. The importance of each covariate included in the final model was then investigated by means of backwards elimination. Each of the covariates included in the final model was removed, and the resulting objective function value of the reduced model was compared to that of the full model.

Estimation of Individual-Specific Parameters: Individual-specific values of each pharmacokinetic parameter were obtained by Bayesian analysis with the final model. The following steady-state pharmacokinetic parameters could subsequently be calculated for each individual according to the following equations based on compartment modeling theory.

$$Ke = \frac{CL}{V}$$

$$t_{1/2} = \frac{0.693}{Ke}$$

$$AUC = \frac{Dose \cdot 1000}{CL}$$

$$t_{max} = \frac{1}{Ka - Ke} \cdot \ln \left[\frac{Ka \cdot (1 - e^{-Ke \cdot \tau})}{Ke \cdot (1 - e^{-Ka \cdot \tau})} \right]$$

$$C_{max} = \frac{Dose \cdot 1000}{V} \cdot \left(\frac{1}{1 - e^{-Ke \cdot \tau}} \right) \cdot e^{-Ke \cdot t_{max}}$$

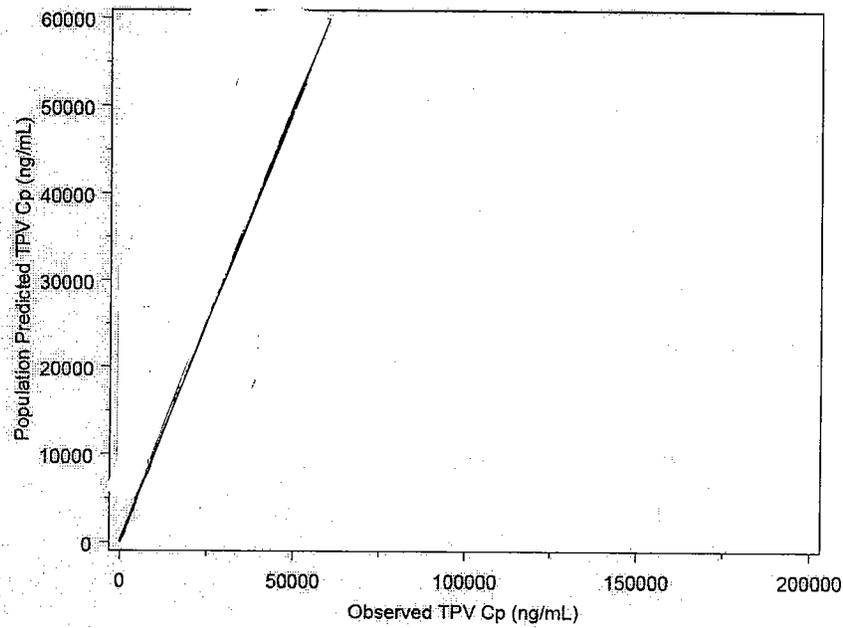
$$C_{min} = \frac{Ka \cdot Dose \cdot 1000}{V \cdot (Ka - Ke)} \cdot \left[\left(\frac{1}{1 - e^{-Ke \cdot \tau}} \right) \cdot e^{-Ke \cdot \tau} - \left(\frac{1}{1 - e^{-Ka \cdot \tau}} \right) \cdot e^{-Ka \cdot \tau} \right]$$

POPULATION PHARMACOKINETIC RESULTS:

Base Model:

A one-compartment model was fit to the plasma tipranavir concentration-time data, parameterized in terms of apparent oral clearance (CL, in L/h), apparent volume of distribution (V, in L), and absorption rate constant (Ka, in h⁻¹). Individual variability of each pharmacokinetic parameter was described by an exponential error model. A proportional error model was found to adequately describe the error in the data.

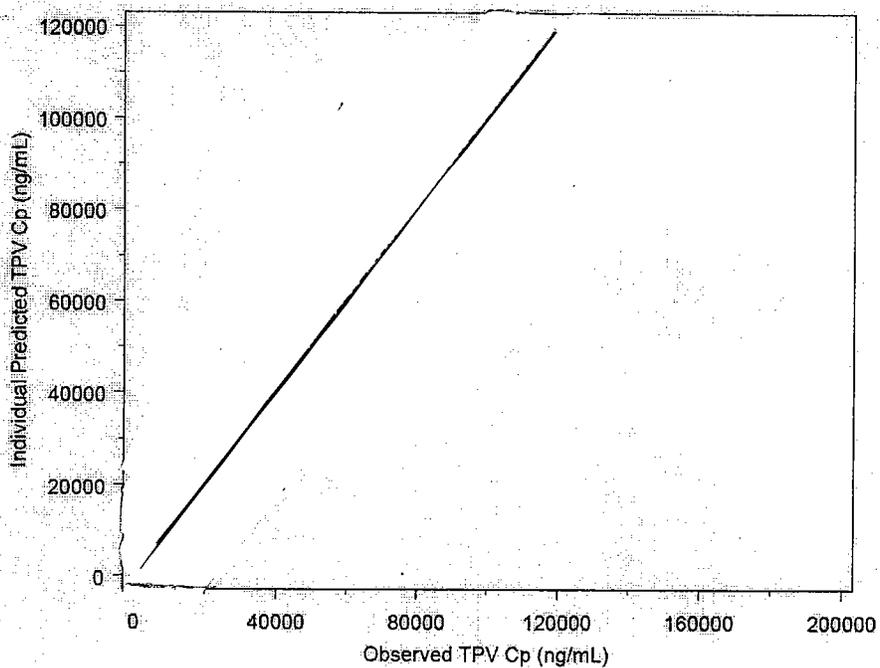
Figure 1. Base model: predicted population tipranavir Cp (PRED) vs. observed tipranavir Cp (DV)



Note: The solid line represents the line of identity.

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Figure 2. Base model: predicted individual tipranavir Cp (IPRED) vs. observed tipranavir Cp (DV)



Note: The solid line represents the line of identity.

Figure 3. Base model: weighted residual (WRES) vs. observed tipranavir Cp (DV)

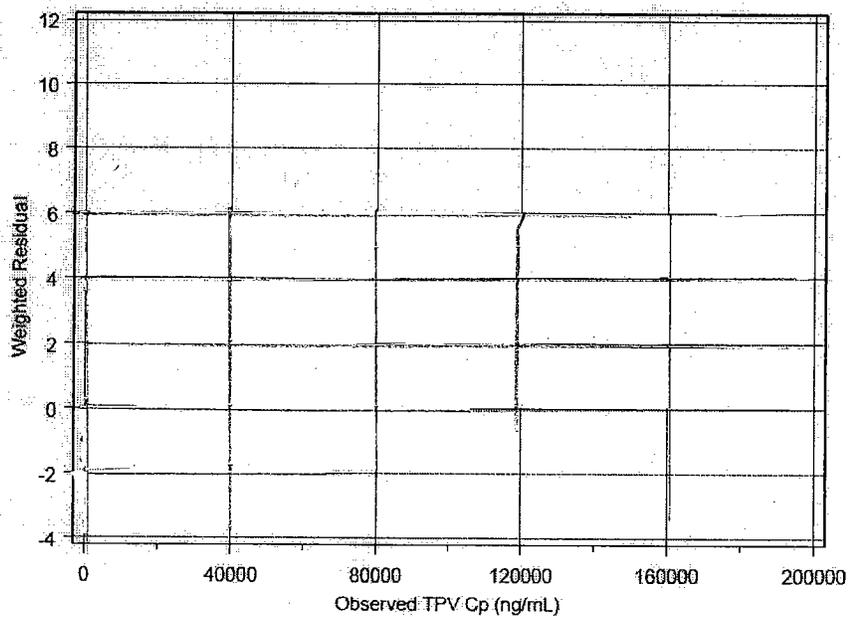
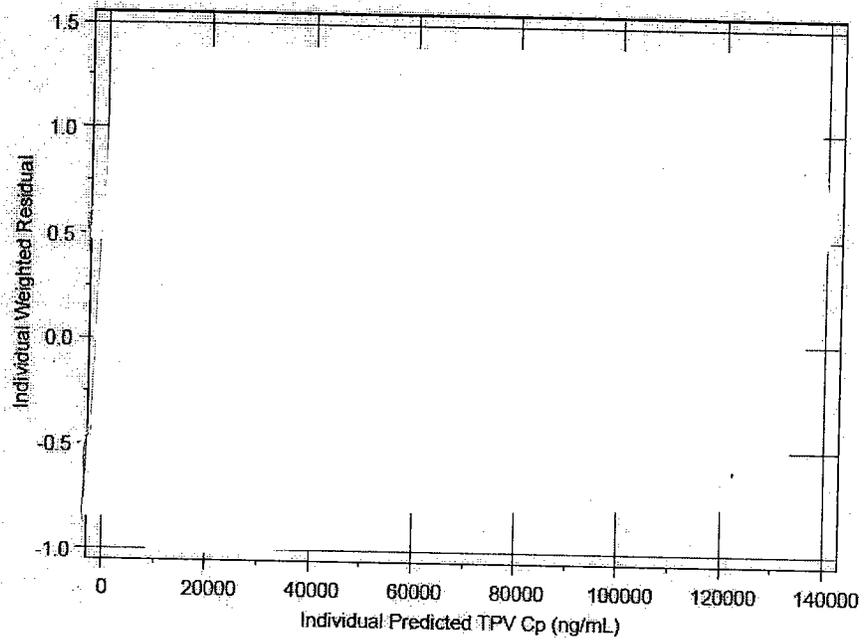


Figure 4. Base model: individual weighted residual (IWRES) vs. individual predicted tipranavir Cp (IPRED)



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Univariate Analysis:

Following the determination of the base population model, potential covariates were examined to determine whether they improved the overall fit and reduced variability in the model. These covariates included gender, age, race, body weight, body surface area and HIV status.

Table 1. Univariate analysis of the potential covariates for tipranavir pharmacokinetic parameter typical values

Model No.	Parameter	Covariate	Equations Used	OFV	Change in OFV*
Base	Ka, CL, V	---	$Ka = \theta_{Ka}$, $CL = \theta_{CL}$, $V = \theta_V$	36978.576	n/a
U1	CL	BSA	$CL = \theta_{CL} \cdot (1 + \theta_{CBSA} \cdot CBSA)$, where $CBSA = -1 + (BSA/1.73)$	36947.457	-31.119
U2	CL	WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CWT} \cdot (CWT))$, where $CWT = -1 + (WTKG/70)$	36948.457	-30.119
U3	CL	SEX	$CL = \theta_{CL} \cdot (1 + \theta_{Sex} \cdot SEX)$	36965.490	-13.086
U4	V	SEX	$V = \theta_V \cdot (1 + \theta_{Sex} \cdot SEX)$	36966.782	-11.794
U5	V	HIV	$V = \theta_V \cdot (1 + \theta_{HIV} \cdot HIV)$	36967.291	-11.285
U6	CL	HIV	$CL = \theta_{CL} \cdot (1 + \theta_{HIV} \cdot HIV)$	36970.081	-8.495
U7	V	WTKG	$V = \theta_V \cdot (1 + \theta_{CWT} \cdot (CWT))$, where $CWT = -1 + (WTKG/70)$	36974.081	-4.495
U8	CL	RACE	$CL = \theta_{CL} \cdot 1$, for White $CL = \theta_{CL} \cdot \theta_{Black}$, for Black $CL = \theta_{CL} \cdot \theta_{Others}$, for Others	36975.574	-3.002
U9	Ka	HIV	$Ka = \theta_{Ka} \cdot (1 + \theta_{HIV} \cdot HIV)$	36976.985	-1.591
U10	CL	AGE	$CL = \theta_{CL} \cdot (1 + \theta_{CAGE} \cdot (CAGE))$, where $CAGE = -1 + (AGE/40)$	36978.286	-0.290
U11	CL, V	WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CWT} \cdot (CWT))$; $V = \theta_V \cdot (1 + \theta_{CWT} \cdot (CWT))$	36935.453	-13.004 (to U2)

* Comparing to the base unless indicated.

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Final Model Building:

Based on the univariate analysis results, significant covariates were added to the base model to assess their effect on clearance and volume of distribution. The full fixed effects models were built by eliminating or adding the significant covariates sequentially. A covariate was included in the full model if it improved the overall fit and reduced variability. Model 10 was considered as the final model with all remaining covariates evaluated by means of backwards elimination.

Table 2. List of models in the multivariate analysis of the potential covariates for tipranavir pharmacokinetic parameter typical values

No.	Parameter	Covariate	Equations Used	OFV	Change in OFV*
Base	K_a , CL , V	---	$CL = \theta_{CL}$; $V = \theta_V$; $K_a = \theta_{Ka}$	36978.576	---
1	K_a	---	$K_a = \theta_{Ka}$	36931.447	---
	CL	$\frac{+HIV, +AGE, +WTKG, +SEX}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{AGE} \cdot AGE) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG) \cdot (1 + \theta_{CL}^{SEX} \cdot SEX)$		
	V	$\frac{+WTKG}{-}$	$V = \theta_V \cdot (1 + \theta_V^{WTG} \cdot WTKG)$		
2	K_a	---	$K_a = \theta_{Ka}$	36943.029	11.582 (to No. 1)
	CL	$\frac{HIV, AGE, WTKG, SEX}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{AGE} \cdot AGE) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG) \cdot (1 + \theta_{CL}^{SEX} \cdot SEX)$		
	V	$\frac{-WTKG}{-}$	$V = \theta_V$		
3	K_a	---	$K_a = \theta_{Ka}$	36934.649	3.202 (to No. 1)
	CL	$\frac{-HIV, AGE, WTKG, SEX}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{AGE} \cdot AGE) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG) \cdot (1 + \theta_{CL}^{SEX} \cdot SEX)$		
	V	$\frac{WTKG}{-}$	$V = \theta_V \cdot (1 + \theta_V^{WTG} \cdot WTKG)$		
4	K_a	---	$K_a = \theta_{Ka}$	36931.447	0 (to No. 1)
	CL	$\frac{HIV, AGE, WTKG, SEX}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG) \cdot (1 + \theta_{CL}^{SEX} \cdot SEX)$		
	V	$\frac{WTKG}{-}$	$V = \theta_V \cdot (1 + \theta_V^{WTG} \cdot WTKG)$		
5	K_a	---	$K_a = \theta_{Ka}$	36931.612	0.165
	CL	$\frac{HIV, WTKG, SEX}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG)$		
	V	$\frac{WTKG}{-}$	$V = \theta_V \cdot (1 + \theta_V^{WTG} \cdot WTKG)$		
6	K_a	---	$K_a = \theta_{Ka}$	36935.453	3.841
	CL	$\frac{-HIV, WTKG}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG)$		
	V	$\frac{WTKG}{-}$	$V = \theta_V \cdot (1 + \theta_V^{WTG} \cdot WTKG)$		
7	K_a	---	$K_a = \theta_{Ka}$	36943.634	12.022 (to No. 5)
	CL	$\frac{HIV, WTKG}{-}$	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{WTG} \cdot WTKG)$		
	V	$\frac{-WTKG}{-}$	$V = \theta_V$		

Table 2. List of models in the multivariate analysis of the potential covariates for tipranavir pharmacokinetic parameter typical values (continued)

No.	Parameter	Covariate	Equations Used	OFV	Change in OFV ^a
8	K_e		$K_e = \theta_{K_e}$	36911.297	-20.315 (to No. 5)
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	WTKG, -HIV	$V = \theta_V \cdot (1 + \theta_V^{CWT} \cdot CWT) \cdot (1 + \theta_V^{HIV} \cdot HIV)$		
9	K_e		$K_e = \theta_{K_e}$	36906.247	-5.05
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	WTKG, HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{CWT} \cdot CWT) \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{Sex} \cdot Sex)$		
10 ^b	K_e		$K_e = \theta_{K_e}$	36908.240	1.993
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	WTKG, HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{Sex} \cdot Sex)$		
11	K_e		$K_e = \theta_{K_e}$	36906.844	-1.396 (to No. 10)
	CL	HIV, WTKG, +RACE	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT) \cdot (1 + \theta_{CL}^{Race})$ Where $\theta_{CL}^{Race} = \theta_{CL}^{White}, \theta_{CL}^{Black}, \text{ or } \theta_{CL}^{Others}$		
	V	HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{Sex} \cdot Sex)$		
12	K_e		$K_e = \theta_{K_e}$	36918.193	9.953 (to No. 10)
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{Sex} \cdot Sex)$		
13	K_e		$K_e = \theta_{K_e}$	36932.715	24.475 (to No. 10)
	CL	HIV, -WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV)$		
	V	HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{Sex} \cdot Sex)$		
14	K_e		$K_e = \theta_{K_e}$	36930.264	22.024 (to No. 10)
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	-HIV, SEX	$V = \theta_V \cdot (1 + \theta_V^{Sex} \cdot Sex)$		

Table 2. List of models in the multivariate analysis of the potential covariates for tipranavir pharmacokinetic parameter typical values (continued)

No.	Parameter	Covariate	Equations Used	OFV	Change in OFV ^a
15	K_e		$K_e = \theta_{K_e}$	39919.204	10.964 (to No. 10)
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	HIV, -SEX	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV)$		
16	K_e		$K_e = \theta_{K_e}$	36908.230	-0.010 (to No. 10)
	CL	HIV, WTKG	$CL = \theta_{CL} \cdot (1 + \theta_{CL}^{HIV} \cdot HIV) \cdot (1 + \theta_{CL}^{CWT} \cdot CWT)$		
	V	HIV, SEX, +AGE	$V = \theta_V \cdot (1 + \theta_V^{HIV} \cdot HIV) \cdot (1 + \theta_V^{AGE} \cdot CAGE)$		

Note: Newly added or removed variable is italicized and underlined.

^a Comparing to the preceding model unless indicated in parenthesis.

^b Final population PK model

Table 3. Structural population mean parameters of the final model

No.	θ	Unit	Final Estimate	% RSE ^a
1	θ_{k_a}	h ⁻¹	0.499	10.6
2	θ_{CL}	L/h	0.947	4.5
3	θ_V	L	5.35	9.3
4	θ_{CL}^{HIV}	--	0.188	35.3
5	θ_{CL}^{Age}	--	Fixed to 0	n/a
6	θ_{CL}^{Weight}	--	0.757	23.4
7	θ_{CL}^{Gender}	--	Fixed to 0	n/a
8	θ_V^{Weight}	--	Fixed to 0	n/a
9	θ_V^{HIV}	--	0.445	25.4
10	θ_V^{Gender}	--	0.323	36.2

^a%RSE (% Relative SE), standard error of the parameter estimate divided by the parameter estimate times 100.

Table 4. Magnitude of interindividual variability

No.		Final Estimate ω^2	η (%CV) ^a	%RSE ^b
1	$\omega_{k_a}^2$	0.284	53.3	40.1
2	ω_{CL}^2	0.105	32.4	14.2
3	ω_V^2	0.0201	14.2	55.7

^a η : Square root of ω^2 (i.e. SD) times 100, and expressed as %CV.

^b%RSE (% Relative SE), standard error of the parameter estimate divided by the parameter estimate times 100.

Table 5. Magnitude of residual variability

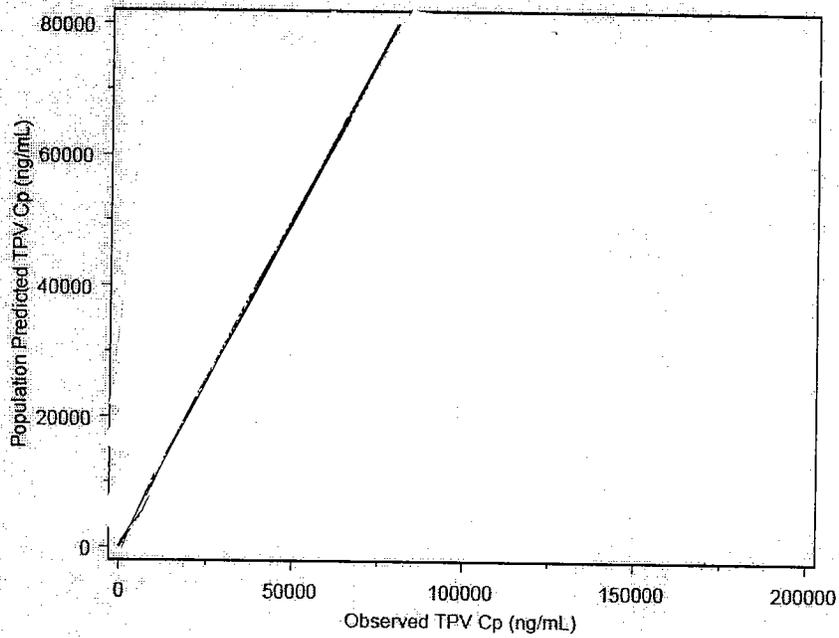
No.		Final Estimate σ^2	ϵ (%CV) ^a	%RSE ^b
1	σ_1^2	0.0810	28.5	8.0

^a ϵ : Square root of σ^2 (i.e. SD) times 100, and expressed as %CV.

^b%RSE (% Relative SE), standard error of the parameter estimate divided by the parameter estimate times 100.

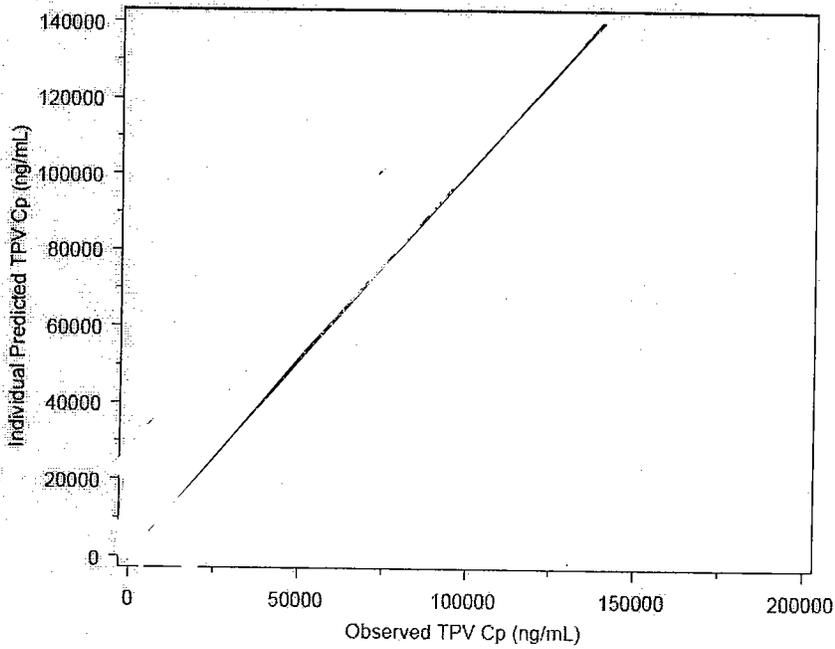
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Figure 5. Final model: population predicted tipranavir Cp (PRED) vs. observed tipranavir Cp (DV)



Note: The solid line represents the line of identity.

Figure 6. Final model: individual predicted tipranavir Cp (IPRED) vs. observed tipranavir Cp (DV)



Note: The solid line represents the line of identity.

Population analysis demonstrated that tipranavir apparent oral clearance (CL) can be significantly affected by body weight ($p < 0.001$) and HIV status ($p < 0.005$). Body weight caused the more prominent linear increase (75.7%) in CL, whereas HIV+ patients exhibited a mild increase (18.8%) in CL when compared to HIV- subjects. Apparent volume of distribution (V) was moderately increased in HIV+ patients (44.5%, $p < 0.001$) and in males (32.3%, $p < 0.001$). Since HIV+ patients exhibited not only higher CL, but also larger V, they tended to have lower tipranavir concentrations when compared to HIV- subjects. The covariates age, gender or race were shown to have no or little effect on the clearance of tipranavir and no effects of age or body weight were shown on the volume of distribution of tipranavir.

The final population model can be best expressed by the following equations:

$$\hat{K}_a \text{ (h}^{-1}\text{)} = 0.499$$

$$\hat{CL} \text{ (L/h)} = 0.947 \cdot (1 + 0.188 [\text{HIV}]) \cdot (1 + 0.757 \cdot \text{CWT})$$

where HIV = 0 for HIV- subjects or 1 for HIV+ patients

and CWT = $-1 + [\text{Weight (Kg)} / 70]$.

$$\hat{V} \text{ (L)} = 5.35 \cdot (1 + 0.445 [\text{HIV}]) \cdot (1 + 0.323 [\text{Gender}])$$

where HIV = 0 for HIV- subjects or 1 for HIV+ patients

and Gender = 0 for females or 1 for males.

Tipranavir Steady-State Model-Derived Pharmacokinetics:

Table 6. Summary of the NONMEM model-derived pharmacokinetic parameters for female and male HIV+ patients and HIV- subjects.

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

Note: Pharmacokinetic parameters are reported as geometric mean, except t_{1/2} which is reported as the arithmetic mean

CONCLUSIONS:

In conclusion, the steady-state population pharmacokinetics of tipranavir 500 mg bid co-administered with low-dose ritonavir 200 mg bid can be adequately characterized by a one-compartment model with first order absorption. Body weight, HIV status and gender were identified as covariates that may affect the steady-state pharmacokinetics of tipranavir. The population pharmacokinetic analysis suggested the mean systemic exposure of tipranavir was slightly lower for HIV-1 infected subjects compared to that of HIV-1 negative subjects. However, this observation does not change conclusions of studies conducted in healthy volunteers.

COMMENTS:

The pharmacokinetic sample collection and the population pharmacokinetic analysis are acceptable.

RECOMMENDATION:

The population pharmacokinetic analysis suggested the mean systemic exposure of tipranavir was slightly lower for HIV-1 infected subjects compared to that of HIV-1 negative subjects. However, this observation does not change conclusions of studies conducted in healthy volunteers.

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U00-3175

Title: In vitro metabolism studies of tipranavir (Study conducted by Pharmacia & Upjohn, Inc.)

OBJECTIVES: To characterize metabolite profiles observed upon incubation with human liver microsomes and hepatocytes and to identify CYP enzymes involved in the metabolism of tipranavir in human liver microsomes

METHODS: Tipranavir metabolism with human liver microsomes: A human liver microsomes bank prepared from 25 human individuals was used in the study. Incubations were conducted in the presence of 1 mg/mL human liver microsomal protein in a final volume of 0.5 mL in 100 mM potassium phosphate buffer (pH 7.4), and 1 mM NADPH for 30 minutes at 37°C. The addition of the cofactor NADPH generating system (5 units ICDH, 10 mM NADP+) started the reaction. The final concentration of [³H] tipranavir was 100 μM (3.67 μCi/mL). The reaction was terminated by the addition of an equal volume of acetonitrile containing 1% TFA followed by centrifugation. Supernatants were analyzed directly by HPLC

Tipranavir metabolism with human hepatocytes: Human hepatocytes were isolated from a freshly preserved human liver obtained from the [] using established protocol. Incubation mixtures of tipranavir with human hepatocytes were of 2 mL total volume containing 25 μM (3.6 μCi/mL) of [³H] tipranavir, and a cell density of 2X10⁶ cells/mL. Incubations were conducted at 37°C in a humidified cell incubator at 5% CO₂. At selected time points cells were sedimented by centrifugation. Supernatants were analyzed directly by HPLC []

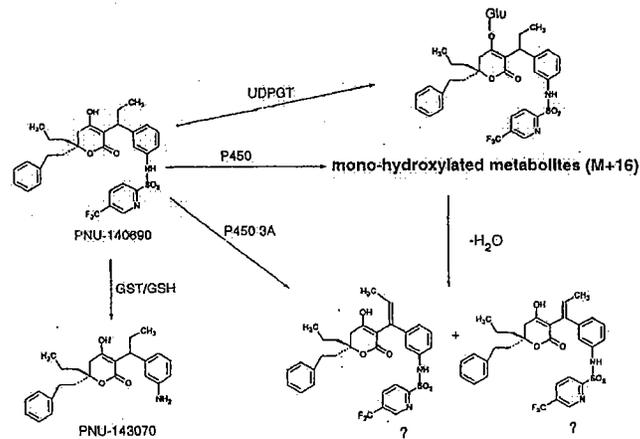
RESULTS:

In vitro biotransformation of tipranavir

Several metabolites of tipranavir were observed and partially characterized by [] []. Among those were oxidized (M+16) and desaturated (M-2) metabolites, a glucuronide conjugate of the parent drug, and a metabolite (PNU-143070) formed via sulfonamide N-S bond cleavage of the parent drug. There appeared to be no single major metabolite that dominated the metabolite profiles.

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Figure 1. Proposed In Vitro Metabolic Pathways of Tipranavir



Identification of major CYPs involved in Tipranavir metabolism in humans

The metabolism of tipranavir was studied in human liver microsomes. In a correlation study, the rate of tipranavir metabolism appeared to be correlated with testosterone 6 β -hydroxylase activity, an indicator of CYP3A4 ($r=0.93$) but poor correlation to other CYPs, e.g., CYP1A1/2, CYP2A, CYP2C9/10, CYP2D6, CYP2E1 and CYP4A.

Table 1. Correlation of Tipranavir Metabolism Rate to Cytochrome P450 Enzyme Marker Substrate Metabolism Rates

Cytochrome P450 Isoform	Activity	Correlation Coefficient
P450 1A1/2	7-Ethoxyresorufin O-dealkylation	$r = + 0.146$
P450 1A2	Caffeine 3-demethylation	$r = + 0.140$
P450 2A	Coumarin 7-hydroxylation	$r = + 0.580$
P450 2C9/10	Tobutamide methylhydroxylation	$r = + 0.126$
P450 2C19	S-Mephenytoin 4'-hydroxylation	$r = - 0.020$
P450 2D6	Dextromethorphan O-demethylation	$r = - 0.161$
P450 2E1	Chlorzoxazone 6-hydroxylation	$r = + 0.076$
P450 3A	Testosterone 6 β -hydroxylation	$r = + 0.930 *$
P450 4A	Lauric acid 12-hydroxylation	$r = + 0.042$

CONCLUSIONS:

This study showed that CYP3A4 appeared to be the CYP enzyme responsible for the oxidation of tipranavir in human liver microsomes as evidenced by the correlation analysis. The sponsor further conducted the inhibition study in human liver microsomes with ketoconazole. Co-administration of ketoconazole at concentrations of 1 μ M or 5 μ M inhibited the metabolism of tipranavir (50 μ M) by 90% and 95%, respectively. The sponsor also confirmed that CYP2D6 was not involved in the metabolism of tipranavir by incubating tipranavir with cDNA-expressed human CYP2D6.

The sponsor may need to confirm the lack of involvement of other major human CYPs, e.g., CYP1A2, CYP2C9, CYP2C19 using either respective specific chemical inhibitors in human live

microsomes or cDNA-expressed systems similar to the experiment that the sponsor did with CYP2D6.

U03-3576

Title: In vitro evaluation of tipranavir as an inhibitor of human cytochrome P450; Determination of IC₅₀ and K_i values

OBJECTIVES: To determine K_i values for the inhibition of CYP1A2, CYP2C9, CYP2C19 CYP2D6 and CYP3A4 by tipranavir and to assess the drug interaction potential of tipranavir

METHODS: The CYP450 isoform specific substrates used were phenacetin (CYP1A2), diclofenac (CYP2C9), (S)-mephenytoin (CYP2C19), bufuralol (CYP2D6), testosterone (CYP3A4) and midazolam (CYP3A4). Each CYP substrate was incubated with human liver microsomes in the presence of various concentrations of TPV (inhibitor). Human liver microsomes used in the study were characterized for CYP450 isoform enzyme activities, microsomal protein concentrations and spectrally apparent CYP450 concentrations. All incubations were carried out at 37°C. An IC₅₀ value for each CYP isoform was determined to optimize inhibitor concentrations for K_i determination. The IC₅₀ value was determined by incubating substrate at one concentration (the apparent K_m for that probe substrate) in the presence of seven inhibitor (TPV or positive) concentrations. Incubations without inhibitors were included as 100% activity values. The tipranavir concentrations used were 0, 0.07, 0.21, 0.62, 1.85, 5.56, 16.67 and 50 µM for all incubations.

Table 1. Summary of assay conditions and substrate concentrations for IC₅₀ determination

CYP Isoform	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrate	Phenacetin	Diclofenac	S-Mephenytoin	Bufuralol	Testosterone
Substrate Concentration (µM) ^a	40	5	40	7.5	60
Solvent for Substrates	Ethanol	Water	Ethanol	Water	Methanol
Metabolite Monitored	APAP ^b	4'-OH-D ^c	4'-OH-M ^d	1'-OH-B ^e	6-β-OH-T ^f
HLM ^g Concentration (mg/mL)	0.5	0.05	0.4	0.5	0.2
Phosphate Buffer (mM)	100	100	100	100	100
Incubation Time (min)	20	10	30	20	6

^a Substrate values are the apparent K_m values determined in house. Up to two-fold variation in K_m have been noted and found acceptable as indicated in reference (4).

^b APAP, acetaminophen;

^c 4'-OH-D, 4'-hydroxydiclofenac;

^d 4'-OH-M, 4'-hydroxymephenytoin;

^e 1'-OH-B, 1'-hydroxybufuralol;

^f 6-β-OH-T, 6-betahydroxytestosterone;

^g HLM, human liver microsomes.

Table 2. Incubation concentrations (μM) of isoform-selective inhibitors (positive controls) for IC_{50} determination

CYP Isoform	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrate	Phenacetin	Diclofenac	S-Mephenytoin	Bufuralol	Testosterone or Midazolam
Inhibitor	Furafylline	Sulfaphenazole	Tranylcypromine	Quinidine	Ketoconazole
Inhibitor Concentrations (μM)					
1	10.00	3.00	50.00	3.00	3.00
2	3.33	1.00	16.67	1.00	1.00
3	1.11	0.33	5.56	0.33	0.33
4	0.37	0.11	1.85	0.11	0.11
5	0.12	0.037	0.61	0.037	0.037
6	0.04	0.012	0.21	0.012	0.012
7	0.01	0.004	0.069	0.004	0.004
8	0	0	0	0	0

K_i values were then generated using five different tipranavir concentrations combined with five different substrate concentrations for each isoform selective substrate. K_i studies for each CYP isoform were conducted on two separate occasions. Incubations with isoform selective CYP450 inhibitors were also included as positive controls in the study (see Table 2).

Table 3. Summary of tipranavir concentrations (μM) for K_i determination

CYP Isoform	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4 ^a	CYP3A4 ^a
Probe Substrate	Phenacetin	Diclofenac ^b	Mephenytoin ^b	Bufuralol ^b	Testosterone	Midazolam
Tipranavir (μM)						
Concentration 1	50.00	1.20	12.00	50.00	10.00	12.00
Concentration 2	25.00	0.60	6.00	25.00	5.00	6.00
Concentration 3	12.50	0.30	3.00	12.50	2.50	3.00
Concentration 4	3.13	0.08	0.75	3.13	0.63	0.75
Concentration 5	0	0	0	0	0	0

^a CYP3A4 assay using either testosterone or midazolam as the substrate.

^b K_i determinations were repeated on two separate occasions. The tipranavir concentrations used in the second replicate assay were the same as used in the first replicate except for the incubations with the following probe substrates (the concentration of tipranavir used is indicated in parenthesis): phenacetin (0, 3.75, 15, 30 and 60 μM), (S)-mephenytoin (0, 2.5, 10, 20 and 40 μM) and bufuralol (0, 3.75, 15, 30 and 60 μM).

Table 4. Summary of assay conditions and substrate concentrations for K_i determination

CYP Isoform	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A4
Substrate	Phenacetin	Diclofenac	Mephenytoin ^a	Bufuralol	Testosterone	Midazolam
Substrate Concentration, A	120	15	120	22.5	180	15
Substrate Concentration, B	40^b	5^b	40^b	7.5^b	60^{b,c}	5^b
Substrate Concentration, C	20	2.5	20	3.75	30	2.5
Substrate Concentration, D	12	1.5	12	2.25	18	1.5
Substrate Concentration, E	8	1	8	1.5	12	1
Solvent for Substrates	Ethanol	Water	Methanol	Water	Methanol	Acetonitrile
Metabolite Monitored	APAP ^d	4'-OH-D ^e	4'-OH-M ^f	1'-OH-B ^g	6-β-OH-T ^h	1'-OH-M ⁱ
HLM ^j Conc. (mg/mL)	0.5	0.05	0.8	0.25	0.2	0.1
Phosphate Buffer (mM)	50	100 ^k	50	50	100	50
Incubation time (min)	20	10	30	10	6	5

^a(S)-Mephenytoin was utilized for the second K_i experiment and was solubilized in 50 % methanol: 50% acetonitrile (v/v).

^b Substrate values in bold are the apparent K_m values determined in house. Up to two-fold variation in K_m have been noted and found acceptable as indicated in reference (4).

^c The second K_i experiment used a 50 μM substrate (testosterone) concentration, a 5 minute time point and 50 mM potassium phosphate buffer, pH 7.4 concentration.

^d APAP, acetaminophen;

^e 4'-OH-D, 4'-hydroxydiclofenac;

^f 4'-OH-M, 4'-hydroxymephenytoin;

^g 1'-OH-B, 1'-hydroxybufuralol;

^h 6-β-OH-T, 6-betahydroxytestosterone;

ⁱ 1'-OH-M, 1'-hydroxymidazolam.

^j HLM, human liver microsomes.

^k The second experiment for the K_i determination for inhibition of the isoform CYP2C9 used a 50 mM potassium phosphate buffer, pH 7.4

The K_i values were fitted using the following competitive inhibition equation:

$$v = V_{max} \cdot [S] / (K_m \cdot (1 + [I]/K_i) + [S])$$

The inhibition of testosterone metabolism by tipranavir exhibited curvilinear kinetics and consequently, the data was analysed using 3-site model (developed by [

RESULTS:

The [I] value used for [I]/K_i values calculation was 95.4 μM (57.5 μg/mL) achieved at a dose of TPV/RTV (500 mg/200 mg) BID at steady-state.

Table 5. Tipranavir IC₅₀, K_i and proposed [I]/K_i values for the major human CYPs

CYP450	IC ₅₀ ^a (μM)	K _i ^b (μM)	[I]/K _i ^c	DDI Potential
CYP1A2	>50	24.2 (31.7, 16.6)	3.9	Likely
CYP2C9	0.26	0.23 (0.18, 0.27)	414.8	Likely
CYP2C19	2.7	5.3 (5.1, 5.4)	18.0	Likely
CYP2D6	16.3	6.7 (8.5, 4.8)	14.2	Likely
CYP3A4 (Test) ^d	2.3	0.88 (0.56, 1.2)	108.4	Likely
CYP3A4 (Mid) ^e	N.D. ^f	1.3 (1.3, 1.3)	73.4	Likely

^a IC₅₀ value calculated from Grafit software based on equation 3.3.4: 1.

^b Average K_i values reported. Values calculated from Grafit software based on equation 3.3.4: 2, except CYP3A4 (testosterone) where the K_i was calculated from Grafit Software based on a 3-site model (equation 3.3.4: 3) (5). Individual values shown in parenthesis.

^c [I], tipranavir. C_{max} concentration of 95.4 μM based on a 500 mg BID dose (co-administered with 200 mg of ritonavir in clinical study 1182.51) (2).

^d Test, testosterone as the substrate.

^e Mid, midazolam as the substrate.

^f N.D., Not determined.

CONCLUSIONS:

The K_i values determined in this study are in agreement with K_i values obtained in a previous study conducted by Pharmacia & Upjohn, Inc. (contracted to [redacted] study report # U00-3194) with K_i values of 13.6, 0.331, 19.2, 1.50 and 2.94 μM for CYP1A2, CYP2C9, CYP2C19, 2D6 and 3A4, respectively. The CYP activity markers were 7-Ethoxyresorufin O-dealkylation (CYP1A2), Tolbutamide hydroxylation (CYP2C9/10), S-Mephenytoin 4'-hydroxylation (CYP2C19), Dextromethorphan O-demethylation (CYP2D6) and Testosterone 6β-hydroxylation (CYP3A4/5). The potential of tipranavir as mechanism-based inhibitors was also investigated by [redacted] by pre-incubated human liver microsomes with tipranavir and NADPH for 10 min. After this 10-min pre-incubation period, an aliquot of treated-microsomes was added to an incubation containing the marker substrate. The incubation was then carried out to measure the residual marker P450 activity. Tipranavir showed little or no capacity to function as an irreversible inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

As [I]/K_i ratios are greater than 1, drug interactions involving above-mentioned major human CYPs are considered likely. So the sponsor needs to conduct follow-up in vivo evaluation to confirm or rule out the

drug interaction potential for tipranavir with CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Other factors that need to be taken into the consideration in the in vivo study design are the co-administration of tipranavir with low dose of ritonavir and for CYP2C enzymes, tipranavir may also be an inducer as it is a CYP3A inducer.

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TITLE: Evaluation of permeability characteristics of tipranavir with Caco-2 and MDCK cells

OBJECTIVES: To determine the permeability of tipranavir across the Caco-2 cell monolayer, to characterize its transport mechanism by examining the effect of efflux pump inhibitors and excipients on the permeability, and to confirm that tipranavir is a substrate for P-gp using wild type and MDR1 transfected MDCK cell lines

METHODS: Caco-2 cells were grown as monolayers on polycarbonate filters and cultured for 21-25 days in HBSS or HBSS supplemented with BSA culture medium. The permeability studies were initiated by adding cell culture medium containing test compound ($[^{14}\text{C}]$ tipranavir at 8.2 μM and inhibitors) to either the apical (apical to basolateral transport) or basolateral (basolateral to apical transport) side of the monolayer. Samples were taken from the opposite side of the cell monolayers and replaced with fresh medium at discrete time intervals. Inhibitors of efflux pumps were added to both sides of the monolayers (throughout) unless otherwise specified. The concentrations of tipranavir were analyzed by a liquid scintillation counter.

MDCK cell lines (wild type and MDR1 transfected) were grown as monolayers on polycarbonate filters and cultured for 5-8 days in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 $\mu\text{g}/\text{mL}$ streptomycin, and addition of colchicine for MDR1-MDCK cells. All permeability experiments were performed as described for Caco-2 cells.

Permeability coefficient (P_c) was calculated according to the following equation: $P_c = dA/(dt \cdot S \cdot C_0)$, where dA/dt is the flux of test compound across the monolayer (nmole/sec), S is the surface area of the cell monolayer (0.33 cm^2), and C_0 is the initial concentration (μM) in the donor compartment. The permeability coefficient values are expressed as cm/sec. The permeability directional ratios (PDR) defined as the ratio of permeability from basolateral to apical direction to permeability from apical to basolateral direction.

RESULTS:

Table 1. Permeability of tipranavir across Caco-2 cell monolayers in the presence of P-gp substrate/inhibitors

Drug with 0.25% (w/v) BSA	Perm. A to B 10^6 (cm/sec)	Mass Balance (%)	Perm. B to A 10^6 (cm/sec)	Mass Balance (%)	PDR
Mannitol	0.49 ± 0.06	93.3	0.31 ± 0.02	95.3	0.6
Tipranavir (TPV)	0.48 ± 0.05	92.6	3.14 ± 0.24	98.4	5.9
TPV + Digoxin 30 μM	0.48 ± 0.02	98.0	2.81 ± 0.12	98.5	5.9
TPV + Quinidine 100 μM	0.78 ± 0.20	92.1	0.98 ± 0.12	87.5	1.3
TPV + Verapamil 100 μM	2.01 ± 0.08	94.6	1.68 ± 0.16	91.0	0.8
TPV + Verapamil 200 μM	3.08 ± 0.20	92.8	1.46 ± 0.04	88.3	0.5
TPV + LY335979 1.0 μM	0.61 ± 0.05	92.0	0.69 ± 0.08	89.6	1.1
Propranolol	33.1 ± 1.28	83.4	32.6 ± 1.12	90.3	1.0

Table 2. Permeability of tipranavir across Caco-2 cell monolayers in the presence of HIV Antiretrovirals

Drug with 0.25% (w/v) BSA	Perm. A to B 10^6 (cm/sec)	Mass Balance (%)	Perm. B to A 10^6 (cm/sec)	Mass Balance (%)	PDR
Mannitol	0.49 ± 0.06	93.3	0.31 ± 0.02	95.3	0.6
Tipranavir (TPV)	0.48 ± 0.05	92.6	3.14 ± 0.24	98.4	5.9
TPV + with Ritonavir throughout	1.28 ± 0.06	94.6	3.30 ± 0.09	94.1	2.6
TPV + Ritonavir 0.2 µg/mL	0.57 ± 0.00	96.2	3.41 ± 0.18	95.4	6.0
TPV + Ritonavir 2 µg/mL	0.55 ± 0.02	97.0	3.26 ± 0.11	92.1	5.9
TPV + BLR355	0.78 ± 0.13	97.5	2.37 ± 0.53	97.4	3.0
TPV + Nevirapine	0.64 ± 0.04	96.6	2.05 ± 0.19	86.1	3.2
Propranolol	33.1 ± 1.28	83.4	32.6 ± 1.12	90.3	1.0

Table 3. Permeability of tipranavir across Caco-2 cell monolayers in the presence of Vitamin E TPGS and Cremophor EL

Drug with 0.25% (w/v) BSA	Perm. A to B 10^6 (cm/sec)	Mass Balance (%)	Perm. B to A 10^6 (cm/sec)	Mass Balance (%)	PDR
Mannitol	0.49 ± 0.06	93.3	0.31 ± 0.02	95.3	0.6
Tipranavir (TPV)	0.48 ± 0.05	92.6	3.14 ± 0.24	98.4	5.9
TPV + 0.01% Vitamin E TPGS	0.84 ± 0.04	96.9	1.59 ± 0.15	97.2	1.9
TPV + 0.02% Vitamin E TPGS	1.13 ± 0.10	94.8	0.96 ± 0.07	76.2	0.8
TPV + 0.36% Cremophor EL	1.19 ± 0.07	95.8	1.26 ± 0.08	96.0	1.1
TPV + 0.55% Cremophor EL	1.17 ± 0.06	95.8	1.21 ± 0.20	95.7	1.0
Propranolol	33.1 ± 1.28	83.4	32.6 ± 1.12	90.3	1.0

Table 4. Permeability of tipranavir across wild-type MDCK and MDR1-transfected MDCK cell monolayers

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

CONCLUSIONS:

Data from Caco-2 cells indicated that tipranavir had a low P_c value, much lower than that of propranolol which is completely absorbed in humans after oral administration. The basolateral to apical permeability (secretory direction) was greater than the apical to basolateral permeability (absorptive direction), suggesting that tipranavir is a substrate of apically located efflux pumps (e.g., P-gp). Data also demonstrated that P-gp inhibitors such as quinidine, verapamil and LY335979 could inhibit the efflux of tipranavir thus increase tipranavir absorption from apical side of cells. Ritonavir also showed some inhibitory effect, but the effect was not significant. The insignificant effect of ritonavir could be due to the limitation of low solubility of ritonavir in cell medium. Cremophor EL, which is currently used in the SEDDS formulation, markedly increased the tipranavir apical absorption, suggesting it may have a similar effect in vivo. Data from MDCK wild type and MDR1-transfected MDCK cell lines confirmed that tipranavir is a substrate for P-gp. These data along with the fact that tipranavir is also a CYP3A4 substrate, inhibitor and inducer suggests that tipranavir may be subject to the complex enzyme-transporter interplay in its absorption, distribution, metabolism and elimination.

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U03-3213

TITLE: In vitro protein binding of tipranavir in mouse, rat, rabbit, dog, and human plasma and in 4% human serum albumin, 0.7% α 1-acid glycoprotein, and 6% fetal bovine serum

OBJECTIVES: To determine the protein binding of tipranavir in mouse, rat, rabbit, dog, and human plasma and in 4% human serum albumin, 0.7% α 1-acid glycoprotein, and 6% fetal bovine serum

METHODS: Dialysis method was used to determine the extent of tipranavir protein binding in various matrices. Briefly, Teflon dialysis cells and dialysis membranes [] with a 12,000-14,000 molecular weight cut-off were used. It was determined that TPV protein binding was achieved by 6 hour at 37°C, so the experiment was performed with a 6 hour-incubation time at 37°C. 1 mL of spiked matrix was added to one side of each dialysis cell. The other side of dialysis cell was filled with 1 mL of a solution containing 0.1 M sodium phosphate buffer (pH= 7.4) and 0.5% sodium chloride. Each test condition was studied using five dialysis cells within the same experiment. At the end of the incubation, each side of each dialysis cell was sampled. Tipranavir concentrations were determined by a [] method. The lower limit of quantitation was – ng/mL.

The percent unbound was calculated as follows:

$$\% \text{ unbound} = 100 \times C_{\text{buffer}}/C_{\text{protein}}$$

wher C_{buffer} and C_{protein} were the post-dialysis concentrations in the buffer and protein solutions.

RESULTS:

Table 1. Percent tipranavir protein binding (mean \pm SD) in several matrices

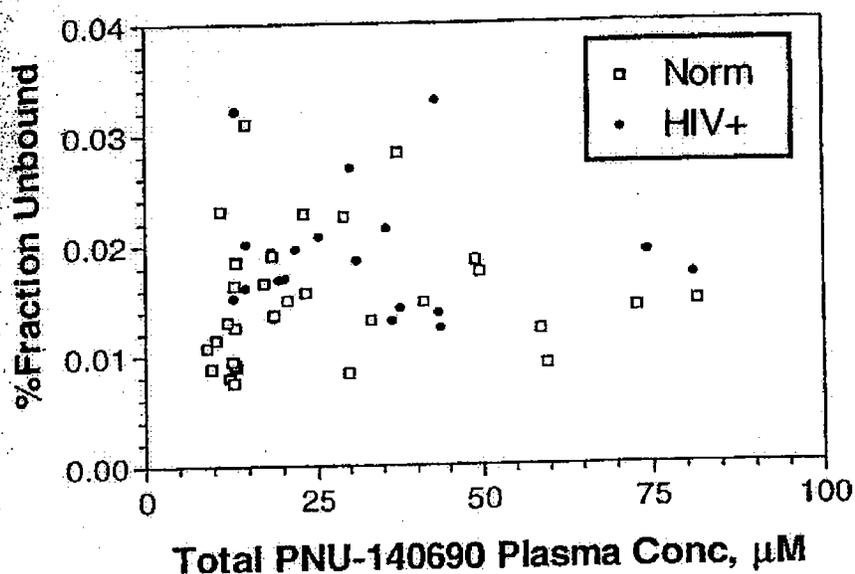
TPV (μ M)	Mouse plasma	Rat plasma	Rabbit plasma	Dog plasma	Human plasma	4% HSA	0.07% AAG	6% FBS
2	NT ^b	NT	NT	NT	NT	NT	NT	99.882 \pm 0.008
10	99.930 \pm 0.003	99.974 \pm 0.009	99.974 \pm 0.002	99.963 \pm 0.004	99.980 \pm 0.005	99.975 \pm 0.005	93.594 \pm 1.342	NT
20	99.928 \pm 0.003	99.962 \pm 0.009	99.965 \pm 0.005	99.952 \pm 0.005	99.974 \pm 0.001	99.961 \pm 0.011	75.351 \pm 2.446	96.298 \pm 0.234
50	99.926 \pm 0.005	99.969 \pm 0.002	99.957 \pm 0.004	99.943 \pm 0.007	99.975 \pm 0.001	99.971 \pm 0.002	NR ^c	NT
100	99.907 \pm 0.010	99.955 \pm 0.007	99.947 \pm 0.006	99.925 \pm 0.004	99.963 \pm 0.003	99.958 \pm 0.004	NR	NT

CONCLUSIONS:

TPV protein binding is very high (ca. 99.9% at 20 μ M) in mouse, rat, rabbit, dog and human plasma. TPV binds to both human serum albumin and α -1-acid glycoprotein. The extent of binding seems concentration independent because the degree of binding is similar over a wide concentration range from 10 to 100 μ M. This result was consistent with tipranavir in vitro protein

binding data determined by Pharmacia & Upjohn, Inc. previously (Study report U00-3139). An ex vivo protein binding study conducted by Pharmacia & Upjohn, Inc. demonstrated that there was similar extent of binding in healthy subjects vs. in HIV+ patients over a concentration range of 9 to 82 μM .

Figure1. Tipranavir (PNU-140690) plasma protein binding in clinical samples



Note: The sponsor also conducted a study to determine the partitioning of tipranavir into human red blood cells using [^{14}C]-tipranavir (Study report U04-3110). They found that tipranavir's RBC partitioning was very low over the TPV blood concentration range from 6 to 30 $\mu\text{g/mL}$.

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TITLE: Dissolution Data for Tipranavir SEDDS 250 mg Capsules

BACKGROUND: To improve bioavailability, tipranavir was formulated as an immediate release soft gelatin capsule containing a lipid-based self-emulsifying drug delivery system (SEDDS). When exposed to an aqueous environment, such as the GI tract, the SEDDS capsule-fill solution forms and maintains a highly dispersed colloidal system (fine emulsion). The dissolution test for tipranavir SEDDS 250 mg capsules is essentially a dispersion test that measures the rate and the extent of emulsification of the SEDDS formulation. The dissolution test procedure was developed and optimized with regards to apparatus, paddle speed, dissolution medium, pH of the medium, bath temperature, sample preparation and HPLC analysis. The proposed dissolution method below is acceptable (It was reviewed prior to the NDA submission in IND 51,979).

METHODS:

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

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

SPECIFICATION:

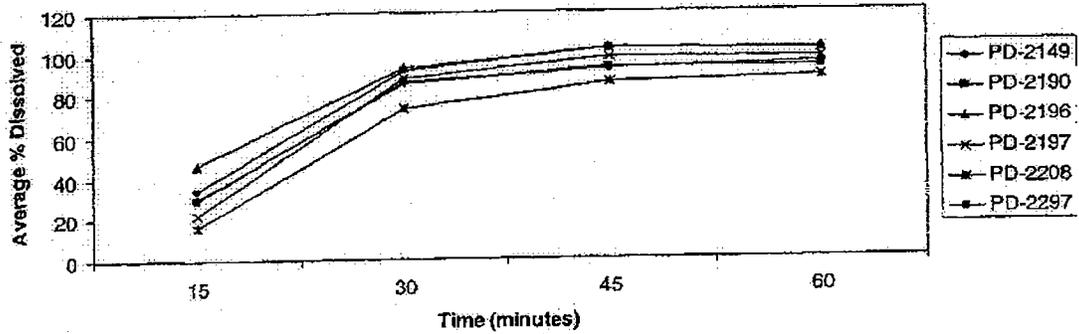
The original proposed dissolution specification for tipranavir SEDDS 250 mg capsule was Q = [] dissolved in 60 minutes. The applicant agreed to change the specification to Q = []

RESULTS:

Table 1. Mean (%RSD) Dissolution Profiles for Six Pivotal Clinical Batches of tipranavir SEDDS 250 mg capsules

Time (minutes)	Average % Dissolved					
	PD-2149	PD-2190	PD-2196	PD-2197	PD-2208	PD-2297
15	30	29	46	22	16	34
% RSD	58.2	54.5	65.7	98.5	61.6	66.1
30	86	87	93	88	74	92
% RSD	10.1	7.4	15.2	11.2	12.0	12.5
45	93	93	102	98	86	102
% RSD	7.5	4.7	9.4	4.7	6.0	4.9
60	95	93	102	97	88	101
% RSD	6.2	3.6	6.3	3.2	5.8	3.3

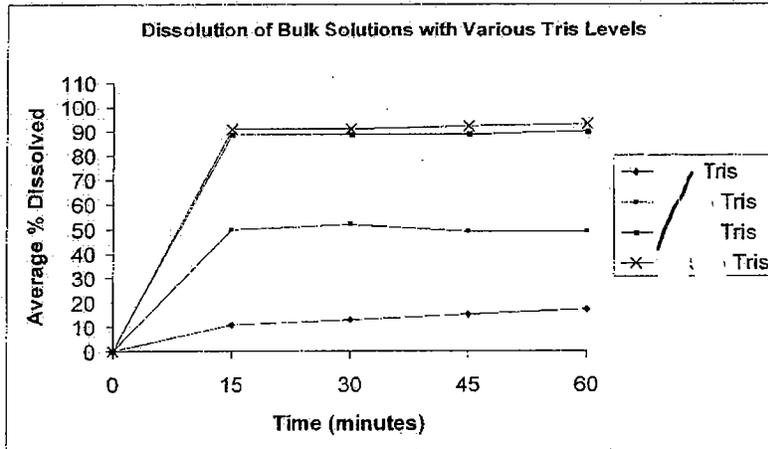
Figure 1. Mean Dissolution Profiles for Six Pivotal Clinical Batches of tipranavir SEDDS 250 mg capsules



CONCLUSIONS: The dissolution results are acceptable.

Note:

Tris was selected as base to enhance the solubility of tipranavir in the lipid based formulation and to emulsify the vehicle on exposure to water. In early formulation development stage, a two-fold enhancement of the oral bioavailability was observed in humans with a 300 mg tipranavir experimental SEDDS formulation containing $\frac{1}{2}$ tris compared to the bioavailability of a SEDDS formulation containing no tris. In the current proposed to-be-marketed SEDDS formulation, The tris levels were found to decrease over time. Under room temperature storage conditions, the tris levels were down from $\frac{1}{2}$ at release to about $\frac{1}{4}$ after two years. However, the dissolution profile remains same unless the tris level is below $\frac{1}{8}$ (See figure below).



4.2 Pharmacometrics Review

PHARMACOMETRIC REVIEW

NDA number: 21-814
Submission date: December 22, 2004
Generic name: Tipranavir
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc
Type of submission: New Drug Application
Primary Reviewer: Derek Zhang, Ph.D.
PM reviewer in DPEIII: Jenny J Zheng, Ph.D.

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Executive Summary

Tipranavir (TPV) is a non-peptidic protease inhibitor (PI) being developed for use in patients with human immunodeficiency virus (HIV) who are treatment experienced and need new treatment options. The worldwide prevalence of drug resistance in HIV-positive treatment-experienced patients and the frequency of drug resistance in treatment-naïve patients are both increasing. As a result of its favorable resistance profile, TPV provides a new therapeutic option for many patients whose viral isolates demonstrate PI resistance.

Exposure response analyses were conducted using the data from a dose-finding study (Study 52, N=160) and two pivotal studies (RESIST 1 and RESIST 2; N=291).

Population pharmacokinetic analysis was conducted on the data obtained from study 52. Three tipranavir/ritonavir (TPV/RTV) treatment arms were included in the study: TPV/RTV 500 mg/100 mg, TPV/RTV 500 mg/200 mg, and TPV/RTV 750 mg/200 mg. The relationship between model predicted tipranavir trough concentration (C_{min}) or inhibitory quotient (IQ) and virological responses at week 2 or week 24 was examined. At week 24, patients had a positive virological response if they had at least 1 log viral load reduction. The probability of having at least 1 log reduction at week 24 is associated with log₁₀ IQ. The phase 2 study showed that odds ratio associated with log₁₀ IQ was 5.94 (90% confidence interval (CI): 2.40-14.77, $p < 0.0001$). Increasing inhibitory quotient in patients with low inhibitory quotient could increase patient's chance to response to TPV treatment. In addition, the association between incidence of grade 3/4 ALT elevation and model predicted TPV C_{min} was also examined by logistic regression analysis. The incidence of grade 3/4 ALT elevation is related to tipranavir exposure (log₂ TPV C_{min}). The logistic regression analysis showed that the odds ratio associated with log₂ TPV C_{min} was 1.96 (90% confidence interval (CI): 1.15-3.37, $p = 0.01$).

Consistently, phase 3 studies also showed that probability of response to tipranavir treatment is associated log₁₀(IQ). In addition, concomitant enfuvirtide (ENF) use significantly increases the patient's probability of responding to the tipranavir treatment. The odd ratios associated with log₁₀(IQ) and ENF use are 4.24 (90% CI: 2.52-7.12) and 2.98 (90% CI: 1.73-5.16), respectively.

The range of IQ values obtained from phase 3 studies was wide after the fixed dose, suggesting that the probability of response in individual patient is not predictable unless IQ is measured. To maximize the likelihood of individual's response, individualized dose strategy should be considered as an optional alternative to the fixed doses treatment.

RECOMMENDATIONS:

This application has been reviewed and recommendations are made in three areas: 1) Labeling changes; 2) Phase IV commitments; and 3) pediatric studies.

1. Labeling changes:

The exposure response analysis of phase 2 and phase 3 studies consistently demonstrated that the probability of a patient's response to tipranavir/ritonavir treatment is related to inhibitory quotient. However, due to the variability in pharmacokinetics of the drug and infected virus, the range of resulting inhibitory quotient are wide, which results in unpredictable virological response for individual patient. In addition, phase 3 studies showed that ENF use significantly increases the probability of patient's response to tipranavir/ritonavir treatment. This analysis suggested that dose increase could be considered for patients who have low IQ therefore fail the treatment. On the other hand, for patients who have high IQ but can not tolerate the conventional dose, dose reduction could be considered.

The examination on IQs in patients with different number of key mutation, presented in following table, indicated that when number of key mutation increases, the median IQ decreases, implying

by above analysis that the probability of response to treatment decreases, especially when number of mutation is greater than 2.

Median IQ in patients with different number of key mutations in RESIST-1 and RESIST-2

# of Key Mutations at Amino Acids 33, 82, 84, 90	0	1	2	3	4
# of subject	9	77	195	9	1
Median	420	164	81	29	15

Based on the results of exposure response analysis, labeling changes are recommended in three sections of the proposed label: CLINICAL PHARMACOLOGY Section, INDICATION AND USAGE, and DOSAGE AND ADMINISTRATION.

The proposed languages are as follows:

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Pharmacodynamics

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

[

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2. Phase IV commitment:

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3. Pediatric studies: Studies in adults have indicated that fixed dosing strategy might not be the best approach to maximize benefit and to avoid unnecessary risk. The sponsor should utilize the study(ies) of TPV/RTV in pediatrics for exploring optimal dosing strategies.

Jenny J Zheng, Ph.D.
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Office Clinical Pharmacology/Biopharmaceutics,

Joga Gobburu, Ph.D.
Team Leader in Pharmacometrics group
Office Clinical Pharmacology/Biopharmaceutics,

Study number: 1182.52

Title: Double-blind, randomized, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/RTV) in multiple antiretroviral drug-experienced subjects

Objective: The purpose of this trial was to identify the dose combination of TPV and RTV in highly treatment-experienced HIV-positive patients that was optimal for both efficacy and safety and that could be used in subsequent Phase III trials.

Study Design: This trial was a Phase IIb multicenter, double-blinded, randomized, dose optimization study of three TPV/r doses (500 mg/100 mg, 500 mg/200 mg, and 750 mg/200 mg) administered BID. Entry requirements included HIV-positive males or females of 18 years of age or older; treatment with at least 3 months of NRTIs and NNRTIs; treatment with at least two PIs; a VL of at least 1000 copies/mL; and a genotype screening of at least one per-protocol protease mutation with more than one of the 82 L/T, 84V, or 90M mutations. After screening, qualifying patients were randomized to one of the three blinded regimens, discontinued from their current PI, and administered TPV/r therapy for 2 weeks while remaining on their current background ARV therapy. After the 2 weeks of functional mono-therapy, background ARV medications were optimized and each patient remained on blinded TPV/r and optimized ARV medications for the remainder of the trial, which was a maximum of 32 weeks. The primary efficacy endpoint was median change from baseline in VL during 2 weeks of functional mono-therapy. The primary safety endpoints were incidences of moderate or severe diarrhea, any vomiting, and any SAE up to Week 4.

Sampling scheme:

Trough plasma samples were collected at day 7 and 14. In subgroup, except the planned trough concentrations additional three plasma samples were collected between 0.5-2 hours, 2-4 hours, and 4-8 hours.

Viral load was measured at prescreening (day -28 - day -14), baseline (day 0), day 3, 7, 10, 14 and week 4, 8, 16, 24 and 32. CD4 cell count was measured at prescreening, baseline, week 2, 4, 8, 16, 24 and 32.

Phenotyping assessments using the Antivirogram were tested at visit 1, 6, and 12.

Adverse effect was documented at week 4, 8, 16, 24 and 32.

Central laboratory tests including hematology, blood chemistry, urinalysis and liver chemistry was conducted at pre-screening, baseline, and week 4, 8, 16, 24 and 32. Additional liver chemistry tests were conducted at day 3, 7, 10, and 14 after commencement of treatment.

RESULTS: A total of 216 patients were evenly distributed among the treatments for demographics, previous treatment experience, baseline VL, and CD4+ cell count.

Pharmacokinetics:

The sponsor conducted population pharmacokinetic analysis using NONMEM. The relationship between reductions in RNA viral load at day 14 and TPV trough plasma concentrations were compared across the three doses. The inhibitory quotient, the ratio of TPV plasma trough concentration to the protein-adjusted TPV IC_{50} was also calculated. The protein adjusted TPV IC_{50} is calculated as $(\text{measured } IC_{50} / \text{reference } IC_{50}) \times 0.058 \times 3.75$ (μM), where 0.058 μM is the mean IC_{50} of wild type HIV virus and 3.75 obtained from in vitro test is the fold change in IC_{50} when plasma was added in the test which is used to account for reduced susceptibility of virus to the drug due to protein binding. The use of reference IC_{50} is to control the variation in IC_{50} measure across different batches of tests. The population pharmacokinetic study showed that one compartment model would be appropriate to describe the data. The summary of tipranavir pharmacokinetic parameters derived from NONMEM analysis is shown in Table 1.

Table 1. Population Pharmacokinetic Results

	Mean (min-max)		
	500 mg/100 mg T/r	500 mg/200 mg T/r	750 mg/200 mg T/r
N	69	72	69
C _{trough} (□M)	21.80	33.92	44.51
AUC _{ss} (h*□M)	451.70	598.05	817.02
CL (L/h)	1.84	1.39	1.52
V (L)	17.83	18.26	18.25
T _{1/2}	6.62	8.55	8.38
% with C _{trough} >20 □M*	42%	86%	100%

* The preliminary 20 μM TPV trough target represented more than 10 times the protein-adjusted IC90 for PI resistant clinical viral isolates.

The relationship between changes in viral load from baseline at week 2 and TPV plasma concentration is summarized in Table 2.

Table 2. Viral Load Reduction vs Plasma Concentrations

Change in viral load (log)	TPV/r dose											
	500/100				500/200				750/200			
	TPV Cp (μM)		TPV Cp (μM)		TPV Cp (μM)		TPV Cp (μM)		TPV Cp (μM)		TPV Cp (μM)	
	N	VL	N	VL	N	VL	N	VL	N	VL	N	VL
>0 to 1.18	4	0.23	7	0.28	5	0.19	6	0.24	4	0.43	6	0.50
-1 to 0	9	-0.43	15	-0.60	5	-0.62	17	-0.57	1	-0.49	9	-0.37
-2 to -1	15	01.4 2	12	-1.39	5	-1.73	21	-1.65	10	-1.42	24	-1.24
<-2	1	-2.20	1	-2.42	0	-	4	-2.15	1	-2.20	5	-2.52

A similar analysis was also conducted for inhibitory quotient (IQ). The results are shown in Table 3. It appeared that the viral dose reduction at week 2 was associated with IQ. The sponsor concluded that IQ of below 30-50 was associated with a significantly reduced antiviral response after 2 week therapy.

Table 3. Viral Load Reduction vs Inhibitory Quotient

Inhibitory Quotient	TPV/r dose (mg)						Total	
	500/100		500/200		750/200			
	N	ΔVL	N	ΔVL	N	ΔVL	N	ΔVL
<5	3	0.05	2	0.28	2	-1.62	7	-0.19
>5 to 30	9	-0.60	10	-0.10	5	-1.01	24	-0.25
>30 to 50	10	-0.57	3	-1.06	4	-0.81	17	-0.49
>50 to 100	10	-1.23	12	-1.30	8	-1.29	30	-0.128
>100 to 150	9	-0.98	10	-0.78	7	-0.58	26	-0.92
>150	13	-1.10	16	-1.55	24	-1.23	53	-1.23
Total	54	-0.87	53	-0.98	50	-1.14	157	-1.05

Efficacy:

The efficacy analysis showed that all doses achieved a >0.5 log₁₀ median reduction in VL at 2 weeks and efficacy was sustained through 24 weeks. The efficacy results are presented in Table 4. The TPV/r 500 mg/100 mg dose consistently showed less VL reduction than the TPV/r 500 mg/200 mg or TPV/r 750 mg/200 mg doses. As shown in the table, there were 29 (45%), 30 (48%), and 40 (67%) subjects had greater than 1 log viral load reduction at week 2, indicating that viral load reduction is dose dependent.

Table 4. Summary of Results of Study 52 - (LOCF*, NCF*)

Study	Treatment	Patients entered / completed 24 weeks	Baseline Median VL log ₁₀ copies/mL	Median VL change (log ₁₀ copies/mL)	Percent (%) achieving >=1 log ₁₀ drop	Percent (%) undetectable (<400 copies/mL)	Percent (%) undetectable (<50 copies/mL)
at 2 weeks	TPV/r 500mg/100mg	73/72	4.49	-0.85	43.1	19.4	2.8
	TPV/r 500mg/200mg	72/69	4.57	-0.93	46.4	20.3	NA
	TPV/r 750mg/200mg	71/69	4.53	-1.18	63.8	18.8	1.4
at 24 weeks	TPV/r 500mg/100mg	73/72	4.49	-0.25	31.5	32.9	24.7
	TPV/r 500mg/200mg	72/69	4.57	-0.55	40.3	37.5	20.8
	TPV/r 750mg/200mg	71/69	4.53	-1.07	45.1	38.0	21.1

*LOCF: last observation carry forward

NCF: non-completer considered as failure

Safety:

In study 52, 90.3% of the 216 treated patients reported 1 or more AEs during the study. Adverse events, regardless of causality, were observed in the following percentages of patients in the following systems according to MedDRA: gastrointestinal system (69.4%), infections and infestations (46.8%), general system (36.6%), nervous system (33.8%), skin and subcutaneous tissue (25.9%), and musculoskeletal and connective tissue (24.1%). For individual types of AEs, the most frequently reported AEs (>10% of all patients), regardless of causality, were observed in the following percentages of patients: diarrhea (38.4%), nausea (30.1%), headache (19.4%), fatigue (16.2%), vomiting (15.3%), and pyrexia (11.6%). All other individual types of AEs, regardless of causality, each occurred in <10% of patients.

Approximately 90% of patients in each of the 3 treatment groups had AEs, regardless of causality; thus, there was no overall relationship between dose and percentages of patients with

AEs. In a similar manner, the percentages of patients with individual AEs did not demonstrate a clear relationship with dose. However, the treatment groups did differ in the percentages of patients reporting vomiting and pyrexia. Vomiting was reported by 21.1% patients in the TPV/r 750 mg/200 mg BID group, 15.1% in the TPV/r 500 mg/100 mg BID group, and 9.7% in the TPV/r 500 mg/200 mg BID group. Pyrexia was reported by 15.3% patients in the TPV/r 500 mg/200 mg BID group, 14.1% in the TPV/r 750 mg/200 mg BID group, and 5.5% in the TPV/r 500 mg/100 mg BID group.

Of the 216 treated patients in Trial 1182.52, 64.4% reported 1 or more AEs (MedDRA) that were considered by investigators to be related to TPV/r. Adverse events, considered to be drug-related and reported by the highest percentages of patients (>20% of patients), were observed in the gastrointestinal system (69.4% of patients). The most frequently reported individual types of AEs (>10% of patients), considered to be related to TPV/r, were observed in the following percentages of patients: diarrhea (31.5%), nausea (23.1%), and vomiting (11.6%). All other individual types of drug-related AEs each occurred in <10% of patients.

For all types of drug-related AEs combined, there appeared to be no relationship to TPV/r dose. Nausea was the only specific event that may have had a relationship to dose. It showed an inverse relationship with dose, with the highest percentage of patients reporting this event in the TPV/r 500 mg/100 mg BID group (28.8%), compared with 23.6% in the TPV/r 500 mg/200 mg BID group and 16.9% in the TPV/r 750 mg/200 mg BID group. Of those patients who had drug-related AEs, 83.5% experienced these events during the first 4 weeks of study therapy.

Severe AEs were reported by 26.9% of patients and showed a clear relationship to dose: 39.4% in the TPV/r 750 mg/200 mg BID group, 23.6% in the TPV/r 500 mg/200 mg BID group, and 17.8% in the TPV/r 500 mg/100 mg BID group. The severe AEs consisted of 62 individual types of AEs, and only 3 types occurred in 2% or more of all patients: diarrhea (4.2%), nausea (2.8%), and hyper-triglyceridemia (2.3%). None of the individual types of severe AEs exhibited a relationship to study dose, perhaps because patient numbers for each type of AE were small. Of the patients who had severe AEs, 46.6% of these events occurred during the first 4 weeks of study therapy.

Discontinuations due to AEs showed a direct relationship to dose: 15.5% in the TPV/r 750 mg/200 mg BID group, 9.7% in the TPV/r 500 mg/200 mg BID group, and 5.5% in the TPV/r 500 mg/100 mg BID group.

Liver toxicity was a concern in Study 1182.52. It appears that the grade 3 or 4 elevations in ALT were dose dependent: 5.5% in the TPV/r 500 mg/100 mg group, 11.1% in the TPV/r 500 mg/200 mg group, and 21.2% in the TPV/r 750 mg/200 mg group.

Conclusion:

Safety analyses demonstrated a dose relationship with higher frequency of severe adverse events, discontinuations due to adverse events and DAIDS Grade 3 or 4 ALT elevations observed with increasing dose. The TPV/r 500 mg/200 mg dose was identified as the optimal combination in terms of efficacy, safety, and PK characteristics for use in highly treatment-experienced patients, and was chosen for further study in Phase III clinical trials.

3 FDA's Analysis on Study 52

Based on the review of Study 52, it appears that the viral load reduction was dose dependent. In addition, it was also found that the occurrence of severe adverse event, discontinuation due to the adverse event and the grade 3/4 ALT elevation was dose dependent. In order to quantitatively understand the relationship between tipranavir exposure and viral load reduction or adverse event, more specifically, incidence of grade 3/4 ALT elevation, the FDA reviewer conducted exploratory analyses. The FDA's analysis was conducted in steps as follows:

1. A population pharmacokinetic model was developed so that the individual exposure can be estimated.
2. The association between TPV exposure and virological response at week 2 and 24 was examined. The exposure measures include model predicted trough concentration (C_{min}), AUC, and inhibitory quotient (IQ). IQ is defined the same as the sponsor defined above. Since predicted C_{min} and AUC are expected to be highly correlated, only the analyses using C_{min} as exposure were presented. The reason for using C_{min} instead of AUC is that the results obtained from this study could be compared with results for the phase 3 studies since trough concentrations were also collected from two phase 3 studies. Virological responses are viral load reduction from baseline at week 2 and responder at week 24. Responder is defined as the subjects who had at least 1 log viral load reduction at week 24.
3. The relationship between TPV C_{min} and grade 3/4 ALT elevation, grade 3/4 AST elevation and GGT was examined.
4. A dose of 200 mg ritonavir (total daily dose of 400 mg) was used in the pivotal studies, which is higher than typical ritonavir booster dose of 100 mg. Since people may believe that the higher incidence of liver enzyme elevation may at least in part be due to the use of higher ritonavir dose. To understand dose related liver enzyme elevation, ritonavir and tipranavir C_{min} observed from this trial were compared across doses.

I. Population Pharmacokinetic Analysis:

NONMEM analysis was conducted on the concentration data the sponsor provided. A one-compartment model was used in this analysis. Since two ritonavir dose levels, 100 mg and 200 mg were used to boost tipranavir level, the effect of ritonavir dose on TPV exposure was evaluated. The estimated parameters from population pharmacokinetic (PPK) analysis are presented in Table 5. The observed concentrations and predicted population concentration vs time is presented in Figure 1 and the goodness of fit of this model is presented in Figure 2.

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Table 5. Summaries of PPK analysis

Parameters	Estimate	Standard error
CL/F (L/h)	1.48	0.25
V/F (L)	21.4	4.93
Ka	0.835	0.145
Ritonavir effect on TPV CL/F at 100 mg relative to 200 mg	0.847	0.167
CV% on CL	41%	0.035
CV% on V	39%	0.34
Residual variance	0.158	0.0204

As indicated by the results shown in Table 5, higher ritonavir dose (200 mg vs 100 mg) further reduced tipranavir apparent clearance (CL/F), by only 15%. Tipranavir apparent clearance when 100 mg ritonavir was co-administered about 85% of apparent CL when 200 mg ritonavir was coadministered. Figure 2 indicated that model can reasonable describe the data which was quite variable. The individual concentrations were reasonably predicted, which is important for next analysis in which individual predictions were used to correlate with viral load reduction and liver enzyme elevation.

II. Exposure vs Virological Response

Viral load reductions within the first two weeks across doses are presented in Figure 3. The dose-dependent viral load reduction was evidenced by the separation of three mean curves. The association of model predicted C_{min} and IQ with viral load reduction at week 2 were presented in Figure 4 and 5, respectively. The points in each figure represent the observations of each individual and dash line is the local mean obtained from lowess function in Splus. It appears that there is a week trend between viral load reduction at week 2 and C_{min} , but the IQ seems to be more informative to describe the viral load reduction at week 2. Viral load reduction at week 2 was further correlated with $\log_{10}(IQ)$ by linear regression. The analysis showed that $\log_{10}(IQ)$ explains about 20% of variability in viral load reduction at week 2 ($R^2=0.21$). This model suggested that observed maximal viral load reduction was about -1.7 and 1 log viral load reduction at week 2 needs an IQ of about 160. The model also suggested that the dose at which the patient could have IQ of 200 might be robust since IQ of 200 was at the relatively flat region of dose response curve. However, based on the exposure data, at dose of 500 tipranavir/200 mg ritonavir, there were about 28% patients who reached IQ of 200, suggesting that the dose of 500 mg tipranavir/200 mg ritonavir was not optimal at least at individual patient level.

This trial was continued up to 32 weeks. The probability of having success treatment at week 24 in related to $\log_{10}(IQ)$ was analyzed by logistic regression analysis. Responder is defined as subjects who had at least 1 log viral load reduction from baseline at week 24. The logistic regression analysis, as shown in Figure 6, showed the odds ratio associated with $\log_{10}(\text{inhibitory quotient})$ is 5.95 (95% CI: 2.34-14.77). Solid line represents the model predicted probability of success. According to the rank of IQ, patients are divided into 4 groups (0-25 percentile, 25 -50 percentile, 50-75 percentile, 75-100 percentile). The observed response rate at the median IQ in each group is shown as a symbol in the plot. The analysis showed that the probability of having 1 log viral load reduction at week 24 is associated with IQ value. Increasing IQ could increase the probability of being a responder.

III. Exposure vs Toxicity

An exploratory analysis was first conducted to explore any dose related side effects such as changes from baseline in cholesterol, triglyceride, ALT, GGT, and AST. The local mean of those markers across the time course and dose levels were graphically presented in Figure 7-11. It appears that treatments cause cholesterol and triglyceride increase, but the increase did not appear to be tipranavir dose related. For liver enzyme abnormality, it appears that the elevations of ALT, GGT and AST are tipranavir dose dependent, especially for ALT and GGT. The

association of liver toxicity with tipranavir exposure was focused on ALT since the preliminary analysis indicated SGOT elevation was not significantly associated with tipranavir exposure and GGT was not believed to be a good marker for liver function.

The proportion subjects who experienced severe adverse events, discontinuation rate, and grade 3/4 elevation of liver ALT during treatment with 500/100 TPV/RTV, 500/200 TPV/RTV, and 750/200 TPV/RTV are shown in Table 6. An apparent dose-response relationship was observed for those events. However, the logistic regression analysis did not demonstrate a significant association between incidence of severe adverse event and tipranavir trough concentration. Neither did discontinuation rate, indicating that the severe adverse event may not directly related to systemic exposure.

Table 6. Percent of subjects with severe adverse event, discontinuation and grade 3/4 ALT elevation across treatments

	500/100 TPV/RTV	500/200 TPV/RTV	750/200 TPV/RTV
Severe AE	17.8%	23.6%	39.4%
Discontinuation due to AE	5.5%	9.7%	15.5%
Grade 3/4 ALT	5.5%	11.1%	21.2%

The association of liver enzyme elevation with TPV C_{min} was further examined. Total of 210 subjects was included in safety analysis. A logistic regression analysis was conducted between the incidence of grade 3/4 ALT elevation and predicted $\log_2(TPV C_{min})$. One unit change in the log concentration represents 1-fold increase in the drug concentrations. The analysis results showed that the odds ratio associated with $\log_2(C_{min})$ is 2.40 (95% CI: 1.43-4.02, $p=0.00066$), suggesting that when TPV C_{min} doubles, the odds of having grade 3/4 ALT abnormality increases by 140% (Figure 12). The solid line represents the regression fit. The grade 3/4 ALT elevation rates observed in 5 concentration groups (0-20 percentile, 20-24 percentile, 40-60 percentile, 60-80 percentile, 80-100 percentile) at the median concentration in each group are presented as symbols to assess the goodness-of-fit.

Even though the logistic analysis showed that the incidence of grade 3/4 ALT elevation was related to tipranavir exposure, the assessment of ritonavir effect on the ALT elevation was also necessary since ritonavir dose was not constant across treatments. To understand whether dose dependent higher incidence of grade 3/4 ALT elevation is more related to tipranavir or higher dose of ritonavir, the following analysis were conducted.

Ritonavir and tipranavir trough concentrations, which are defined in this analysis as the observed concentrations between 9 and 15 hours after the dose, at day 14 are compared across treatments in Study 52. The time window was used to account for the fact that not every trough concentration was collected at exactly 12 hours. Day 14 was selected to minimize the induction effect of tipranavir, assuming that steady state was achieved by day 14. The median ritonavir concentrations are 0.0962 $\mu\text{g/mL}$ ($n=40$), 0.281 $\mu\text{g/mL}$ ($n=56$), and 0.217 $\mu\text{g/mL}$ ($n=47$), respectively for dose level of 500/100 TPV/RTV, 500/200 TPV/RTV, and 750/200 TPV/RTV. The median tipranavir concentrations are 17.46 $\mu\text{g/mL}$ ($n=60$), 21.26 $\mu\text{g/mL}$ ($n=63$) and 30.75 $\mu\text{g/mL}$ ($n=56$), respectively.

The comparison of incidence of ALT elevation between treatment of 500mg/200 mg TPV/RTV and 750 mg/200 mg TPV/RTV suggested that the increased ALT elevation in higher tipranavir arm most likely resulted from increased tipranavir exposure instead of ritonavir, because ritonavir exposure was lower in 750mg/200mg arm. However, since both ritonavir and tipranavir exposure are higher in 500 mg/200 mg TPV/RTV arm than in 500 mg/100 mg TPV/RTV arm, it is difficult to assess if the higher incidence of ALT toxicity in 500 mg/200 mg TPV/RTV arm as compared with 500 mg/100 mg TPV/RTV is more related to tipranavir or ritonavir.

To further characterize the relationship between ALT elevation and tipranavir or ritonavir exposure, logistic regression analyses were conducted using the data pooled from three arms. The ALT data were available from 216 subjects. Tipranavir and ritonavir trough concentrations at day 14 were available from 179 and 143 subjects, respectively. Therefore, the ALT, tipranavir and ritonavir trough concentration from 143 subjects are pooled for the analyses.

The logistic regression analysis was conducted between incidence of grade 3/4 ALT abnormality and observed log₂ tipranavir trough concentration. The analysis showed that the odds ratio associated with log₂ tipranavir trough concentration was 1.96 (95% confidence interval (CI): 1.15-3.37, p=0.01), suggesting that when tipranavir trough concentration doubles, the odds of having grade 3/4 ALT abnormality was increased by 96%. The estimated odd ratio in this analysis is slightly different from the analysis above. The potential reason could be that 1) observed tipranavir concentration rather than predicted tipranavir concentration was used in this analysis. The predicted concentrations presumably are more precise than observed concentrations because observed trough concentrations were obtained from a time window, the samples collected at time other than 12 hours were considered as samples collected at 12 hours after the dose. In contrast, the predicted concentrations are the concentration at exactly 12 hours after the dose for every subject. 2) The number of subject in this analysis was 143, but was 210 in above analysis.

The similar analysis was conducted between incidence of grade 3/4 ALT abnormality and observed ritonavir trough concentrations. The odd ratio associated with ritonavir trough concentration is 1.37 (95% CI: 0.98-1.22, p=0.065). However, when both tipranavir and ritonavir trough concentration were included in the model, the significance of tipranavir remained not changed but the significance of ritonavir decreased with p value changed from 0.065 to 0.72, indicating the incidence of grade 3/4 abnormality was not likely related to ritonavir, or was weakly related at most.

The ritonavir trough concentration after 500/200 mg TPV/RTV treatment was also compared with the reported ritonavir trough concentration after Kaletra treatment in which 100 mg ritonavir was used. The median ritonavir concentration was 0.281 μ g/mL after 500/200 mg TPV/RTV treatment in Study 52, which is slightly lower than 0.315 (range: 0.087–1.697) μ g/mL, the median ritonavir trough concentration after Kaletra treatment (Canta et al J Antimicrob Chemother 55(2), 280), indicating that higher incidence of liver toxicity are more likely resulted from tipranavir use.

IV. CONCLUSION

1. One compartment model can be used to describe pharmacokinetic of tipranavir.
2. Tipranavir exposure increased by about 15% when the dose of boosting agent, ritonavir, was increased from 100 mg to 200 mg.
3. There is a weak relationship between TPV C_{min} and viral load reduction at week 2.
4. IQ is a better predictor of virological response to the TPV treatment, compared to C_{min} .
5. The probability of having at least 1 log reduction at week 24 is associated with log₁₀ IQ. The odds ratio associated with log₁₀ IQ was 2.17 (90% confidence interval (CI): 1.46-3.22, p<0.0001). Increasing inhibitory quotient in patients with low inhibitory quotient could increase patient's chance to response to the treatment.
6. The incidence of grade 3/4 ALT elevation is related to tipranavir exposure (log₂ TPV C_{min}). The logistic regression analysis showed that the odds ratio associated with log₂ TPV C_{min} was 1.96 (90% confidence interval (CI): 1.15-3.37, p=0.01).

Analysis on Phase 3 Studies:

The exposure response analysis was also conducted for 2 phase 3 studies, RESIST 1 and RESIST 2. Please refer to Dr. Bhore's statistic review for the details of study design. Data used in the following analysis are obtained from the sponsor's submission on December 29, 2004. Specific data set for TPV concentrations, baseline IC₅₀ and efficacy are as follows:

TPV concentration data:

N_000\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0012

N_000\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0048

Baseline IC₅₀ data:

N_000\2004-12-29\crt\datasets\analysis datasets\resistance\datasets\base.res

Efficacy data:

N_000\2004-12-29\crt\datasets\analysis datasets\efficacy\1182_0012\datasets\FDA datasets\master

N_000\2004-12-29\crt\datasets\analysis datasets\efficacy\1182_0048\datasets\FDA datasets\master

I. Tipranavir Trough Concentration (TPV C_{min})

Participants in the RESIST trials had TPV C_{min} determined at Weeks 2 and 4 (both RESIST trials), Week 16 (RESIST 2 only) and Week 24 (RESIST 1 only). There are total of 620 subjects with TPV C_{min} including 143, 223, 253, and 1 with 1, 2, 3, and 4 measures, respectively (n=257 from RESIST 1 and n=362 from RESIST 2). The median TPV C_{min} calculated for the subjects who had more than 1 sample was used to represent tipranavir exposure for the subject. The distribution of median TPV C_{min} in 620 subjects from phase 3 studies is presented in Figure 14. TPV C_{min} ranged from 1.34 to 113.93 µg/mL and with median of 22.01 µg/mL. Since TPV C_{min} were measured more than 1 occasions in 477 subjects, which allows the intra- and inter-subject variability estimates. A linear mixed effect model was used to estimate inter- intra- subject variability. It has been estimated that the inter-subject and intra-subject variability are 50% and 47%, respectively. Noted that in this analysis, observed TPV C_{min}s from week 2 to 16 or 24, were used. Samples may not be collected at the exact 12 hours after the dose, therefore, the intra-subject variability may include the deviation due to uncontrolled sampling time.

II. Baseline IC₅₀

There are 356 subjects with IC₅₀ baseline value including 142 and 151 from RESIST 1 and RESIST 2, respectively. The distribution of corrected baseline IC₅₀, as defined above, is presented in Figure 15. As shown in the figure, corrected IC₅₀ values widely distributed and can be described by a log-normal distribution.

III. Inhibitory Quotient (IQ)

IQ values were calculated as a ratio of average TPV C_{min}, if more than one C_{min} were available for the subject, to corrected baseline IC₅₀. Among the 291 subjects who had calculated IQ, 91 subjects received TPV with enfuvirtide (ENF) and 200 subjects received TPV alone.

IV. Logistic Regression Analysis on Predictors for Responder

Logistic regression analysis was conducted to examine the predictors for responder, who are defined as patients with at least 1 log viral load reduction at week 24. At first, the predictors, including TPV C_{min}, corrected baseline IC₅₀, IQ, number of key mutation, number of FDA mutation, and ENF use were tested by including only one predictor in the model. The results are presented in Table 7. The results show TPV C_{min}, corrected baseline IC₅₀, log₁₀(IQ) and ENF are

significantly associated with probability of being responder at week 24. The number of key mutation is a better predictor than FDA mutation in predicting response.

Table 7. Univariate Analysis on Predictor for Responder at Week 24

model		intercept	slope	p
1	Log10(TPV C _{min})	-8.91±2.25	2.00±0.515	<0.0001
2	Log10(Corrected IC ₅₀)	-0.989±0.217	-1.18±0.266	<0.0001
3	Inhibition quotient	-3.04±0.525	1.41±0.25	<0.0001
4	Key mutation	0.365±0.364	-0.339±0.202	0.09
5	FDA mutation	0.0848±0.367	-0.088±0.103	0.39
6	ENF	-0.554±0.147	1.07±0.261	<0.0001

Multi-variate analyses were conducted to further evaluate the predictors of response and the results are presented in Table 8. The analysis suggested that both log10(IQ) and ENF use are the predictors of response. After including log10(IQ) and ENF use in the model, the number of key mutations is no longer a predictor for response. There are total of 195 subjects with 2 key mutation including 65 subjects received TPV with ENF and 130 received TPV alone. The analysis in this sub-population (model 4 in Table 8) showed that log10(IQ) and ENF use are still significantly related to response, indicating that the number of mutations itself can not explain the difference in response in those patients. In HIV treatment, genotyping is more commonly used than phenotyping due to the cost and time required to receive test results. Attempts have been made to examine if genotyping, e.g. the number of mutation could replace phenotyping e.g. corrected IC₅₀ to predict response. The results of model 5 and 6 suggested that after including TPV C_{min} and ENF in the model, both number of FDA mutation and number of key mutation did not provide extra information on predicting response, indicating that phenotyping as measured as corrected IC₅₀ did provide information which genotyping can not provide.

Table 8. Multiple Variates Analysis

model		intercept	slope	p
1	Log10(C _{min})+ log10(corrected IC ₅₀)	-10.45±2.39	C _{min} : 2.17±0.541 IC ₅₀ : -1.237±0.272	<0.0001 <0.0001
2	Log10(IQ)+ENF	-3.457±0.565	IQ: 1.445±0.264 ENF : 1.094±0.279	<0.0001 <0.0001
3	Log10(IQ)+ENF +key mutation	-3.079±0.757	IQ: 1.40±0.27 ENF : 1.13±0.28 Key mutation: -0.17±0.23	<0.0001 <0.0001 =0.46
4	ENF +log10(IQ) in subjects with number of mutation 2 (n=195)	-3.358±0.676	ENF :1.315±0.322 IQ: 1.389±0.334	<0.0001 <0.0001
5	Log10(C _{min})+ FDA mutation+ENF	-2.10±0.82	C _{min} :1.48±0.54 ENF :0.86±0.28 FDA mutation: -0.11±0.11	<0.0001 =0.0019 =0.48
6	Log10(C _{min})+ key mutation+ENF	-1.67±0.82	C _{min} :1.44±0.54 ENF :0.93±0.28 Key mutation: -0.45±0.22	<0.0001 =0.001 =0.12

Based on above analysis, the final model for predicting responder at week 24 includes log10(IQ) and ENF use. The results are presented in Figure 16. The lines represent the model predicted response and associated 90% confidence intervals and the symbols represent observed response rate in 6 groups, corresponding to 0-10 percentile, 25-50 percentile, 50-75 percentile, 75-90 percentile, and 90-100 percentile of IQ values in the patients. The odd ratios associated with log10(IQ) and ENF use are 4.24 (90% CI: 2.52-7.12) and 2.98 (90% CI: 1.73-5.16), respectively. The analysis indicated the response rate is related to inhibitory quotient. Increasing inhibitory quotients can increase response rate when tipranavir was used with or

without ENF. ENF use significantly increased response rate, e.g. at an inhibitory quotient of 100, the predicted response rate is increased from 36% when TPV is given alone to 63% when given concomitantly with ENF. After the fixed doses of 500 mg tipranavir/ 200 mg ritonavir, patients with low inhibitory quotient had low response rate especially when ENF was not used. The number of responder and the response rate in four groups of patients: ENF use+IQ>100, ENV use +IQ<100, no ENV use +IQ>100 and no ENV use +IQ<100, are presented in Table 9. In this observed data, it showed that when inhibitory quotients were greater than 100, 54% of patients responded to TPV alone and 73% (34/45) of patients responded to TPV+ENF. When inhibitory quotients are less than 100, 21% of patients responded to TPV alone and 52% of patients responded to TPV+ENF.

Table 9. Number of Responder and Response Rate in Relation to ENF use and IQ Values

ENF use	IQ >100 or not	Responder	non-responder	Total umber of patient (responder + non-responder)	Response rate
Yes	Yes	33	12	45	73%
	No	24	22	46	52%
No	Yes	50	42	92	54%
	No	23	85	108	21%

Expert opinion on what a desired target IQ should be. From exposure response perspective, a target of IQ value of 100 is reasonable since it is approaching to the flat region of exposure response curve, which would increase the robustness of target. At the selected dose of 500 mg/200 mg tipranavir/ritonavir dose, the percent of patients who reached arbitrary selected target IQ of 50, 100, and 150 which associated different probability of having 1 log vial reduction at week 24 are shown in Table 10. It shows that only about half of patients reached IQ of 100 after the fixed doses of 500 mg/200 mg tipranavir/ritonavir.

Table 10. Total of 281 Subjects with IQ Value and Key Mutation <3

Target IQ	Probability of having 1 log viral reduction at week 24	% subject above target
150	70	38%
100	63	48%
50	52	70%

Since IQ is related to the patient's response to the treatment, it is interesting to examine the IQ distribution after the fixed doses of 500 mg/200 mg tipranavir/ritonavir. The distribution of IQ in RESIST 1 and 2 studies is presented in Figure 17. It shows that IQ values are very variable and ranged from 0.885 to 2852 and median of 93.29, suggesting that at fixed doses the patient's response was not predictable unless IQ was calculated. The wide range of IQ after the fixed dose also suggested that individualization of TPV dose might be an optional alternative to the fixed dose regimen.

IQ values from combined RESIST 1 and 2 studies are divided into 5 groups according to their number of key mutation and presented in Figure 18 and Table 11. It shows that IQ values dramatically decreased when number of key mutation is increased. Even though only 9 and 1 subjects with number of key mutation of 3, and 4, the IQ values are low, suggesting that at the current dose of 500 mg/200 mg TPV/RTV, the likelihood of having successful treatment in patient infected with virus with more than 3 key mutations is minimal.

Table 11. IQ values in Patients with Different Number of Key Mutation

# of mutation	0	1	2	3	4
# of subject	9	77	195	9	1
Median min-max	420 29-2852	164 10-1585	81 1-1476	29 13-138	15 NA

V. Conclusion:

1. It has been consistently demonstrated by phase 3 studies that the response of patient to the treatment of 500 mg/200 mg TPV/RTV is related to IQ value.
2. ENF use significantly increases the patient's probability of responding to the tipranavir treatment.
3. Phenotyping is more informative than genotyping in predicting virological response.
4. IQ values widely ranged after the fixed doses of 500 mg/200 mg TPV/RTV, suggesting that the response is unpredictable unless TPV C_{min} and baseline IC_{50} are measured and so that IQ be calculated.
5. Individualized dose strategy should be considered as an optional alternative to the fixed doses treatment.

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Figure 1. The Observed and Predicted Population Concentrations vs Time for Three Dose Levels: 750/200 TPV/r, 500/200 TPV/r, and 500/100 TPV/r

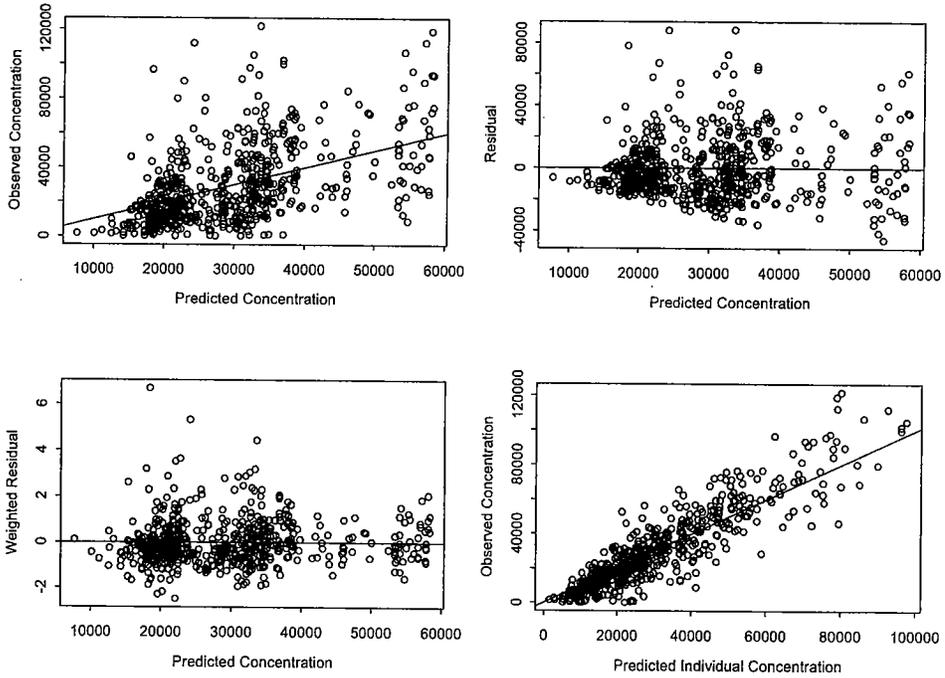
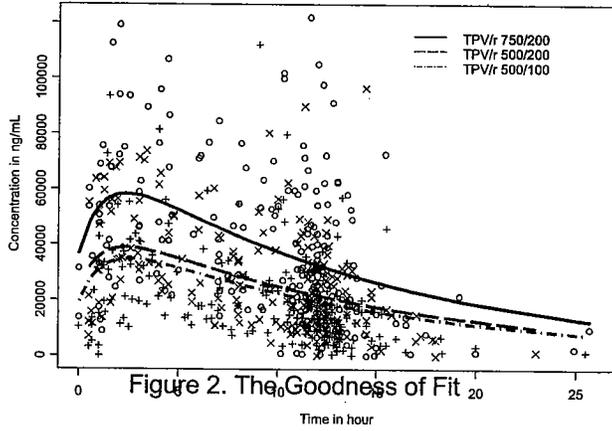


Figure 3. Viral Load Reduction in First Two Weeks

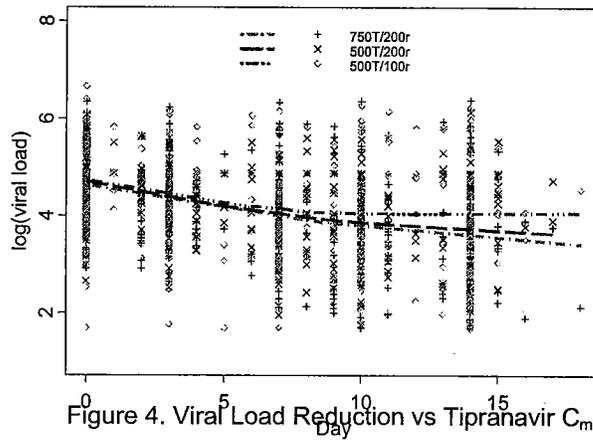


Figure 4. Viral Load Reduction vs Tipranavir C_{min}

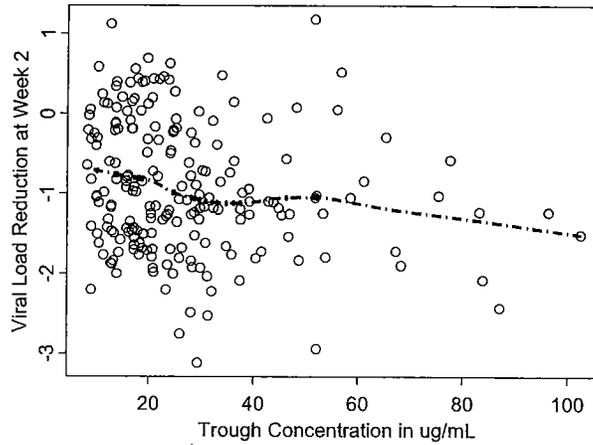


Figure 5. Viral Load Reduction at Week 2 vs Inhibitory Quotient ($C_{min}/\text{corrected } IC_{50}$)

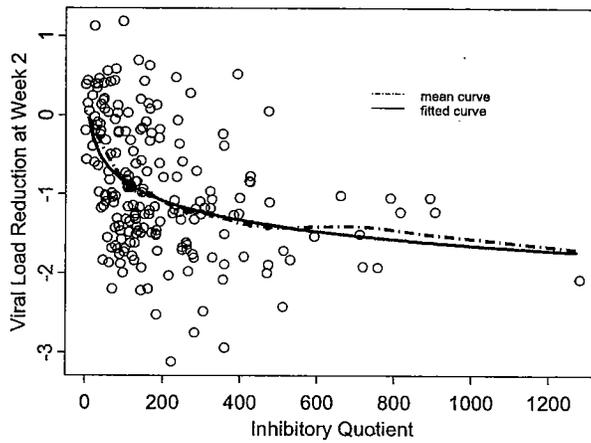


Figure 6. Probability of patients achieving at least one log viral load reduction increases with higher inhibitory quotient.

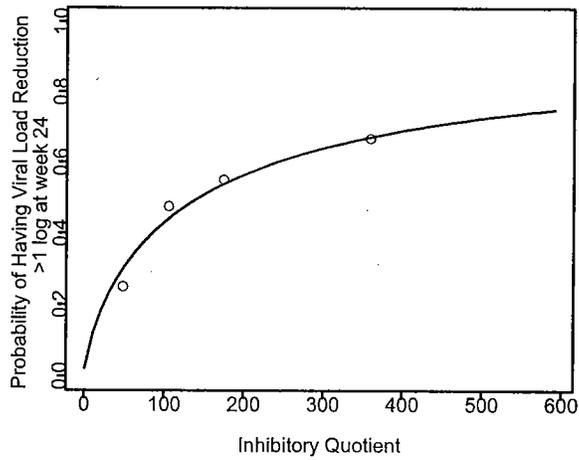


Figure 7. Cholesterol changes from baseline after tipranavir treatment at three dose levels: 500 mg Tipranavir/100 mg ritonavir; 500 mg Tipranavir/200 mg ritonavir; and 750 mg Tipranavir/200 mg ritonavir

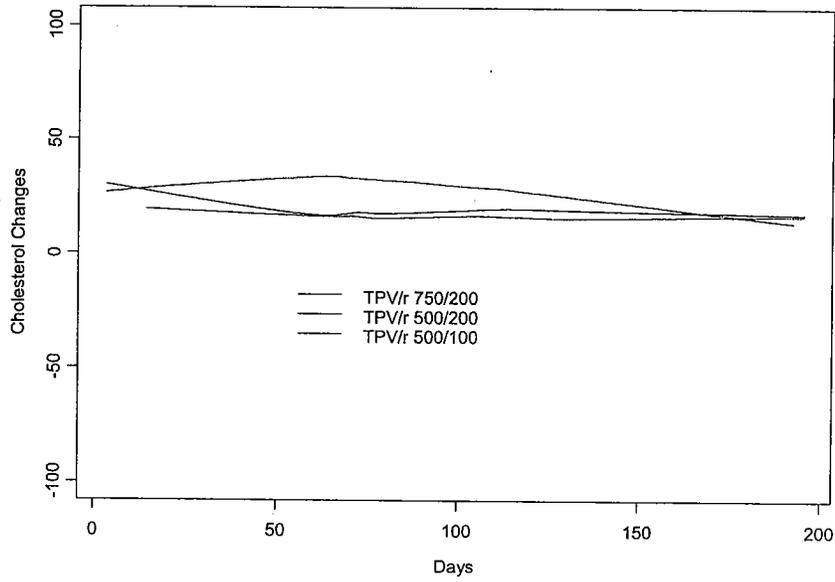


Figure 8. Triglyceride changes from baseline after tipranavir treatment at three dose levels: 500 mg Tipranavir/100 mg ritonavir; 500 mg Tipranavir/200 mg ritonavir; and 750 mg Tipranavir/200 mg ritonavir

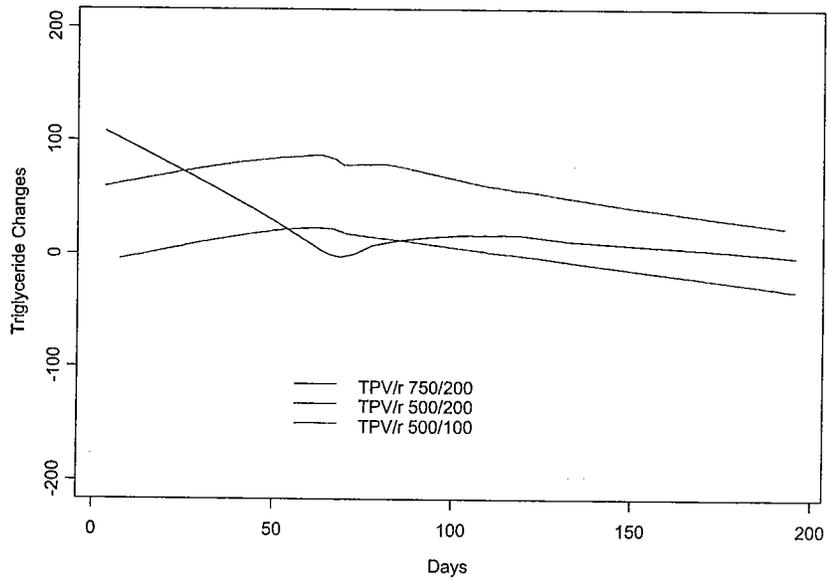


Figure 9. ALT changes from baseline after tipranavir treatment at three dose levels: 500 mg Tipranavir/100 mg ritonavir; 500 mg Tipranavir/200 mg ritonavir; and 750 mg Tipranavir/200 mg ritonavir

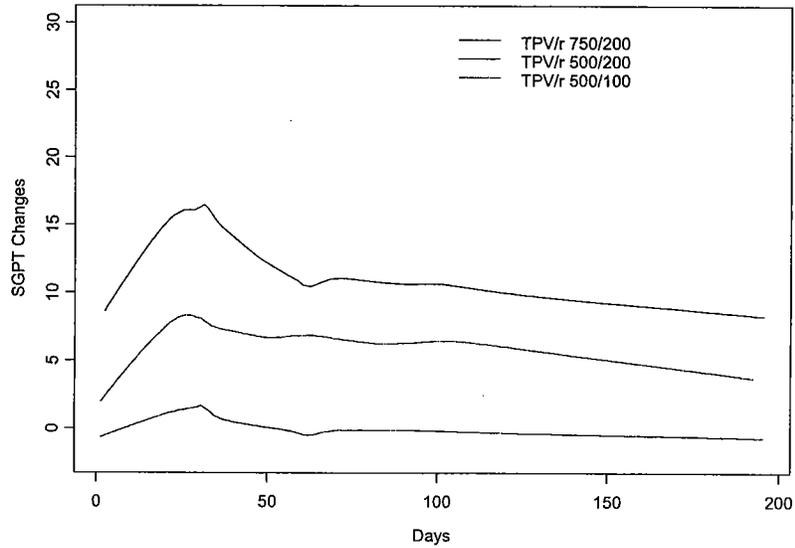


Figure 10. GGT changes from baseline after tipranavir treatment at three dose levels: 500 mg Tipranavir/100 mg ritonavir; 500 mg Tipranavir/200 mg ritonavir; and 750 mg Tipranavir/200 mg ritonavir

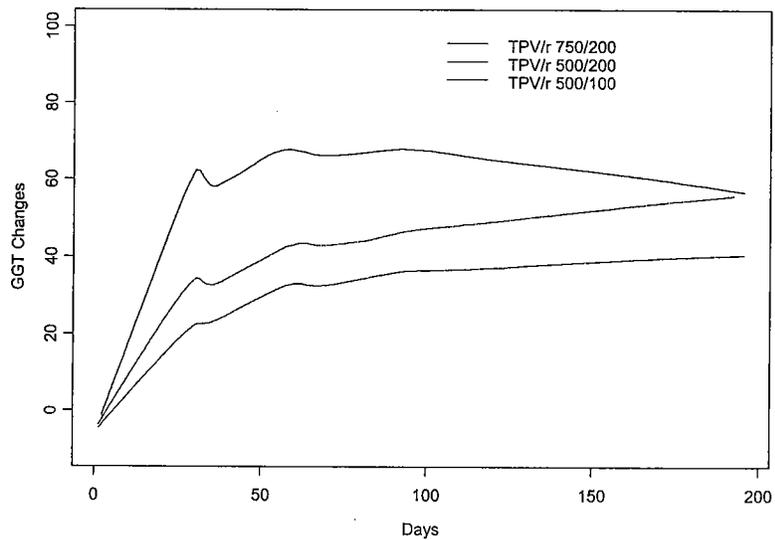


Figure 11. SGOT changes from baseline after tipranavir treatment at three dose levels: 500 mg Tipranavir/100 mg ritonavir; 500 mg Tipranavir/200 mg ritonavir; and 750 mg Tipranavir/200 mg ritonavir

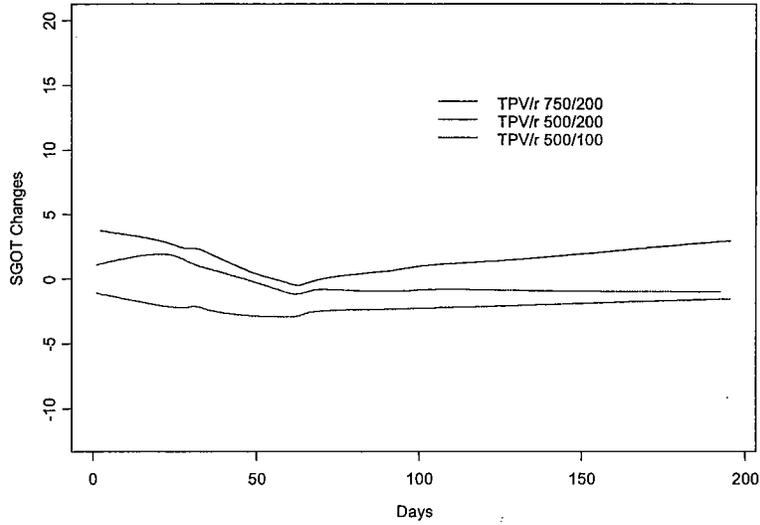


Figure 12. Probability of Patients Having a Grade 3/4 ALT Elevation vs. TPV Cmins

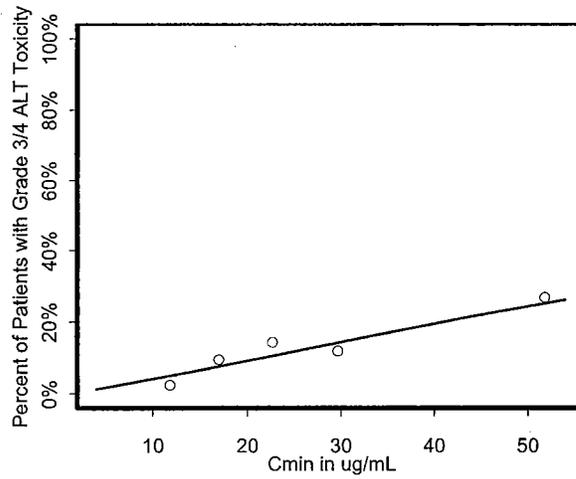


Figure 13. Range of Ritonavir and Tipranavir Trough Concentrations at the 3 Dose Levels in Study 52.

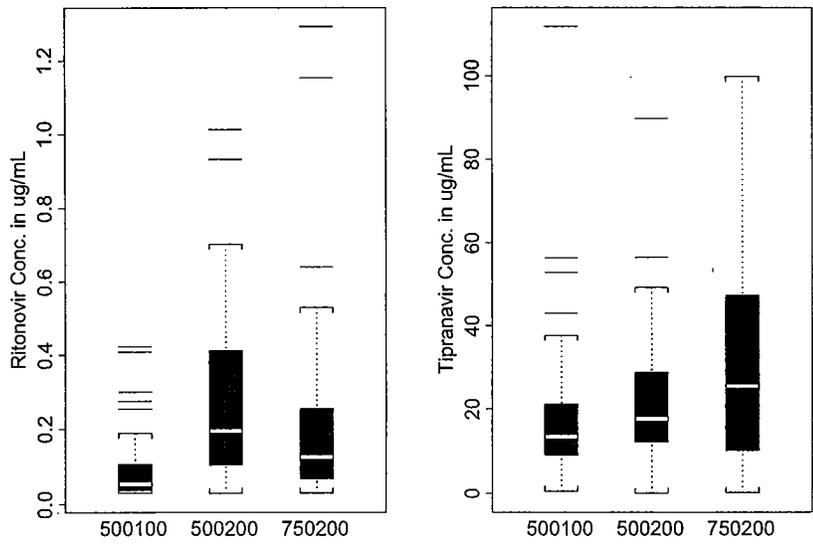


Figure 14. Distribution of Tipranavir Trough Concentrations from Combined Phase 3 Studies (n=620)

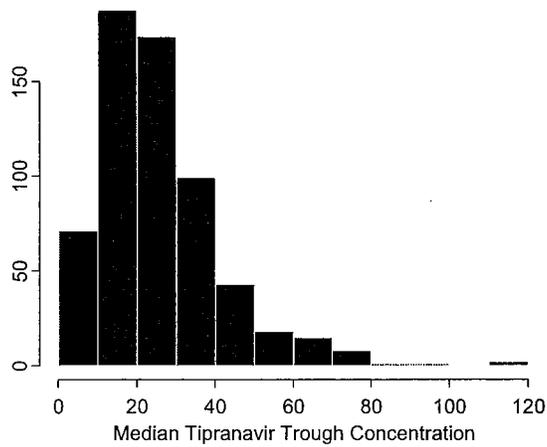


Figure 15. Distribution of Baseline IC₅₀ in RESIST 1 and 2 Studies (n=356)

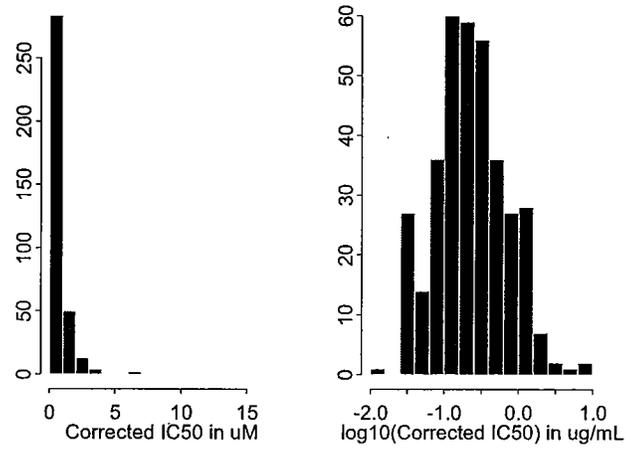


Figure 16. Viral Response at Week 24 vs IQ and ENF in Combined RESIST 1 and 2 Studies

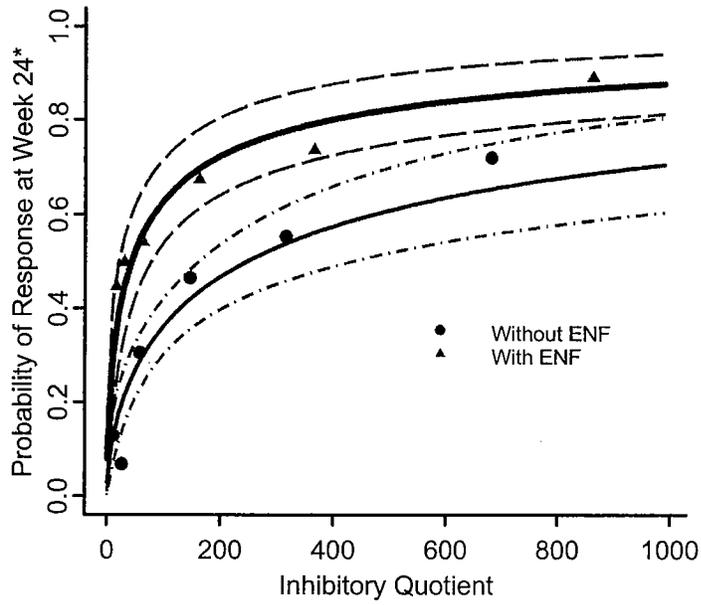


Figure 17. Distribution of log₁₀(IQ) in Combined 2 Phase 3 Studies
 Min=0.885, median=93.293 and Max.= 2852.069

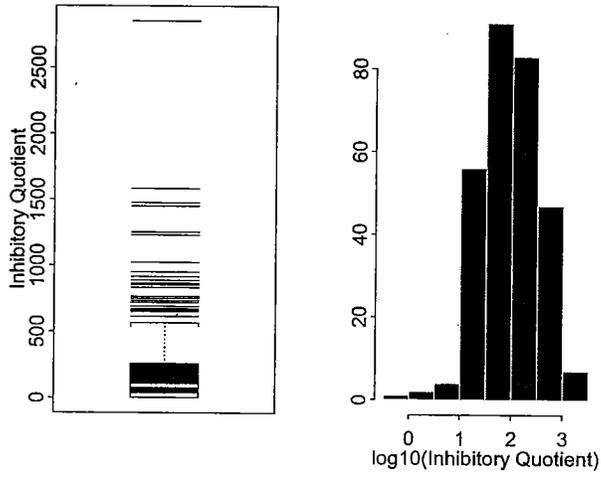
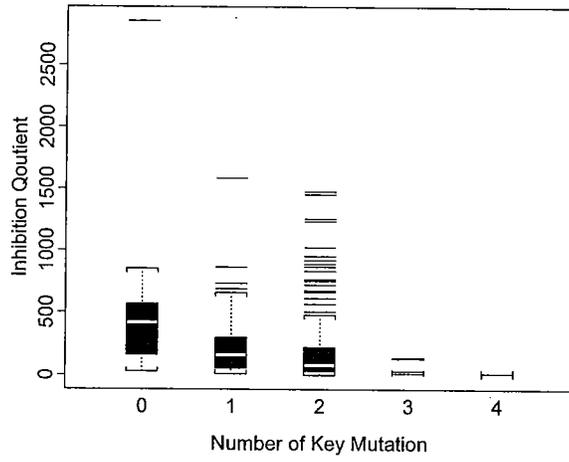


Figure 18. IQ Distribution in Patients with Different Number of Key Mutation



Appendix:

Additional figures generated for Study 52 and the 2 phase 3 studies are included in this section.

Study 52:

Viral load reduction rate during the two weeks mono-therapy was calculated using nonlinear mixed effect model by NONMEM. The model is described by the equation below:

$$ViralLoad = BaseVL * \exp(-Rate * Time)$$

BaseVL and Rate for each individual was estimated. The viral load observations and population prediction are presented in Figure 1 and 2. In figure 1, open circles are observations and solid line is the population prediction.

Figure 1:

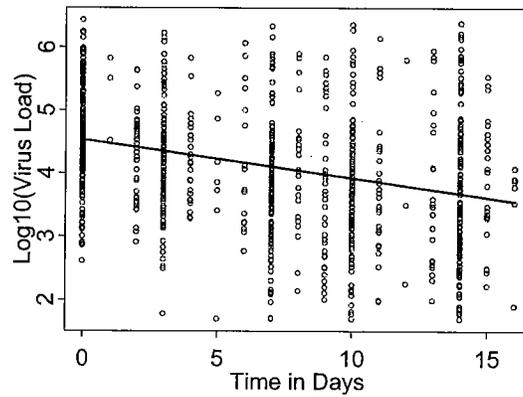
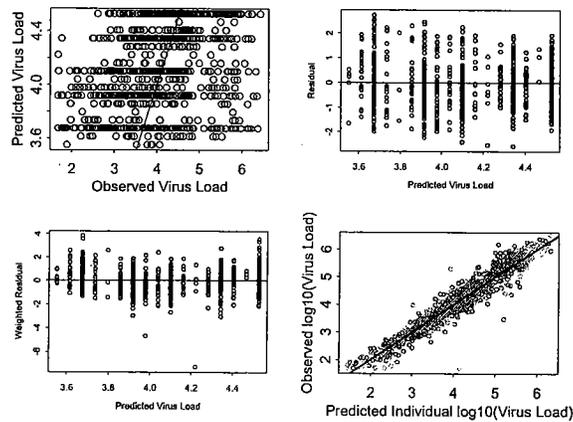
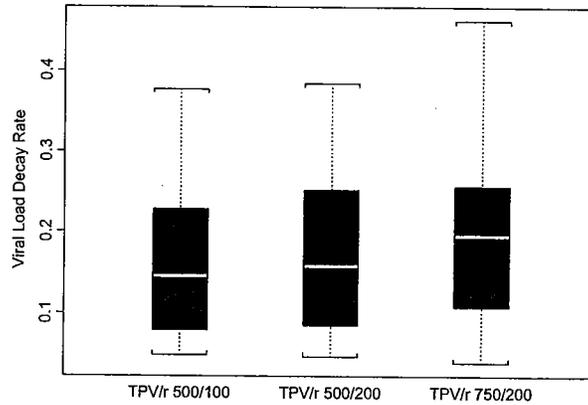


Figure 2: Goodness of fit for viral load dynamic model

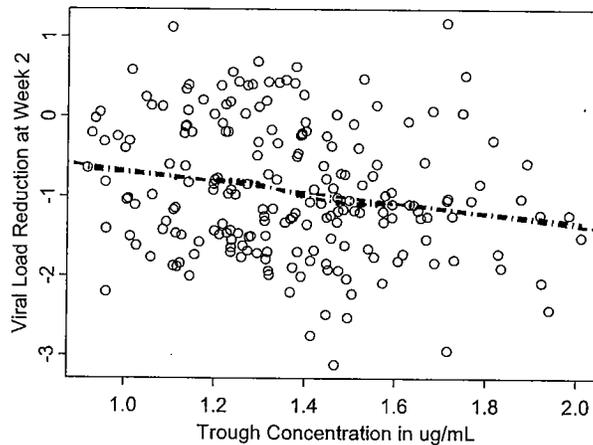


The viral load decay rate across treatments is presented in Figure 3. Figure 3.



The correlation between viral load reduction at week 2 and $\log_{10}(C_{\min})$ was explored by linear regression analysis and the results are shown in Figure 4. Red dashed line represents fitted line and black dash represents the local mean by lowess function in Splus. It shows that there is a very weak relationship between $\log_{10}(C_{\min})$ and viral load reduction at week 2 ($R^2=0.04$).

Figure 4.



Correlation between viral load reduction at week 2 and $\log_{10}(IQ)$ was also examined by linear model and the results are shown in Figure 5A and 5B. The results indicated that inhibition quotient explains about 20% variability in viral load reduction at week 2 but C_{\min} explains only 4%.

Figure 5A: x in log10 scale

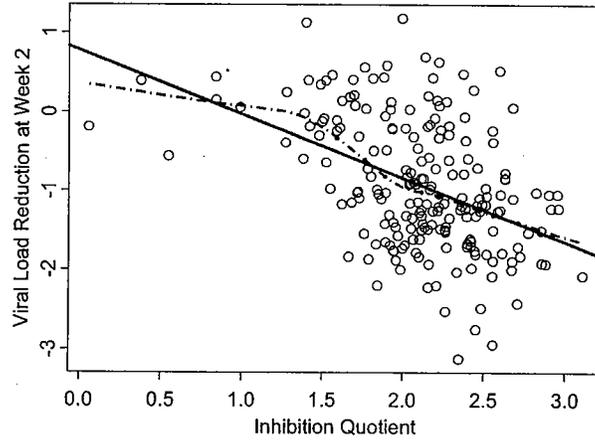
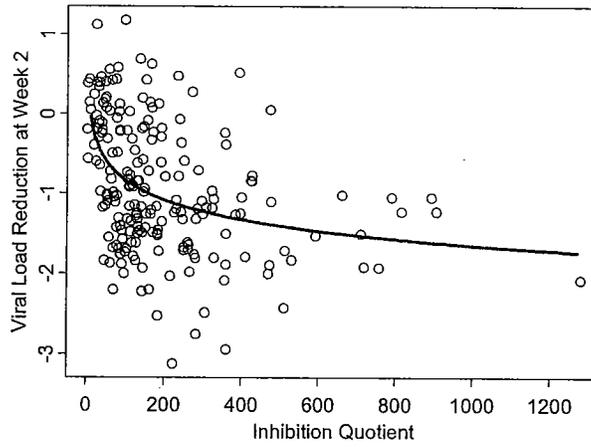
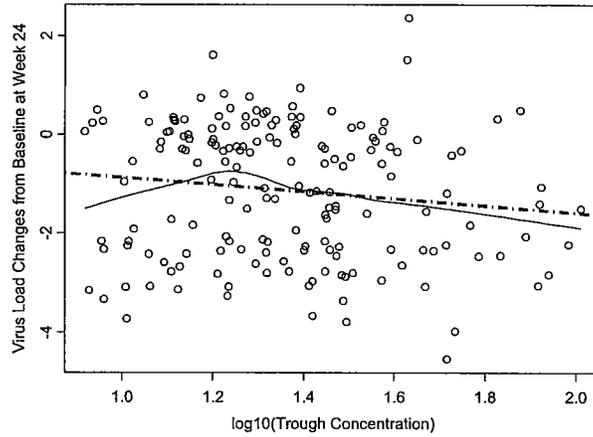


Figure 5B: x in normal scale



The correlation between viral load reduction at week 24 vs $\log_{10}(C_{min})$ is even weaker (Figure 6). Only 2% of variability in viral load reduction at week 24 can be explained by C_{min} .

Figure 6.



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2 Phase 3 studies (Study 12 and Study 48):

The correlation between viral load reduction at week 24 and $\log_{10}(\text{IQ})$ was examined by linear model and results is shown in Figure ($R^2 = 0.12$). In figure 7A, x axis is in \log_{10} scale and in figure 7B, x axis is in normal scale. Solid line is model fitted line and dash line is local mean obtained from lowess function from Splus.

Figure 7A:

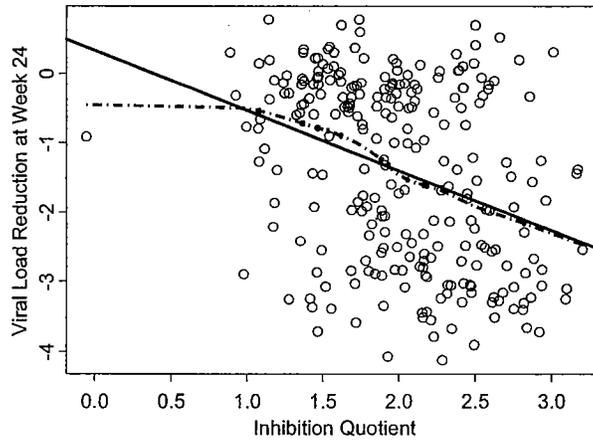
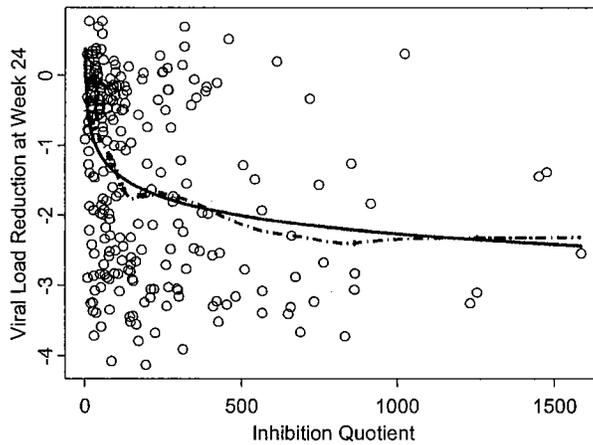
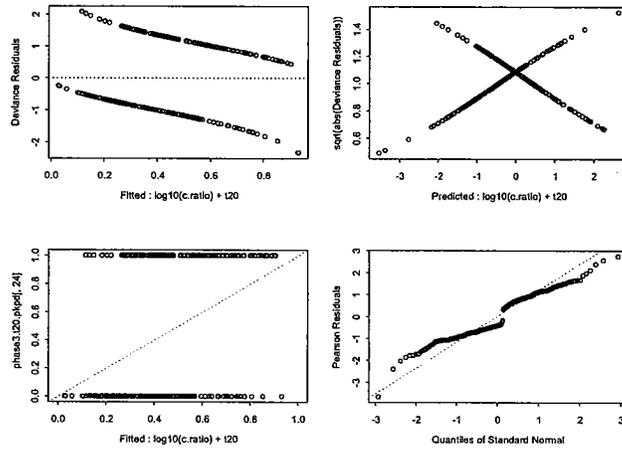


Figure 7B:



The figures for assessing goodness of fit of the final model for the 2 phase 3 study was presented in Figure 8.

Figure 8.

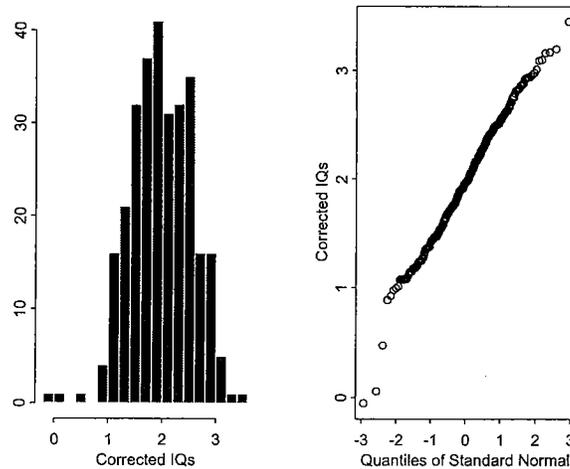


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To examine the distribution of $\log_{10}(IQ)$, a QQ plot was generated and shown in Figure 9. It shows that it is reasonable to assume that $\log_{10}(IQ)$ is normal distributed.

Figure 9:

Q-Q plot of $\log_{10}(IQ)$



4.3 DPEIII Division Director's Concurrence on PMCs

-----Original Message-----

From: Lazor, John A

Sent: Tuesday, June 21, 2005 5:11 PM

To: Zhang, Derek Yuanchao; Reynolds, Kellie S

Subject: RE: NDA 21-814 Aptivus (tipranavir) Post Marketing Commitments

Sensitivity: Confidential

Concur. These are studies that BIPI has proposed, completed, or are ongoing.

-----Original Message-----

From: Zhang, Derek Yuanchao

Sent: Tuesday, June 21, 2005 4:44 PM

To: Lazor, John A

Cc: Reynolds, Kellie S

Subject: NDA 21-814 Aptivus (tipranavir) Post Marketing Commitments

Importance: High

Sensitivity: Confidential

John,

We need your official concurrence to the clinical pharmacology related PMCs for NDA 21-814. See attached list. Thanks,

Derek

4.4 OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
<i>General Information About the Submission</i>				
	Information		Information	
NDA Number	21-814, 21-822	Brand Name	APTIVUS	
OCPB Division (I, II, III)	DPE III	Generic Name	Tipranavir	
Medical Division	HFD-530	Drug Class	HIV protease inhibitor	
OCPB Reviewer	Derek Zhang	Indication(s)	HIV infection	
OCPB Team Leader	Kellie Reynolds	Dosage Form	Capsule and oral solution	
		Dosing Regimen	500 mg/200 mg ritonavir b.i.d.	
Date of Submission	December 21, 2004	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	Boehringer Ingelheim	
PDUFA Due Date	June 22, 2005	Priority Classification	Priority Review	
	May 3, 2005			
Division Due Date				
<i>Clin. Pharm. And Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	1		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X	1		1182.5
Patients-				
single dose:				
multiple dose:	X	1		1182.52
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:	X	12		Same studies for effects on and of
In-vivo effects of primary drug:	X	12		
In-vitro:	X	3		
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		1182.2, 1182.4, 1182.52
Phase 3 clinical trial:	X	2		1182.12, 1182.48
Population Analyses -				
Data rich:	X	1		1182.51
Data sparse:	X	1		1182.52
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		1182.45
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Other Studies	X	8		vitro studies and bioanalytical assay validation reports
Pediatric development plan				
Literature References	X			
Total Number of Studies				
		37		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Drug-drug interactions	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Derek Zhang
6/22/05 12:36:54 PM
BIOPHARMACEUTICS

Jenny Zheng
6/22/05 12:39:01 PM
BIOPHARMACEUTICS

Jogarao Gobburu
6/22/05 01:12:25 PM
BIOPHARMACEUTICS

Kellie Reynolds
6/22/05 01:17:18 PM
BIOPHARMACEUTICS