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]
$AUC_{0\text{-}12h}$ (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]
$AUC_{0\text{-}12h}$ (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]
$AUC_{0\text{-}\infty}$ (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]
$AUC_{0-\infty}$ (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
Cp_{12h} (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

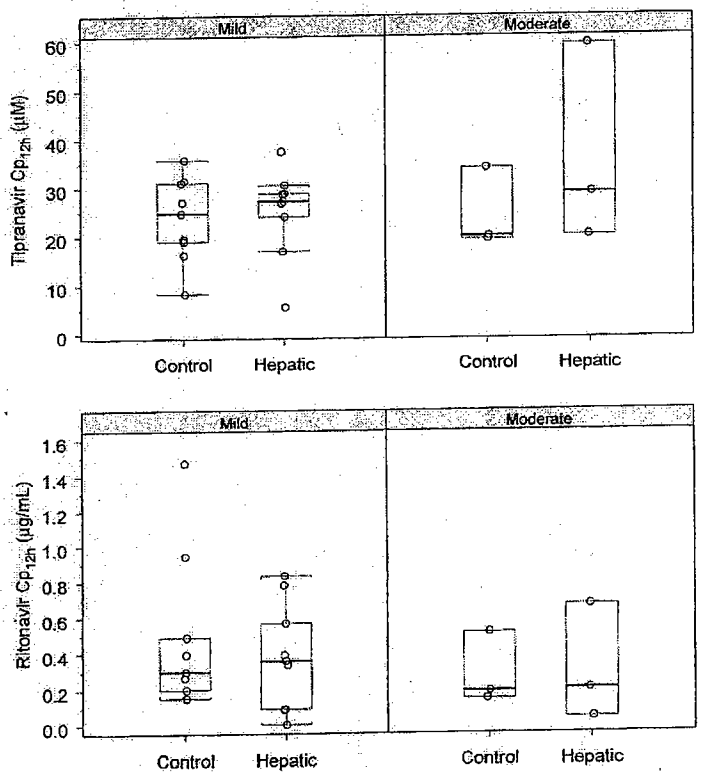


Figure 2. Plasma tipranavir and ritonavir C_{max} for subjects with mild or moderate hepatic insufficiency and their matched controls following a single dose of TPV/r

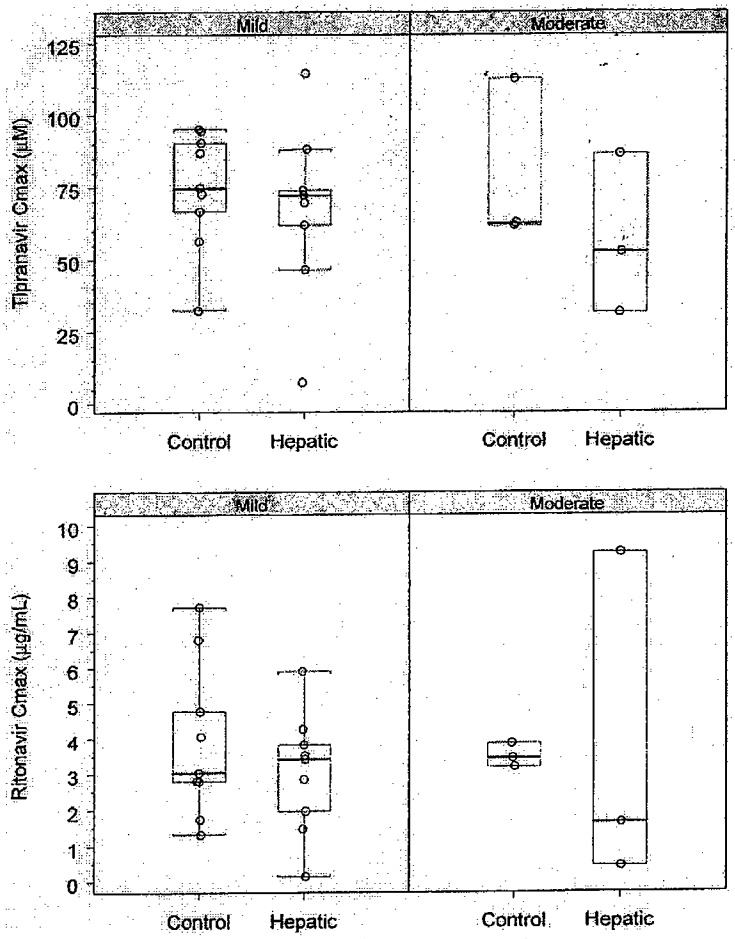


Figure 3. Plasma tipranavir and ritonavir AUC for subjects with mild or moderate hepatic insufficiency and their matched controls following a single dose of TPV/r

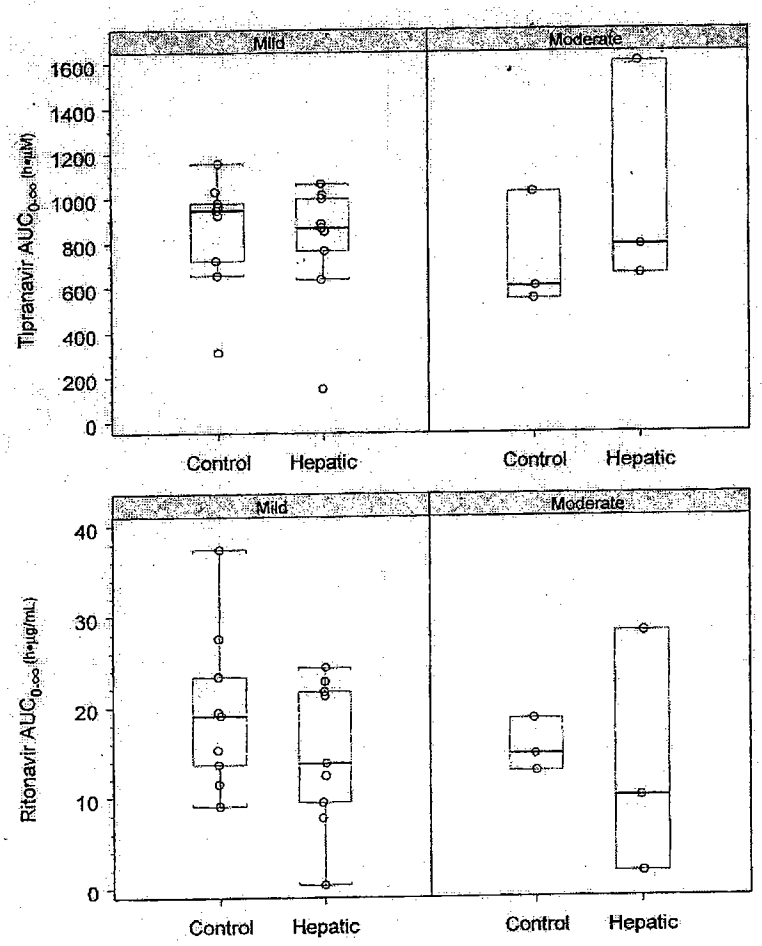


Figure 4. Steady-state plasma tipranavir and ritonavir C_{p12h} for subjects with mild hepatic insufficiency and their matched controls

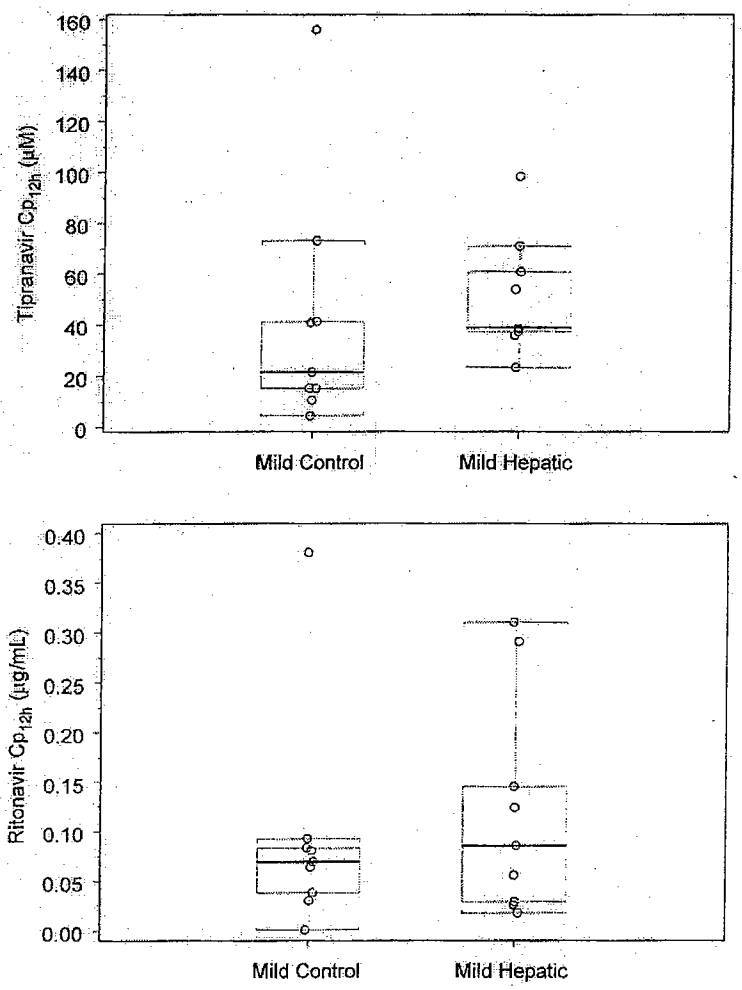


Figure 5. Steady-state plasma tipranavir and ritonavir C_{max} for subjects with mild hepatic insufficiency and their matched controls

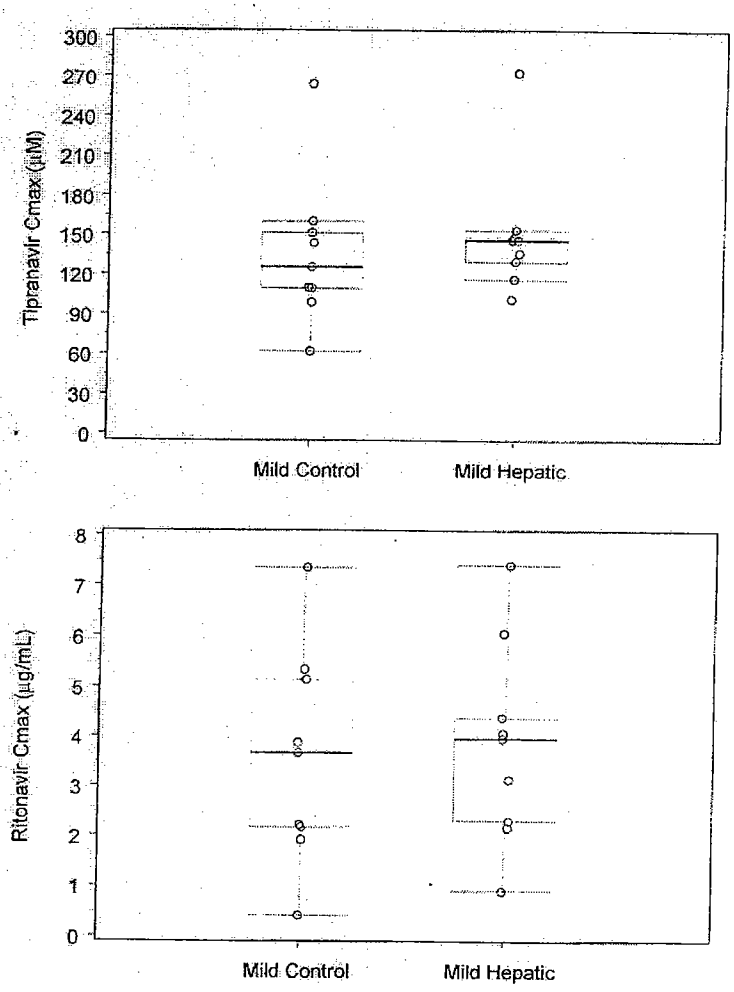
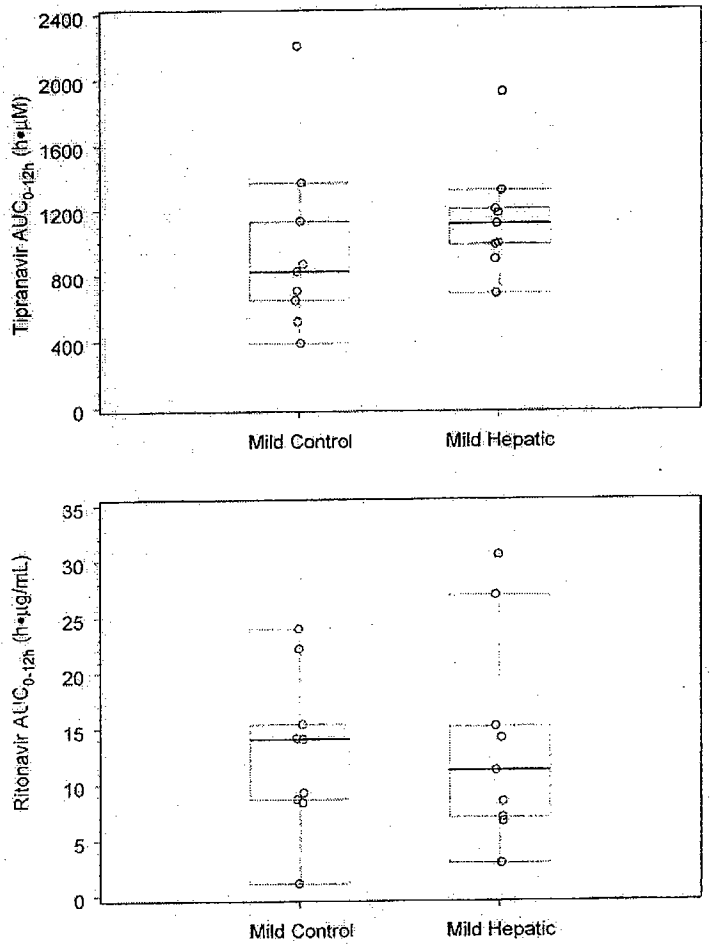


Figure 6. Steady-state plasma tipranavir and ritonavir AUC for subjects with mild hepatic insufficiency and their matched controls



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

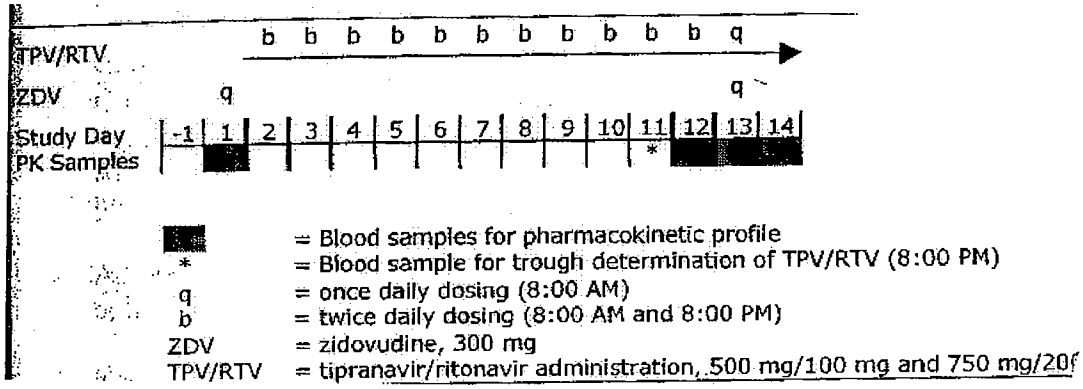
population will be made based on safety considerations as discussed in the Medical Officer's review. Since liver is considered as the major organ to eliminate tipranavir from systemic circulation, for anticipated safety concerns, tipranavir/ritonavir should be contraindicated for patients with severe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

1182.37

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: [redacted]

FORMULATION: Tipranavir: 250 mg soft elastic capsules, self-emulsifying drug delivery system (SEDDS) formulation. Norvir: 100 mg soft elastic capsules. Retrovil: 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 [redacted] using a validated high performance liquid chromatography [redacted] method. The calibration curve ranged from [redacted] ng/mL to [redacted] ng/mL. ZDV/GZDV concentrations were performed also by [redacted] using a validated high performance liquid chromatography [redacted] method. The calibration curves ranged from [redacted] to [redacted] ng/mL for ZDV and from [redacted] 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 $AUC_{0\text{-}12h}$ were provided for TPV/RTV (with and without ZDV) and geometric means and coefficients of variation for C_{max}, C_{p6h} and $AUC_{0\text{-}12h}$ 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	Geometric Range Lower Limit	Geometric 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
CMAX	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	Geometric Range Lower Limit	Geometric Range Upper Limit
AUC 0-12h	h*ug/mL	gZDV WITH TPV 500MG/RTV 1	13	29		16.10		15.00	12.13	18.56
		gZDV WITHOUT TPV 500MG/RT	1	29		15.33		14.75	12.06	18.04
	h*ug/mL	gZDV WITH TPV 750MG/RTV 2	13	25		15.85		15.77	12.76	19.50
		gZDV WITHOUT TPV 750MG/RT	1	25		13.85		14.46	11.64	17.97
C6h	ug/mL	gZDV WITH TPV 500MG/RTV 1	13	29		0.24		0.25	0.15	0.41
		gZDV WITHOUT TPV 500MG/RT	1	29		0.16		0.17	0.11	0.25
	ug/mL	gZDV WITH TPV 750MG/RTV 2	13	25		0.34		0.31	0.20	0.48
		gZDV WITHOUT TPV 750MG/RT	1	25		0.16		0.16	0.09	0.30
CMAX	ug/mL	gZDV WITH TPV 500MG/RTV 1	13	29		7.87		7.68	6.26	9.41
		gZDV WITHOUT TPV 500MG/RT	1	29		9.51		9.40	6.74	13.12
	ug/mL	gZDV WITH TPV 750MG/RTV 2	13	25		7.76		7.60	5.98	9.65
		gZDV 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	Minimum	Median	Maximum	Geometric Mean	Geometric Range Lower Limit	Geometric Range Upper Limit
AUC 0-12h	umoL	TPV 500MG WITH ZDV	13	29		814.77		850.76	667.53	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	2926.58
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
CMAX	umoL	TPV 500MG WITH ZDV	13	29		130.26		130.81	92.22	185.54
		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

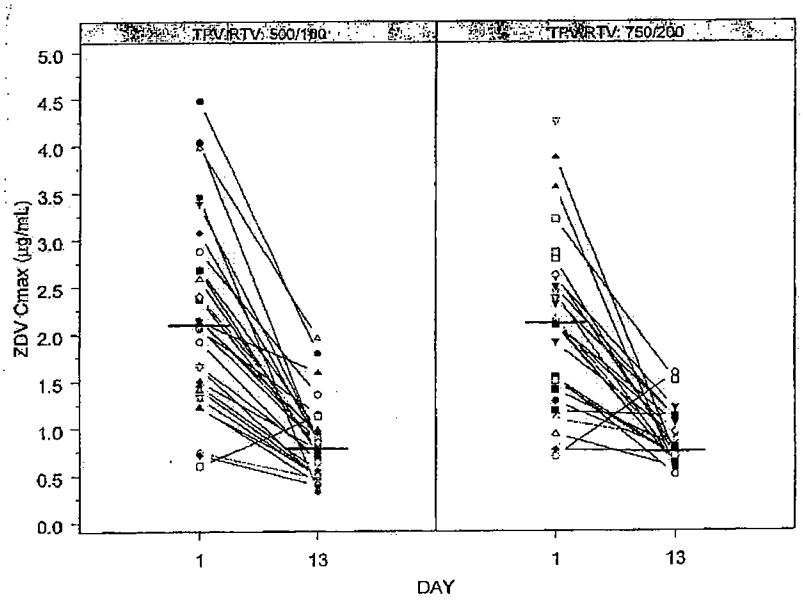
Table 4. Summary of the steady-state pharmacokinetic parameters of RTV with and without ZDV and their geometric means with 90% confidence intervals

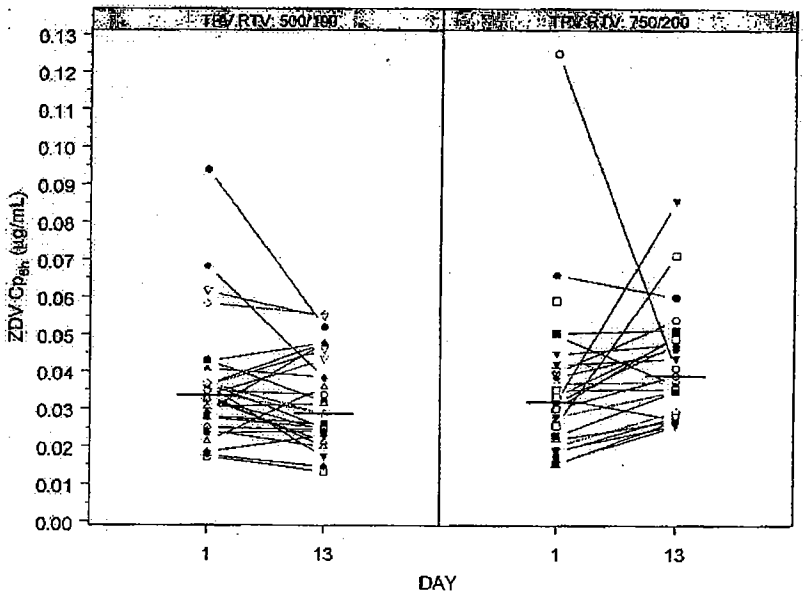
PK PARAMETER	LAB UNIT	TREATMENT	DAY	N	Minimum	Median	Maximum	Geometric Mean	Geometric Range Lower Limit	Geometric Range Upper Limit
AUC 0-12h	h*ug/mL	RTV 100MG WITH ZDV	13	29		3.39		3.32	2.03	5.44
		RTV 100MG WITHOUT ZDV	12	29		5.45		3.94	1.96	7.90
	h*ug/mL	RTV 200MG WITH ZDV	13	24		11.54		11.40	6.95	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
CMAX	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		3.06	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)

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TPV/RTV: 750/200
ZDV Cp_{ss} (ug/mL)
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
1
13
1
13
DAY

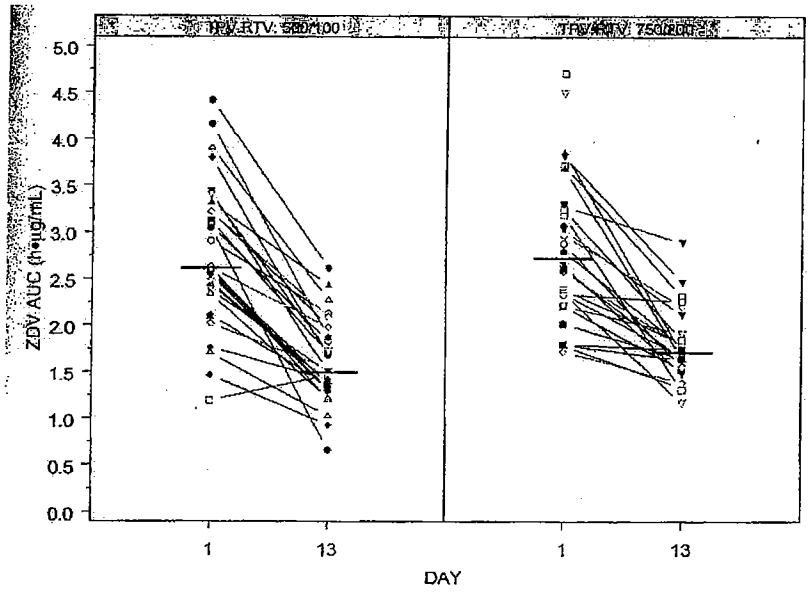
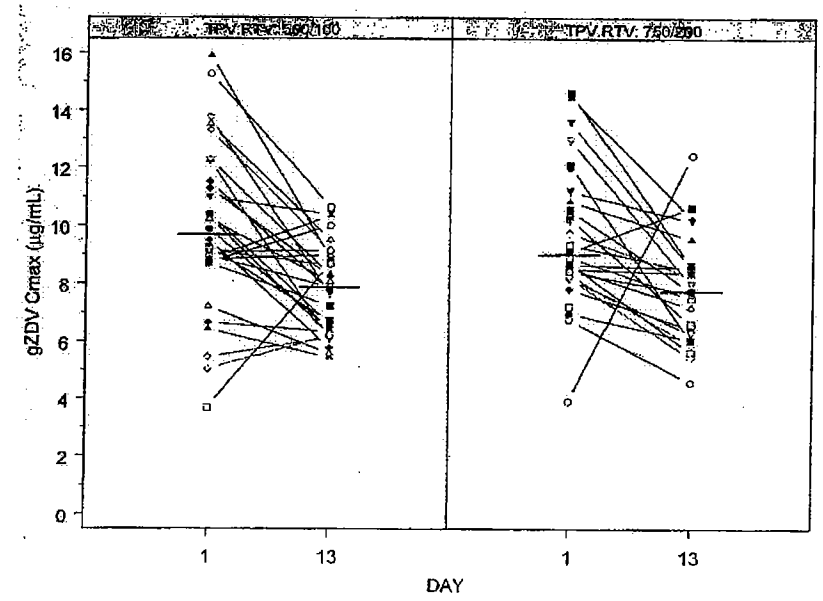
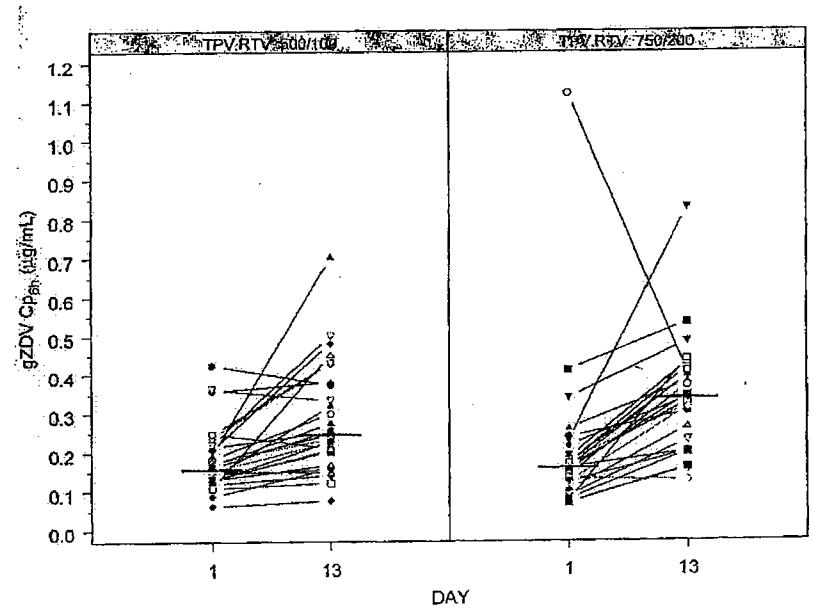

TPV/RTV: 500/100
TPV/RTV: 750/200
ZDV AUC (h•ug/mL)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
13
1
13
DAY

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





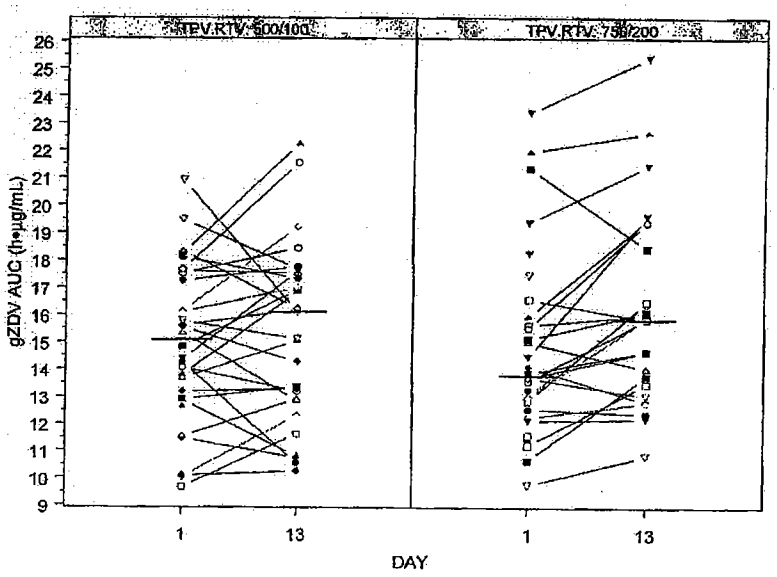
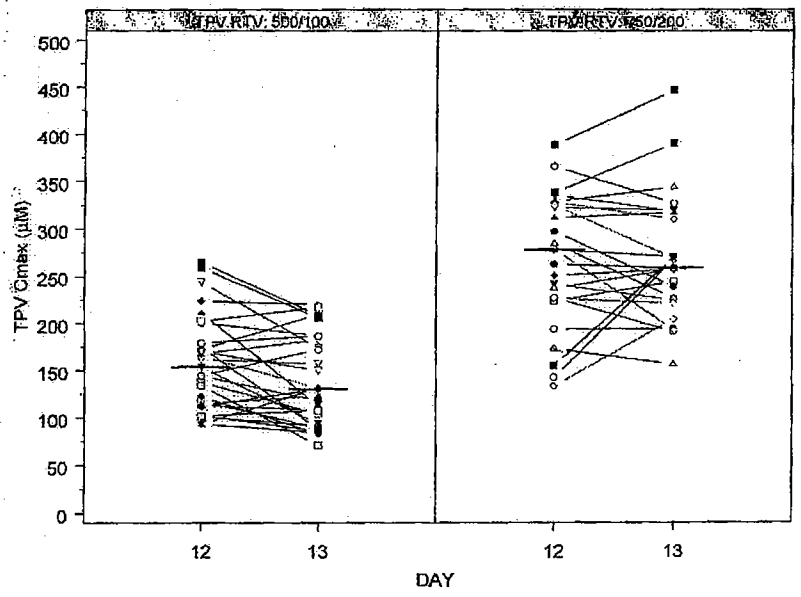


Figure 3. TPV C_{max}, C_{p12h} and AUC_{0-12h} with and without ZDV by subjects (Solid line represents median value)



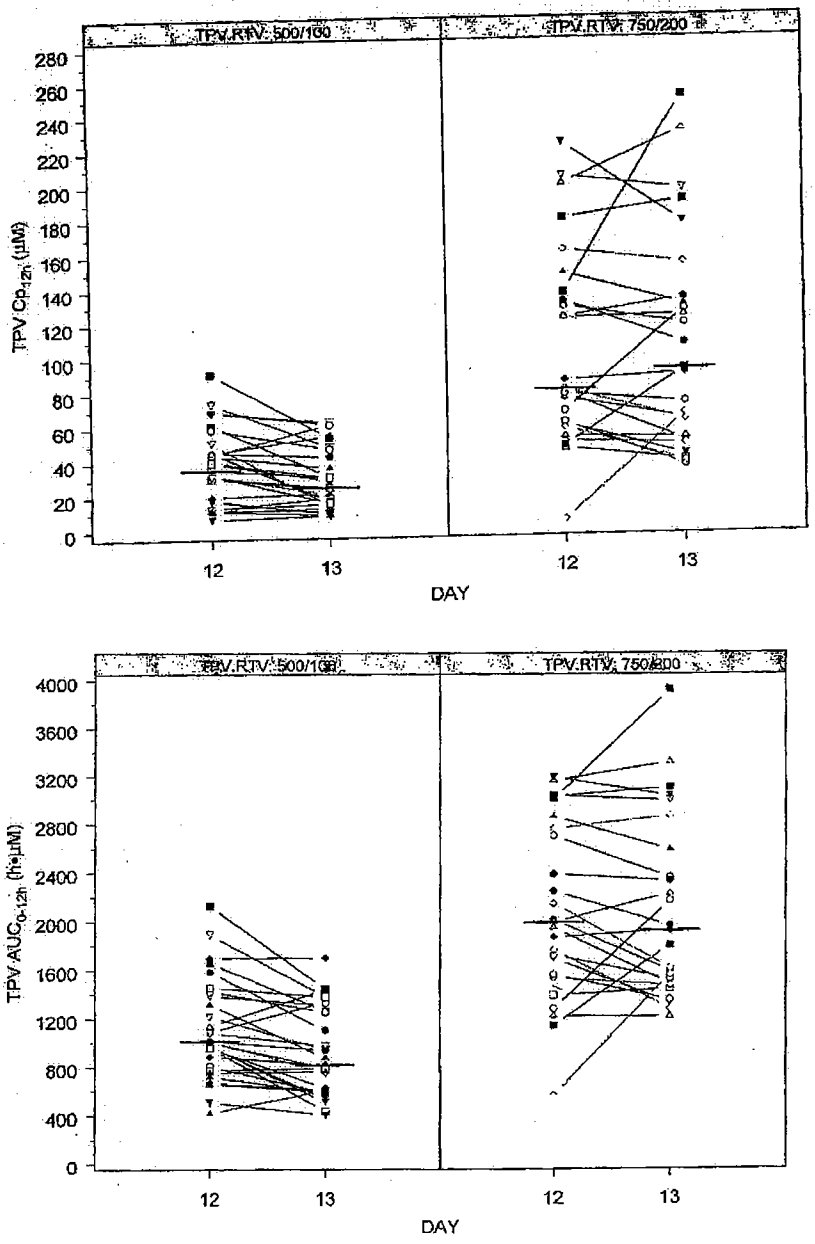
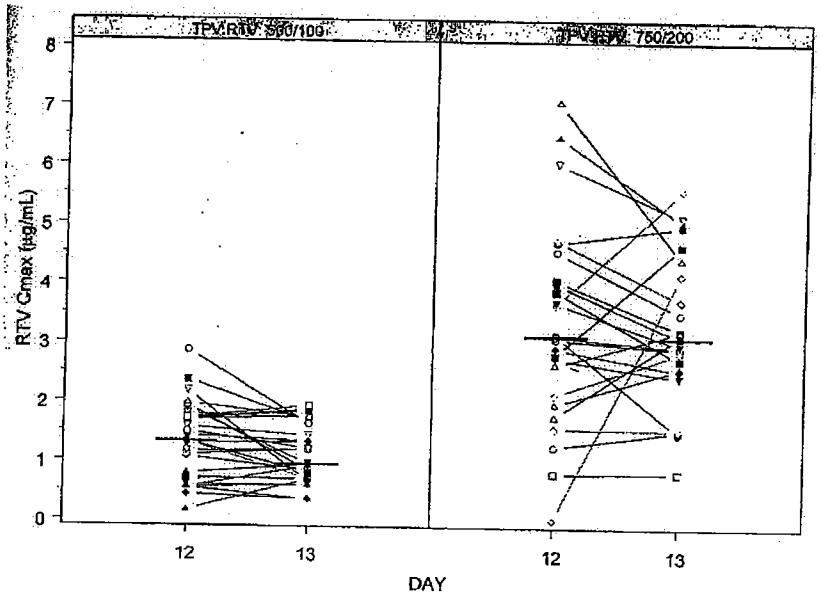
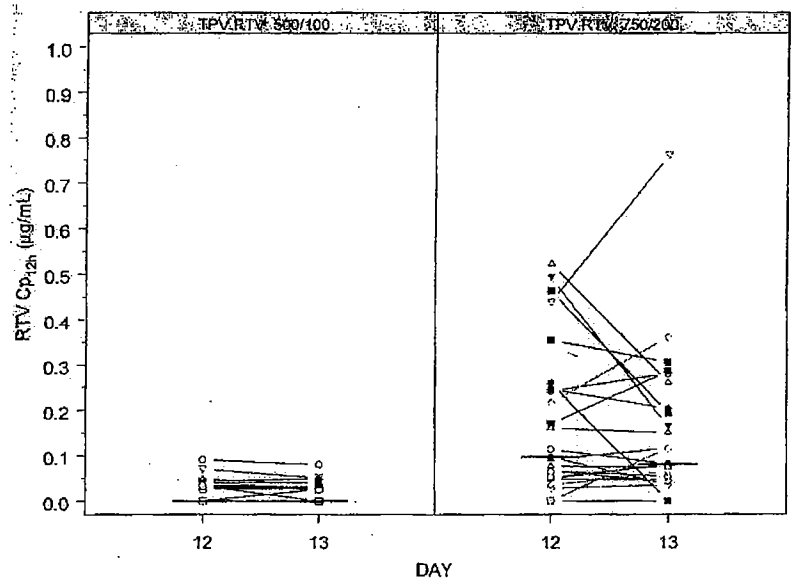


Figure 4. RTV C_{max}, C_{p12h} and AUC_{0-12h} with and without ZDV by subjects (Solid line represents median value)


TPV/RTV 500/100
TPV/RTV 750/200
RTV Cmax (µg/mL)
0
1
2
3
4
5
6
7
8
12
13
12
13
DAY


TPV/RTV 500/100
TPV/RTV 750/200
RTV Cp12h (µg/mL)
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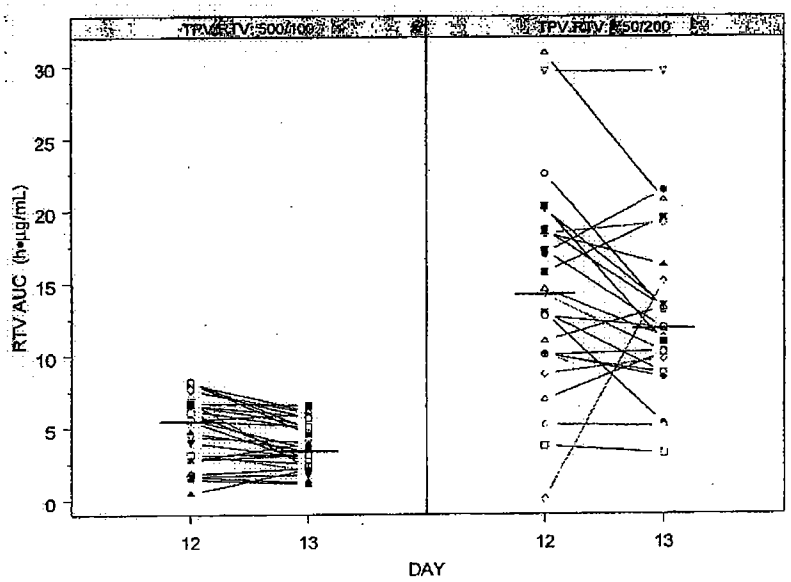
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
12
13
12
13
DAY



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 coadministraion of TPV/RTV. Tipranavir exposure (C_{max}, C_{p12h} and $AUC_{0\text{-}12h}$) 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 reminder 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 tiprnavir 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: [redacted]

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 [redacted] method. The calibration curve ranged from — ng/mL to — ng/mL. EFV concentrations were determined by a validated high performance liquid chromatography [redacted] 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

		EFV in TPV/RTV 500/100 mg group				EFV in TPV/RTV 750/200 mg group		
Day	n	C_{p24h} (µmol)	C_{max} (µmol)	AUC_{0-24h}(µmol*h)	n	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

		TPV 500 mg/RTV 100 mg				TPV 750 mg/RTV 200 mg			
				90% CI				90% CI	
Drug Name (Substrate)	**PK Parameter**	**Number Subjects**	**Ratio**	**Lower**	**Upper**	**Number Subjects**	**Ratio**	**Lower**	**Upper**
		Day 1 (EFV (sd) single dose) vs. Day 5 (EFV, TPV/RTV sd)							
	AUC	30	1.19	1.05	1.34	26	1.08	0.98	1.20
	Cmax	30	1.48	1.35	1.62	26	1.30	1.18	1.44
	C24h	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
Efavirenz	Cmax[1]	30	1.37	1.24	1.50	26	1.19	1.08	1.32
	C24h[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
	Cmax	28	1.18	1.12	1.25	28	1.22	1.15	1.29
	C24h	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
	Cmax	24	1.09	0.99	1.19	22	1.12	0.98	1.28
	C24h	24	1.02	0.92	1.12	22	0.94	0.84	1.04

[1]Day 5 AUC, Cmax and C24h corrected for carryover efavirenz concentrations from Day 1

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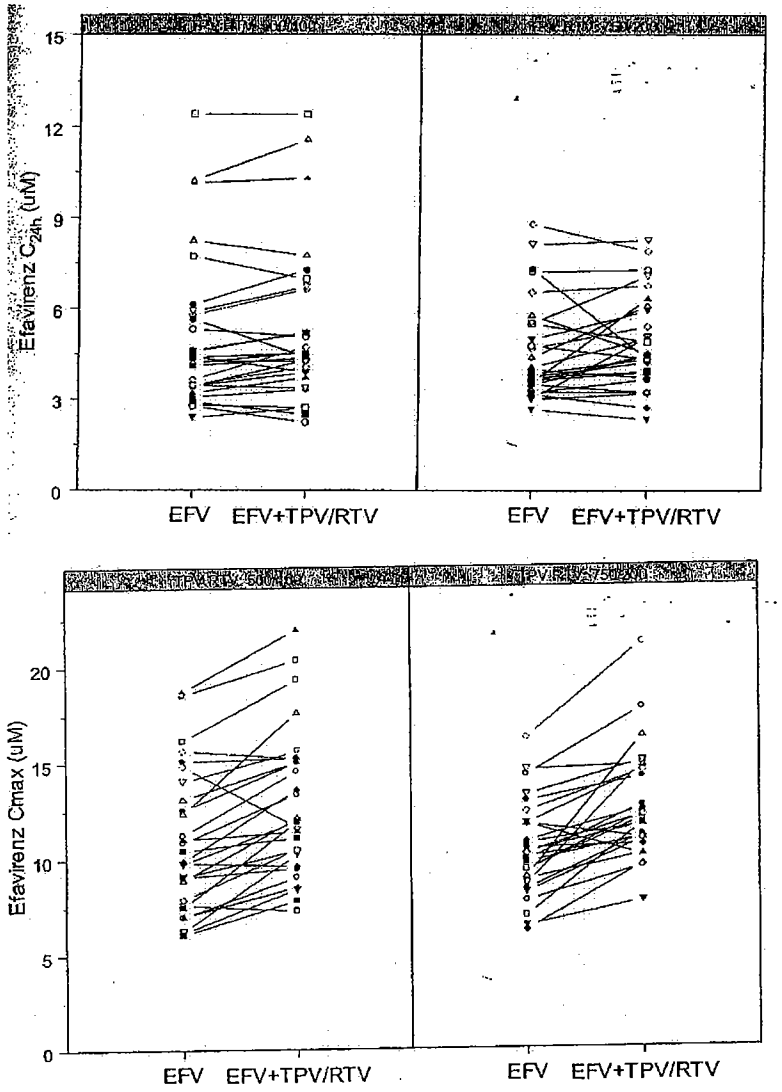
Figure 1. Effect of single-dose TPV/RTV 500/100 mg or 750/200 mg (Day 14) on the steady-state EFV pharmacokinetic parameters (Day 13) (C_{p24h}, C_{max} and AUC_{0-24h})



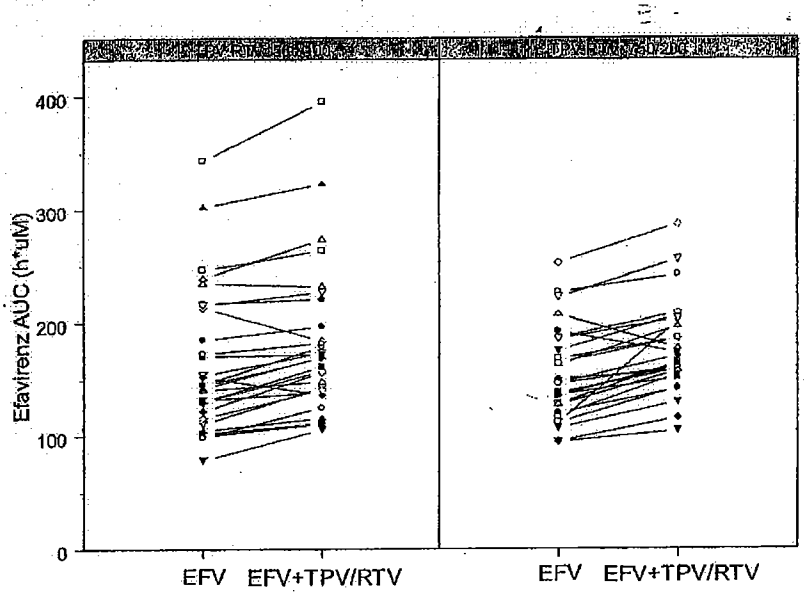


Figure 2. Median steady-state plasma concentration vs. time profile of EFV alone (Day 13) and in combination with steady-state TPV/RTV 500/100 mg or 750/200 mg BID (Day 21)

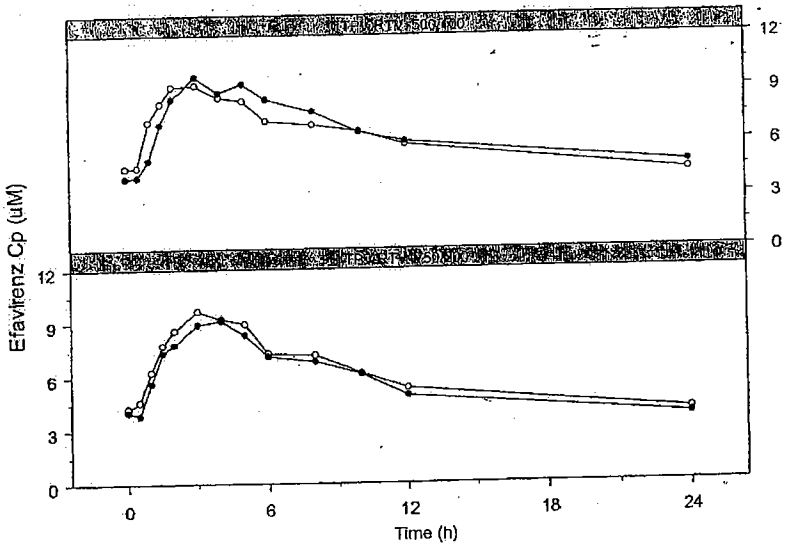


Table 3. Geometric means of the single-dose and steady-state pharmacokinetic parameters of TPV and RTV in combination with single-dose and steady-state EFV

	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/mLl)	C_{max} (µg/mL)	AUC_{0-12h}(µg/mL*h)	C_{p12h} (µg/mLl)	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

		TPV 500 mg/RTV 100 mg				TPV 750 mg/RTV 200 mg			
				90% CI				90% CI	
Drug Name (Substrate)	**PK Parameter**	**Number Subjects**	**Ratio**	**Lower**	**Upper**	**Number Subjects**	**Ratio**	**Lower**	**Upper**
		Day 3 (TPV/RTV (sd) single dose) vs. Day 5 (TPV/RTV and EFV sd dose)							
	AUC	24	0.92	0.81	1.04	26	0.93	0.79	1.10
	Cmax	24	0.93	0.82	1.06	26	0.91	0.81	1.03
	C12h	24	0.90	0.78	1.04	26	0.88	0.69	1.11
Tipranavir		Day 3 (TPV/RTV sd) vs. Day 14 (TPV/RTV sd and EFV at (ss) steady state)							
	AUC	21	0.43	0.35	0.52	25	0.66	0.56	0.79
	Cmax	21	0.61	0.51	0.72	25	0.69	0.58	0.83
	C12h	21	0.23	0.16	0.33	25	0.64	0.52	0.79
		Day 3 (TPV/RTV sd) vs. Day 21 (TPV/RTV and EFV at ss)							
	AUC	19	0.86	0.71	1.05	19	1.30	1.11	1.52
	Cmax	19	1.35	1.14	1.60	19	1.62	1.42	1.84
	C12h	19	0.39	0.24	0.61	19	1.38	0.95	1.99
		Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)							
	AUC	18	1.94	1.57	2.40	19	1.78	1.54	2.07
	Cmax	18	2.17	1.75	2.69	19	2.14	1.81	2.54
	C12h	18	1.71	1.10	2.67	19	1.92	1.47	2.51
		Day 3 (TPV/RTV sd) vs. Day 5 (TPV/RTV and EFV sd dose)							
	AUC	22	0.59	0.44	0.78	21	0.88	0.63	1.22
	Cmax	22	0.60	0.46	0.77	21	0.88	0.68	1.14
	C12h	22	0.57	0.34	0.96	21	0.74	0.45	1.22
Ritonavir		Day 3 (TPV/RTV sd) vs. Day 14 (TPV/RTV sd and EFV at ss)							
	AUC	12	0.24	0.14	0.42	25	0.43	0.31	0.60
	Cmax	12	0.32	0.22	0.47	25	0.44	0.34	0.57
	C12h	12	0.07	0.01	0.36	25	0.44	0.27	0.72
		Day 3 (TPV/RTV sd) vs. Day 21 (TPV/RTV and EFV at ss)							
	AUC	16	0.49	0.27	0.86	19	0.90	0.58	1.40
	Cmax	16	0.67	0.39	1.13	19	1.02	0.71	1.47
	C12h	16	0.21	0.09	0.48	19	0.51	0.25	1.03
		Day 14 (TPV/RTV sd and EFV at ss) vs. Day 21 (TPV/RTV and EFV at ss)							
	AUC	7	1.53	0.63	3.71	20	1.84	1.41	2.39
	Cmax	7	1.49	0.97	2.29	20	2.23	1.73	2.87
	C12h	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	Cmax (μM)	AUC (μM•h)	Cmin (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 $AUC_{0\text{-}12h}$, 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).

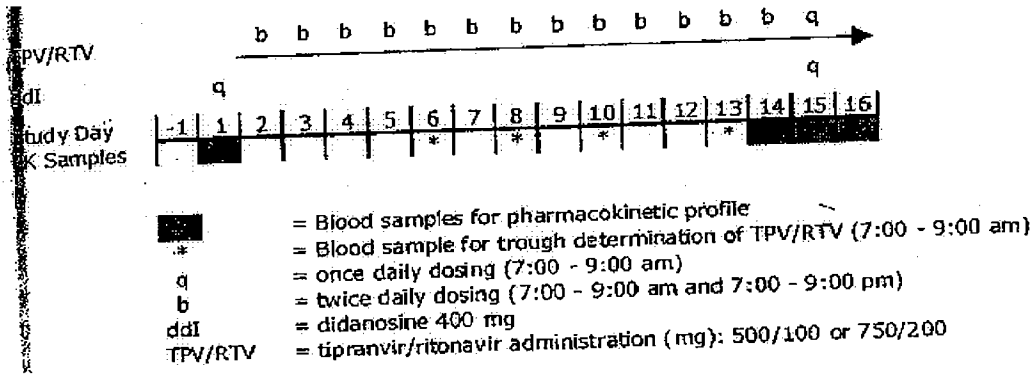
The change of pharmacokinetic parameters of TPV was less pronounced in the RTV 200 mg group, suggesting that inhibition of CYP3A by the 200 mg RTV partially counteracted the effects of CYP3A induction by EFV. It is anticipated the effect of EFV on TPV/RTV 500/200 mg would be less than or similar to that 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 ddI) and geometric means and coefficients of variation for C_{max}, C_{p6h} and AUC_{0-12h} were provided for ddI (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 ddI with and without TPV/RTV

		Day 1 Mean (SD)				Day 15 Mean (SD)		
TPV/RTV (mg/bid)	N	C_{max} (µg/mL)	C_{p6h} (µg/mL)	AUC_{0-12h} (hr-µg/mL	N	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 ddI

		Day 14 Mean (SD)				Day 15 Mean (SD)		
TPV/RTV (mg/bid)	N	C_{max} (µmol/mL)	C_{p12h} (µmol/mL)	AUC_{0-12h} (hr-µmol/mL)	N	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

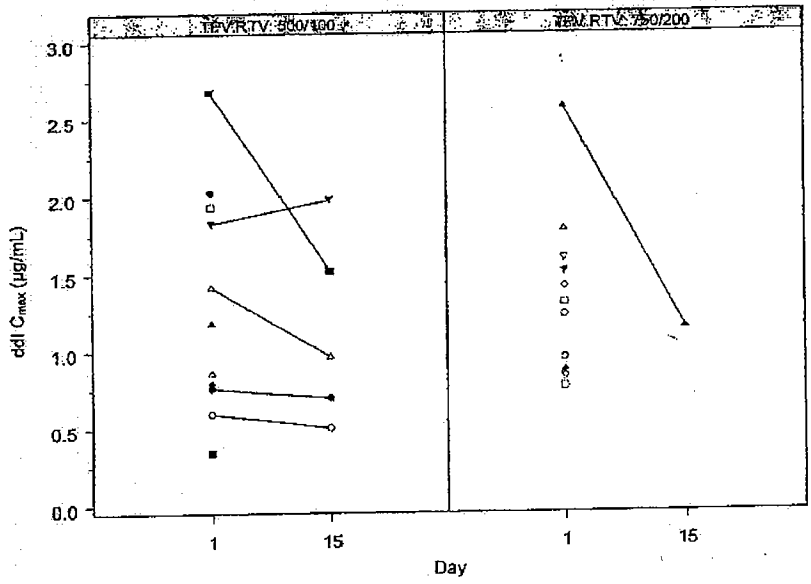
Table3 . Summary of the steady-state pharmacokinetic parameters of RTV with and without ddI

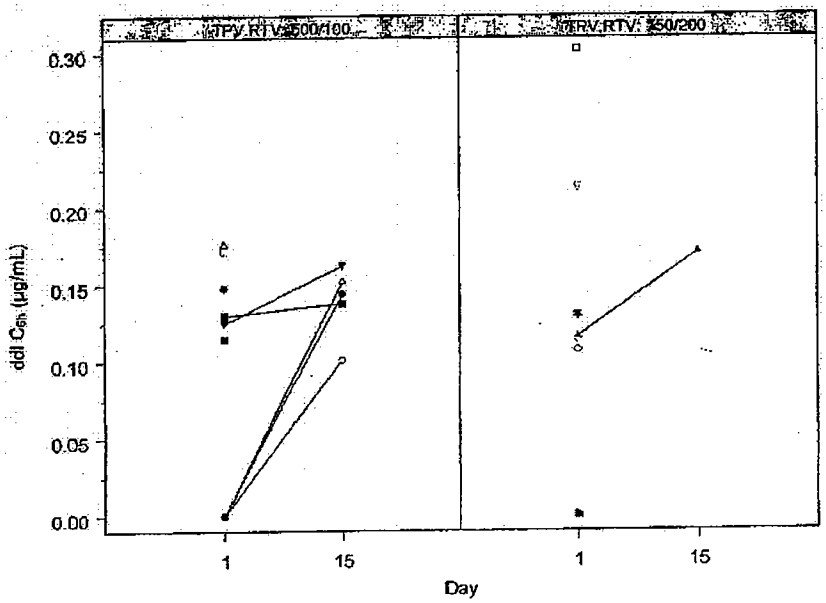
		Day 14 Mean (SD)				Day 15 Mean (SD)		
TPV/RTV (mg/bid)	N	C_{max} (µg/mL)	C_{p12h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)	N	C_{max} (µg/mL)	C_{p12h} (µg/mL)	AUC_{0-12h} (hr-µg/mL)
500/100	5	0.47 (0.23)	0.00 (0.00)	1.71 (1.12)	5	0.52 (0.35)	0.00 (0.00)	1.78 (1.13)
750/200	1	0.62	0.00	2.24	1	0.90	0.00	3.70

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

		TPV 500/RTV 100 mg			TPV 750 mg /RTV 200 mg		
		N	Ratio	90% CI	N	Ratio	90% CI
ddI	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. ddI C_{max}, C_{p6h} and AUC_{0-12h} with (Day 15) and without TPV/RTV (Day 1) by subjects




TPV/RTV 500/100
TPV/RTV 750/200
ddI C_{6h} (µg/mL)
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1
15
1
15
Day

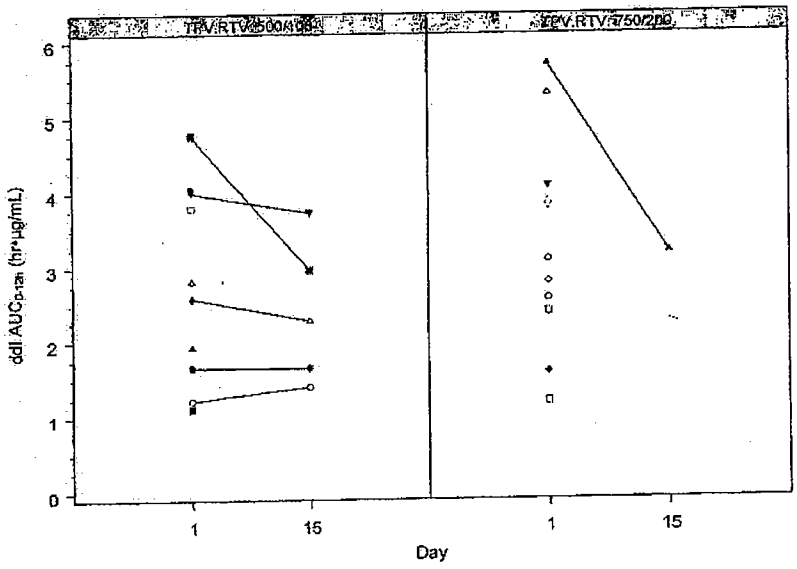
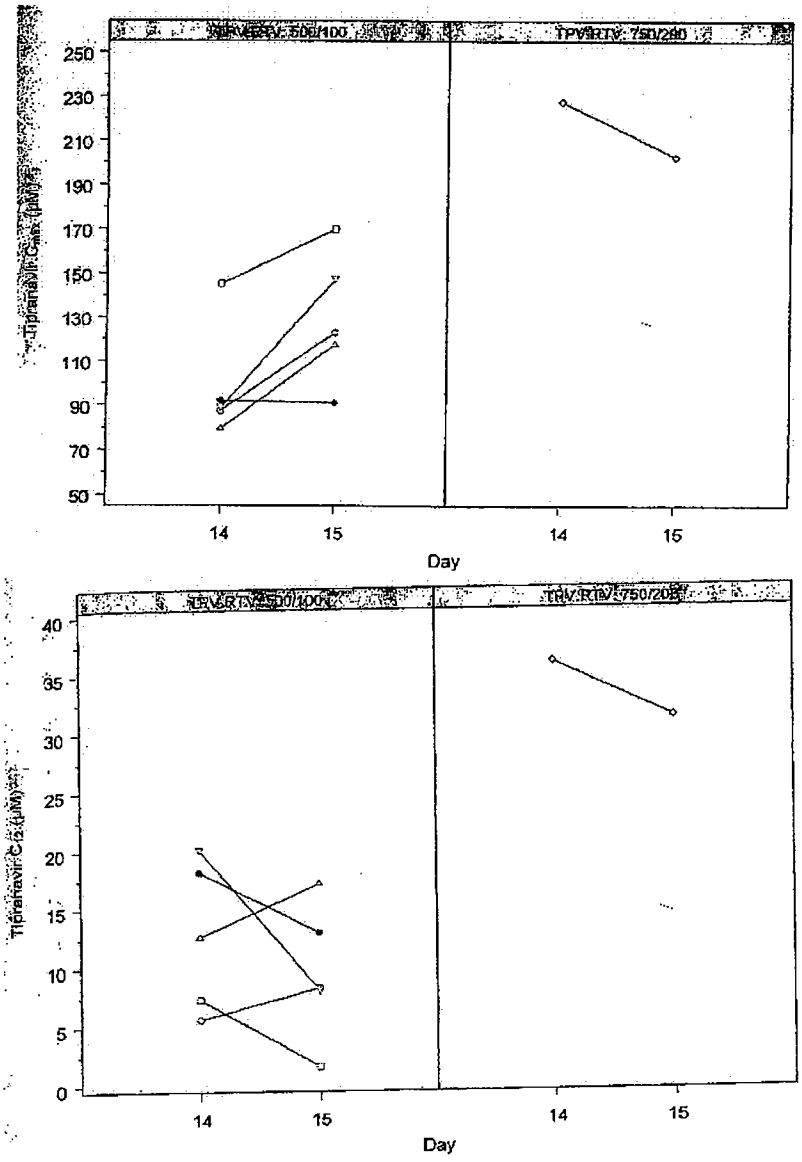

TPV/RTV 500/100
TPV/RTV 750/200
ddI AUC_{0-12h} (hr•µg/mL)
6
5
4
3
2
1
0
1
15
1
15
Day

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



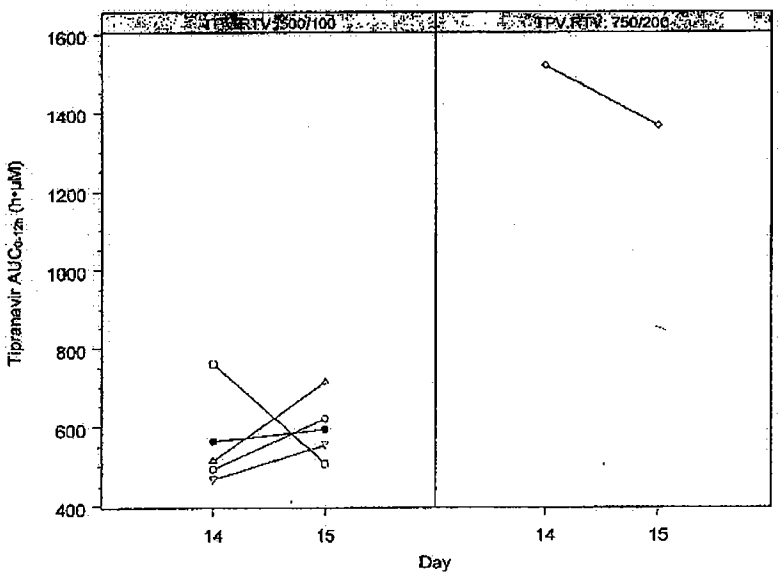


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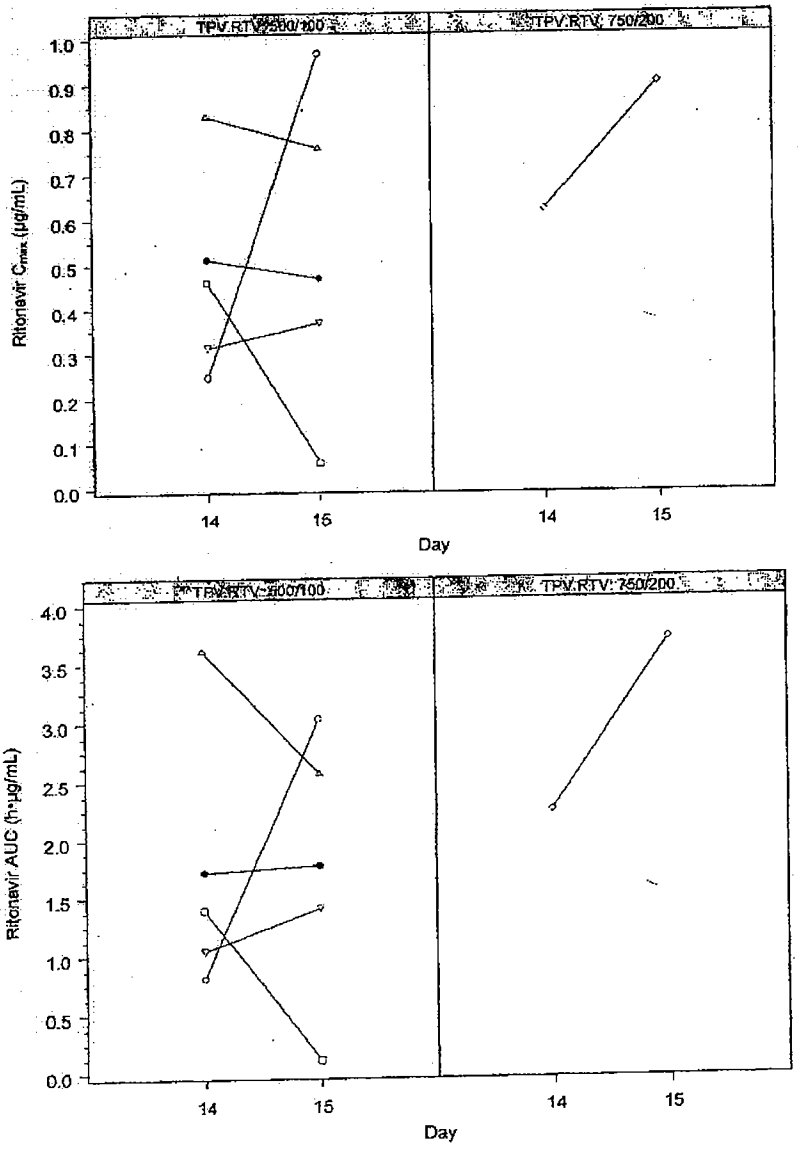
Figure 3. RTV C_{max} and AUC_{0-12h} with and without ddI by subjects



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

CONCLUSIONS AND DISCUSSION: The interaction of tipranavir with ddI 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 ddI 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 ddI 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 ddI 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 ddI, 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 ddI 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 ddI 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 ddI and TPV/RTV at the proposed dose level, 500 mg/200 mg.

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: [redacted]

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-desacytal-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 [redacted] using a validated high performance liquid chromatography [redacted] method. The calibration curve ranged from [redacted] ng/mL to [redacted] ng/mL. RFB and 25-O-desacetyl-RFB concentrations were performed by [redacted] using HPLC, [redacted] 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	
Cp_{12h} (ng/mL)	1	50.75	23.32		48.95		46.71	
	15	103.26	27.72		99.25		100.06	
$AUC_{0-\infty}$ (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	
Cp_{last} (ng/mL)	1	2.93	1.19		2.55		2.78	
	15	11.05	3.40		10.70		10.50	
Cl/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