Protocol 016

TITLE: An Open-label, 2-Period, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of MK-0518 on the Pharmacokinetics of Midazolam in Healthy Adult Subjects

OBJECTIVES: To compare the pharmacokinetic profile ($AUC_{0-\infty}$, C_{max}, and T_{max}) of midazolam following a single oral 2 mg dose of midazolam given alone or after multiple doses of MK-0518 and to evaluate the safety and tolerability of MK-0518 administered at doses of 400 mg every 12 hours for 14 days and concurrent administration of MK-0518 with oral midazolam in healthy adult subjects

SUBJECTS AND STUDY DESIGN: This was an open-label, 2-period, fixed-sequence study to evaluate the effect of MK-0518 (400 mg every 12 hours) for 14 days on the pharmacokinetics of midazolam. In Period 1, on Day 1, all 10 subjects received a single oral dose of 2.0 mg midazolam HCl syrup (2 mg/mL). In Period 2, all subjects received 400 mg (1 x 400 mg tablet) MK-0518 every 12 hours for 14 days. On Day 14, the morning dose of MK-0518 was co-administered with a single oral dose of 2.0 mg midazolam HCl syrup (2 mg/mL). In Period 1 on Day 1 and in Period 2 on Day 14, when pharmacokinetic sampling occurred, each treatment was administered after an overnight fast with approximately 240 mL of water, with water restricted 1 hour prior to and after study drug administration. At other times, MK-0518 was dosed without regard to food. Blood samples were collected pre-dose and at various time points for 24 hours after administration of midazolam in Period 1 on Day 1, and in Period 2 on Day 14 for determination of plasma midazolam concentrations.

Subject Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0151	Male	Hispanic	44	161.3	75.9
0152	Female	Hispanic	42	157	60
0153	Male	Hispanic	26	172.7	77.3
0154	Male	Hispanic	35	176	89.5
0155	Male	White	19	171.5	62
0156	Male	Black	26	177.8	64.1
0157	Male	Hispanic	25	160	62.5
0158	Female	Hispanic	39	158.8	77.9
0159	Female	Hispanic	22	160	71.4
0160	Male	Hispanic	24	171.4	70.9
		Arithmetic Mean	30.2	166.7	71.2
		Range	19-44	157-177.8	60-89.5

AN = allocation number.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 poloxamer formulation tablets, 400 mg, Midazolam HCl syrup

SAMPLE COLLECTION: On Day 1 in Period 1 and Day 14 in Period 2, blood samples for midazolam assay were obtained at predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, and 24 hours postdose. In Period 2, blood samples were collected prior to study drug administration on Days 11, 12, 13, 14 for determination of trough plasma MK-0518 concentrations.

ASSAYS: Plasma samples were analyzed for midazolam concentrations at the contract laboratory by an HPLC-MS/MS assay. The lower limit of

PHARMACOKINETIC DATA ANALYSIS: The plasma pharmacokinetic parameters (e.g., $AUC_{0-\infty}$, C_{max}, T_{max}, and apparent $t_{½}$) of midazolam were calculated for each subject after a single dose of midazolam administered with and without multiple doses of MK-0518. Geometric mean ratios (midazolam + MK-0518/midazolam) and associated 90% confidence intervals (CIs) of primary plasma midazolam PK parameters were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean Midazolam Plasma Concentration Profiles Following Administration of Single Oral Doses of 2-mg Midazolam with or without Administration of 400-mg MK-0518 Twice Daily to Young, Healthy, Male and Female Subjects (Inset = Semilog Scale)

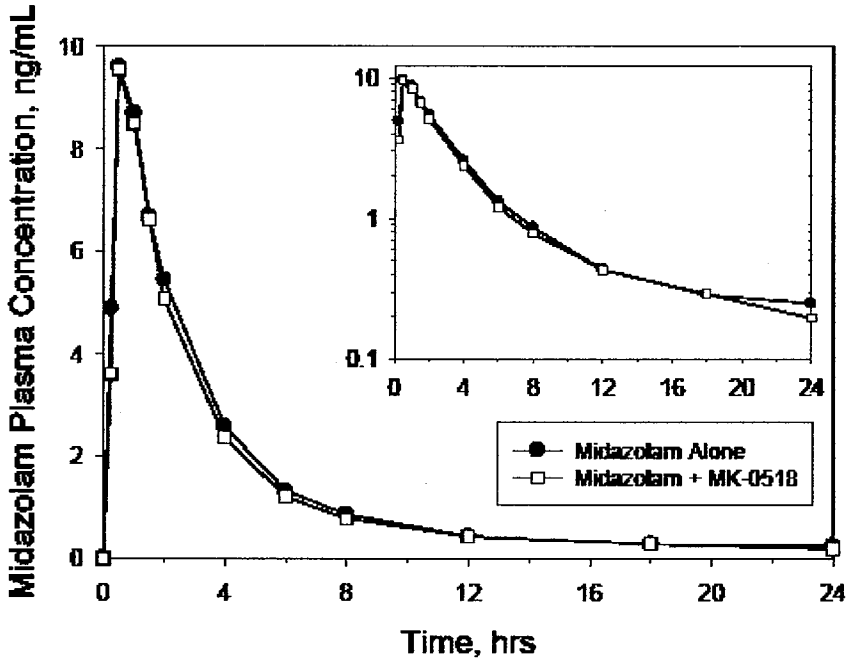

Table 1. Comparison of Midazolam Plasma Pharmacokinetics in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 2-mg Midazolam with or without Administration of 400-mg MK-0518 Twice Daily

	Midazolam + MK-0518			Midazolam			(Midazolam + MK-0518 / Midazolam)			
Pharmacokinetic Parameter	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	MSE†
$AUC_{0-\infty}$ (ng·hr/mL)‡	10	29.0	(21.7, 38.9)	10	31.5	(23.6, 42.2)	10	0.92	(0.82, 1.03)	0.019
C_{max} (ng/mL)‡	10	9.87	(8.14, 11.97)	10	9.58	(7.90, 11.61)	10	1.03	(0.87, 1.22)	0.043
T_{max} (hr)	10	0.5§		10	0.5§		10	0.3‖	(-0.5, 1.0)‖	
$t_{\frac{1}{2}}$ (hr)	10	3.6¶		10	4.0¶		10	-0.3‖	(-1.0, 0.3)‖	

† Mean square error on log-scale.
‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
§ Median reported for T_{max}.
‖ Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.
¶ Harmonic mean reported for $t_{\frac{1}{2}}$.

Figure 2. Individual Midazolam AUC0-∞ Ratios [Midazolam Coadministered with MK-0518 / Midazolam Administered Alone] with Geometric Mean Ratio and 90% Confidence Interval (n=10)

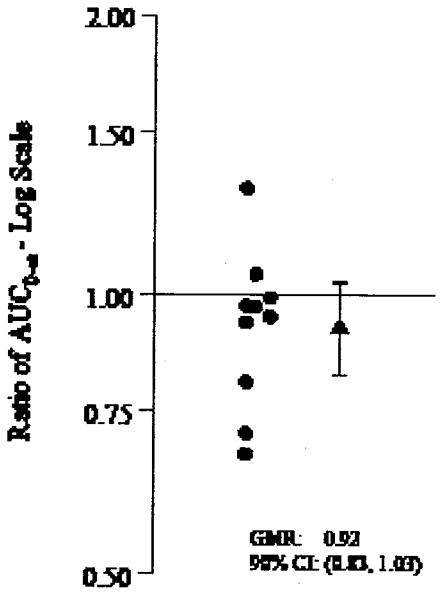

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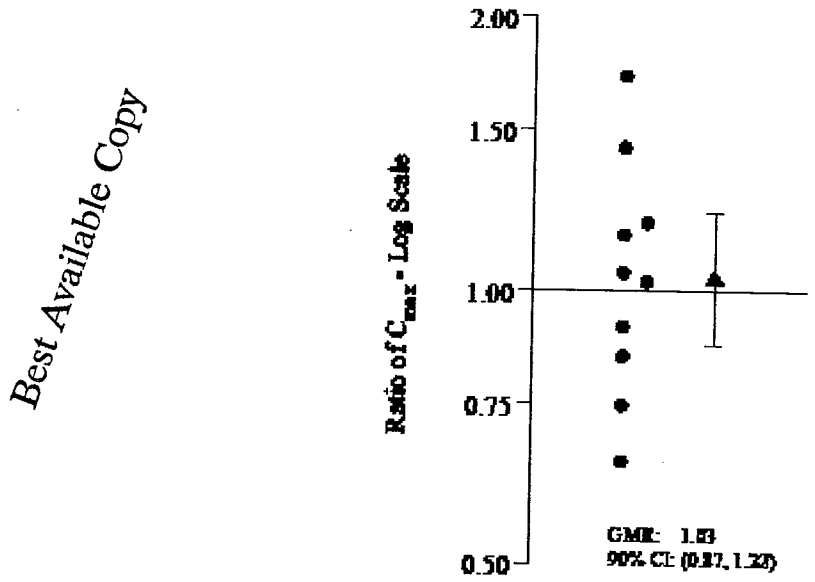
Figure 3. Individual Midazolam Cmax Ratios [Midazolam Coadministered with MK-0518 / Midazolam Administered Alone] with Geometric Mean Ratio and 90% Confidence Interval (n=10)



SAFETY RESULTS: Administration of MK-0518 with concurrent administration of midazolam was generally well-tolerated. No serious clinical adverse experiences were reported and no subject discontinued due to an adverse experience. A total of 2 subjects (in Period 2) reported a total of 2 non-serious clinical adverse experiences, 1 of which was deemed by the investigator to be possibly drug related. There were no laboratory adverse experiences reported in this study.

DISCUSSION AND CONCLUSIONS: Overall, the pharmacokinetic data from this study support that coadministration of midazolam with MK-0518 has no effect on the pharmacokinetics of midazolam.

Because midazolam is a sensitive CYP3A4 substrate, MK-0518 d is not expected to affect the pharmacokinetics of drugs that are substrates of CYP3A4.

Protocol 017

TITLE: An Open-Label, 3-Period Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-0518 Coadministered With Tipranavir and Ritonavir in Healthy Subjects.

OBJECTIVES: To determine the effect of multiple dose administration of tipranavir and ritonavir coadministered with multiple oral doses of MK-0518 on the plasma pharmacokinetics of MK-0518 (e.g. $AUC_{0-\infty}$, $C_{12\ hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of tipranavir and ritonavir coadministered with multiple doses of MK-0518

SUBJECTS AND STUDY DESIGN: This was an open label, 3-period fixed sequence study in young, healthy subjects. In Period 1, 18 subjects received 400 mg oral doses of MK-0518 twice daily for 4 days, with no evening dose given on Day 4. There was no washout required prior to the start of Period 2. In Period 2, the same subjects received 500 mg of tipranavir and 200 mg of ritonavir twice daily for 7 days. In Period 3, all subjects received a combination of 500 mg tipranavir and 200 mg ritonavir and 400 mg MK-0518, twice daily for 4 days with no evening dose given on Day 4. Period 3 was required to immediately follow Period 2. All subjects received active study drug in all 3 periods.

All doses of study drug were administered without regard to food on all dosing days with the exception of pharmacokinetic sampling days where study drug was administered in the fasted state.

Subject Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0301	Female	white	37	170.2	57.0
0302	Male	white	37	184.2	93.4
0303	Female	white	45	160.0	70.0
0304	Male	white	28	182.9	87.3
0305	Male	black	37	177.8	108.2
0306	Male	white	26	182.9	101.7
0307	Male	white	21	193.0	82.3
0308	Male	white	31	182.9	100.8
0309	Female	white	44	160.0	83.8
0310	Male	white	23	182.9	76.5
0311	Female	Hispanic	24	160.0	80.2
0312	Female	black	19	160.0	62.8
0313	Male	white	23	165.1	56.2
0314	Male	white	33	180.3	101.3
0315	Female	white	22	158.1	59.6
0316	Male	white	47	188.0	90.9
0317	Female	white	22	166.4	57.0
0318	Male	white	25	168.9	69.4
		Arithmetic Mean:	30.2	173.5	79.9
		Range:	19 to 47	158.1 to 193.0	56.2 to 108.2

AN= Allocation Number.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 final poloxamer formulation tablets 400 mg, NORVIR 100 mg capsules

SAMPLE COLLECTION: Serial blood samples were obtained for plasma concentrations of MK-0518 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours postdose.

ASSAYS: Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations.

PHARMACOKINETIC DATA ANALYSIS: Plasma concentrations of MK-0518 were used to calculate pharmacokinetic parameters including $AUC_{0\text{-}12hr}$, C_{max}, $C_{12\,hr}$, T_{max}, and apparent $t_{½}$ for each subject in the presence or absence of multiple doses of tipranavir + ritonavir. Geometric mean ratios (MK-0518 + tipranavir + ritonavir/MK-0518) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{0\text{-}12hr}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Multiple Oral Doses of 400-mg MK-0518 Twice Daily With or Without Coadministration of Multiple Oral Doses of 500-mg Tipranavir + 200-mg Ritonavir Twice-Daily to Young, Healthy, Male and Female Subjects (Inset = Semilog Scale)

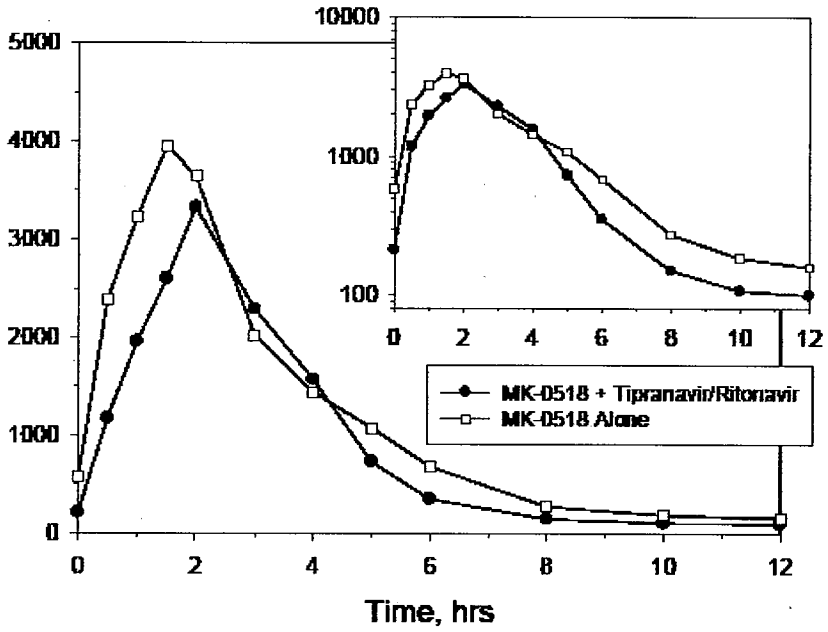


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Table 1. Comparison of MK-0518 Plasma Pharmacokinetics for Young, Healthy, Male and Female Subjects Administered Multiple Twice-Daily Oral Doses of 400-mg MK-0518 with or without Coadministration of Multiple Twice-Daily Oral Doses of 500-mg Tipranavir + 200-mg Ritonavir

Pharmacokinetic Parameter	MK-0518 + Tipranavir + Ritonavir			MK-0518			(MK-0518 + Tipranavir + Ritonavir/MK-0518)			MSE†
	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	
C_{12hr} (nM)‡	15	59	(39, 89)	14	129	(84, 198)	14	0.45	(0.31, 0.66)	0.318
AUC_{0-12hr} (μM·hr)‡	15	7.61	(4.64, 12.48)	15	9.97	(6.58, 16.35)	15	0.76	(0.48, 1.19)	0.471
C_{max} (μM)‡	15	3.33	(1.21, 4.48)	15	2.85	(1.48, 5.48)	15	0.82	(0.46, 1.46)	0.809
T_{max} (hr)	15	2.0§		15	4.0§		15	-0.5¶	(-1.5, 0.3)¶	

† Mean square error on log-scale.
‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
§ Median reported for T_{max}.
¶ Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Table 2 Individual MK-0518 Plasma Pharmacokinetic Values and Summary Statistics Following Multiple Oral Doses of 400 mg MK-0518 Twice Daily With or Without Coadministration of Multiple Oral Doses of 500 mg Tipranavir + 200 mg Ritonavir Twice-Daily to Young, Healthy, Male and Female Subjects

	C_{12hr}, nM			AUC_{0-12hr}, μM·hr			C_{max}, μM			T_{max}, hr		
AN	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B
301	247	418	0.59	31.20	9.38	3.33	12.87	2.48	5.19	2.0	5.0	-3.0
302	90	151	0.33	14.70	48.24	0.32	7.16	17.00	0.42	2.0	1.0	1.0
303	73	189	0.39	14.24	9.38	1.52	6.82	3.35	2.04	1.0	2.0	-1.0
304	824	154	4.05	5.31	6.59	0.81	1.38	1.51	0.78	5.0	6.0	-1.0
305	43	68	0.63	14.39	3.86	3.93	4.96	0.80	6.20	1.5	4.0	-2.5
306	39	104	0.38	0.97	2.41	0.40	0.20	0.35	0.57	1.5	4.0	-2.5
307	14	57	0.25	1.89	7.15	0.26	0.39	1.31	0.30	5.0	5.0	0.0
308	85	89	0.96	4.12	14.51	0.28	1.18	6.88	0.17	2.0	1.5	0.5
309	37	85	0.44	11.51	3.88	3.13	5.27	1.01	5.22	4.0	4.0	0.0
311	44	NS	–	15.41	22.20	0.69	6.20	10.40	0.60	2.0	1.5	0.5
312	54	318	0.17	9.32	6.77	1.38	2.80	1.15	2.43	3.0	1.0	2.0
313	51	260	0.20	17.98	33.60	0.53	5.96	11.72	0.51	3.0	1.5	1.5
314	51	190	0.27	1.74	9.32	0.19	0.26	2.61	0.10	3.0	5.0	-2.0
315	29	71	0.41	6.01	8.59	0.70	1.83	2.98	0.61	1.5	4.0	-2.5
318	45	66	0.68	14.33	26.22	0.55	3.64	10.90	0.33	1.5	2.0	-0.5
AM	99	158	–	10.87	13.98	–	4.05	4.98	–	2.5	3.2	–
SD	155	108	–	8.02	11.64	–	3.50	5.15	–	1.3	1.7	–
Med	50	128	–	11.51	9.32	–	3.64	2.61	–	2.0	4.0	-0.8[a]
GM‡	59	120	0.45	7.61	9.97	0.76	2.33	2.85	0.82	–	–	–

Treatment A: 500-mg tipranavir q12hr+200-mg ritonavir q12hr x 11 days, 400-mg MK-0518 q12hrx4 days starting on Day 7, Period 2; PK parameters after AM dose on Day 4, Period 3
Treatment B: 400-mg MK-0518 q12hr x 4 days; PK parameters after AM dose on Day 4
AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean; NS = No Sample
[a] For T_{max}, represents Hodges-Lehman estimate of median treatment difference
‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values

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Figure 2. Individual MK-0518 $C_{12\ hr}$ Ratios (MK-0518 + Tipranavir + Ritonavir/MK-0518) with Geometric Mean Ratio and 90% Confidence Interval Following Multiple Oral Doses of 400-mg MK-0518 Twice Daily With or Without Coadministration of Multiple Oral Doses of 500-mg Tipranavir + 200-mg Ritonavir Twice-Daily to Young, Healthy, Male and Female Subjects (n=14)

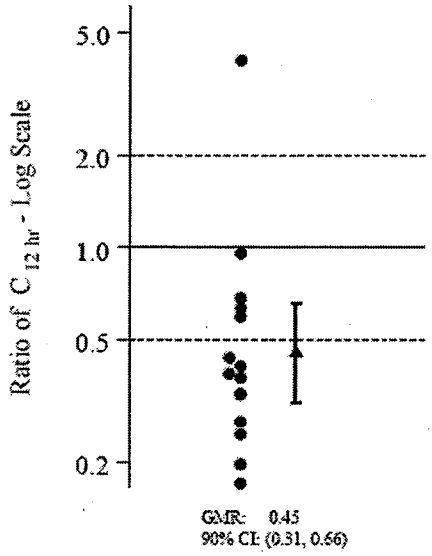


Figure 3. Individual MK-0518 $AUC_{0\text{-}12\ hr}$ Ratios (MK-0518 + Tipranavir + Ritonavir/MK-0518) with Geometric Mean Ratio and 90% Confidence Interval Following Multiple Oral Doses of 400-mg MK-0518 Twice Daily With or Without Coadministration of Multiple Oral Doses of 500-mg Tipranavir + 200-mg Ritonavir Twice-Daily to Young, Healthy, Male and Female Subjects (n=15)

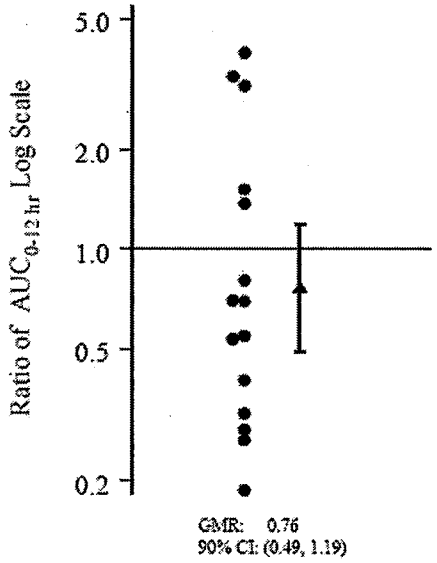
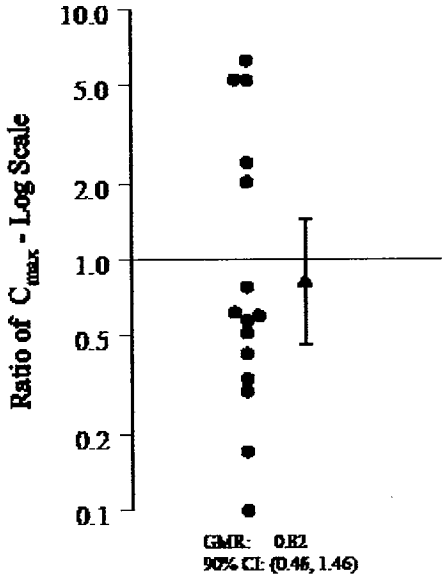


Figure 4. Individual MK-0518 Cmax Ratios (MK-0518 + Tipranavir + Ritonavir/MK-0518) with Geometric Mean Ratio and 90% Confidence Interval Following Multiple Oral Doses of 400-mg MK-0518 Twice Daily With or Without Coadministration of Multiple Oral Doses of 500-mg Tipranavir + 200-mg Ritonavir Twice-Daily to Young, Healthy, Male and Female Subjects (n=15)



SAFETY RESULTS: MK-0518 was generally well tolerated in young, healthy, male and female subjects. No serious clinical or serious laboratory adverse experiences were reported. One subject discontinued because of clinical adverse experiences judged as unrelated to MK-0518 by the investigator. Sixteen subjects reported a total of 33 nonserious clinical adverse experiences, 18 of which were judged by the investigator as possibly or probably drug related. All adverse experiences reported were transient and rated mild to moderate in intensity with the exception of one subject who had an adverse experience judged definitely not related to study drug and was lost to follow-up. There were no laboratory adverse experiences reported.

DISCUSSION AND CONCLUSIONS: With co-administration of 500 mg tipranavir + 200 mg ritonavir twice daily for 7 days, the C_{12hr} geometric mean ratio for (MK-0518 + tipranavir + ritonavir/MK-0518) was 0.45 and the 90% confidence interval for the geometric mean ratio was (0.31, 0.66). The $AUC_{0\text{-}12hr}$ geometric mean ratio (MK-0518 + tipranavir + ritonavir/MK-0518) was 0.76 with a corresponding 90% confidence interval of (0.49, 1.19), while the C_{max} geometric mean ratio was 0.82 with a corresponding 90% confidence interval of (0.46, 1.46).

The lower bound of 90% CI of MK-0518 C_{12hr} ratios was 0.31 (<0.4) and a few individual MK-0518 C_{12hr} ratios were around 0.2.

We agree with the applicant proposal that raltegravir exposure changes up to a 2-fold increase in exposure (AUC) for safety and a 60% decrease (equivalent to geometric mean ratio of 0.4) in trough concentration ($C_{12\ hr}$) for efficacy are not clinically relevant based on available clinical experience.

Tipranavir a potent CYP3A and P-gp inducer. CYP3A, P-gp, and UGT1A1 are all regulated through PXR, and it is possible that tipranavir/ritonavir is also a potent inducer of UGT1A1.

Tipranavir/ritonavir markedly reduces plasma concentrations of MK-0518. However, approximately 100 patients received MK-0518 in combination with tipranavir/ritonavir in Phase III trials. Comparable efficacy was observed in this subgroup relative to patients not receiving

tipranavir/ritonavir. Based on these data, tipranavir/ritonavir may be coadministered with Mk-0518 without dose adjustment of Mk-0518.

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Protocol 025

TITLE: An Open-Label, Randomized, 5-Period Crossover Study to Evaluate the Dose Proportionality of MK-0518 Final Marketing Image Tablets in Healthy Adult Subjects

OBJECTIVES: To assess the dose proportionality (e.g., $AUC_{0-\infty}$, $C_{12\,hr}$, C_{max}) of MK-0518 final market image tablets within the 100 mg to 1600 mg dose range in healthy adult subjects

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, 5-period, crossover study in 20 (7F/13M) healthy, male and female subjects. In each period, subjects received a single 100, 200, 400, 800, or 1600 mg dose of MK-0518 in the fasted state. There was a 4-day washout interval separating each period.

In each period, after an overnight 8-hour fast, each subject received a single dose of MK-0518 administered with 240 mL of water.

Treatment Plan

Period †	1	2	3	4	5
Subjects					
N=2	A	B	D	E	C
N=2	B	C	E	A	D
N=2	C	D	A	B	E
N=2	D	E	B	C	A
N=2	E	A	C	D	B
N=2	A	C	B	E	D
N=2	B	D	C	A	E
N=2	C	E	D	B	A
N=2	D	A	E	C	B
N=2	E	B	A	D	C

Treatment A: 100-mg dose of MK-0518 were administered with 240 mL of water.
Treatment B: 200-mg dose of MK-0518 administered with 240 mL of water.
Treatment C: 400-mg dose of MK-0518 administered with 240 mL of water.
Treatment D: 800-mg (2 x 400 mg) dose of MK-0518 administered with 240 mL of water.
Treatment E: 1600-mg (4 x 400 mg) dose of MK-0518 administered with 240 mL of water.
† There was at least a 4 day wash out between each period.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: Final Market Image (——poloxamer content) tablets:100, 200 and 400 mg

SAMPLE COLLECTION: Serial blood samples were obtained for plasma concentrations of MK-0518 at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48 and 72 hours postdose.

ASSAYS: Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations

PHARMACOKINETIC DATA ANALYSIS: The plasma pharmacokinetic profile (e.g., AUC, C_{max}, $C_{12\ hr}$, T_{max}, and apparent $t_{½}$) of MK-0518 was calculated for each subject at each dose in this study.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 100, 200, 400, 800, or 1600 mg of the Final Market Image (FMI) Formulation of MK-0518 to Healthy, Male and Female Subjects (N=20; inset: semilog scale)

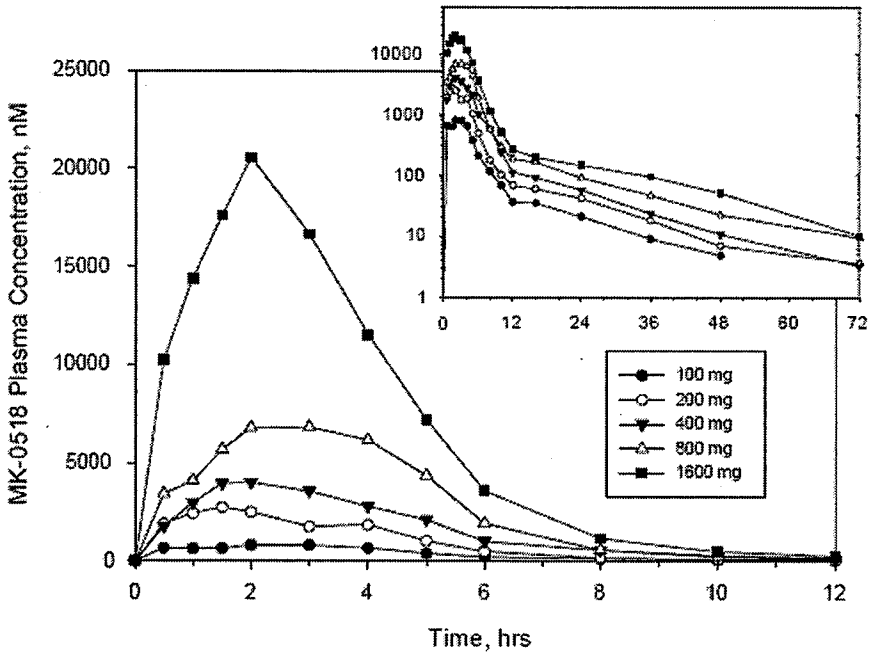

Table 1. Summary Statistics Following Single Dose Administration of 100, 200, 400, 800, or 1600 mg of the Final Market Image (FMI) Formulation of MK-0518 to Healthy, Male and Female Subjects

	$AUC_{0-\infty}$ (nM·hr)					C_{max} (nM)					$C_{12\ hr}$ (nM)				
AN	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg
AM	4.71	12.42	20.43	36.44	84.51	1.46	4.32	6.52	10.59	26.11	36.2	68.1	112.4	186.6	268.6
SD	2.08	6.39	8.74	24.34	50.21	1.10	3.04	3.71	8.97	15.55	18.3	32.3	41.8	73.5	128.0
GM[1]	4.32	10.48	18.30	28.46	65.76	1.20	2.90	5.39	7.01	19.67	32.3	61.8	107.3	172.1	240.8
Med	4.18	12.95	19.60	32.03	85.47	1.10	4.32	5.59	8.90	29.93	31.4	60.6	104.3	185.3	238.6

[1] Least-squares geometric means from mixed-effects ANOVA performed on the log transformed values with terms for period, treatment (categorical fixed effects) and subject (random effect).
AM=Arithmetic Mean; AN = Allocation Number; SD = Standard Deviation; GM = Geometric Mean; Med = Median

	T_{max} (hr)					$t_{½}\ \alpha$ (hr)					$t_{½}\ \beta$ (hr)				
AN	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg
AM	2.8	2.8	3.2	3.4	2.5	0.87[2]	0.86[3]	0.96[2]	0.93[3]	0.92[2]	9.0[3]	8.7[2]	9.5[3]	10.5[2]	11.3[3]
SD	1.9	1.5	1.9	1.2	1.3	0.18[2]	0.22[3]	0.25[2]	0.25[3]	0.19[2]	3.4[3]	3.8[3]	5.6[3]	4.7[3]	3.5[3]
GM	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Med	3.0	5.0	3.0	3.5	2.0	0.90	0.87	0.92	0.95	0.98	9.1	9.3	10.4	10.5	11.2

AM=Arithmetic Mean; AN = Allocation Number; SD = Standard Deviation; GM = Geometric Mean; Med = Median.
ND = Value not determined due to insufficient data.
[1] Harmonic Mean; [3]Jackknife Standard Deviation.
[2] Value determined from a monoexponential rather than biexponential equation.

Table 2. Assessment of Dose-Proportionality for MK-0518 Pharmacokinetics Following Single Oral Dose Administration of MK-0518 to Healthy Male and Female Subjects

MK-0518 PK Parameter	Geometric Mean					Slope (90% CI)[§]	Equivalence Bounds for Slope[‖]	Dose Prop.[¶]
	100 mg	200 mg	400 mg	800 mg	1600 mg			
$AUC_{0-\infty}$ (μM·hr)[†]	4.32	10.48	18.30	28.46	65.76	0.9300 (0.8562, 1.0038)	(0.750, 1.250)	Yes
C_{max} (μM)[†]	1.20	2.90	5.39	7.01	19.67	0.9337 (0.8241, 1.0433)	(0.750, 1.250)	Yes
$C_{12\,hr}$ (nM)[†]	32.3	61.8	107.3	172.1	240.8	0.7277 (0.6638, 0.7915)	(0.750, 1.250)	No
T_{max} (hr)[‡]	3.00	3.00	3.00	3.50	2.00			
$t_{½}$ α (hr)[‡]	0.87	0.86	0.96	0.93	0.92			
$t_{½}$ β (hr)[‡]	8.99	8.67	9.50	10.52	11.33			

† For $AUC_{0-\infty}$, C_{max}, and $C_{12\,hr}$: Least-squares geometric means from mixed-effects ANOVA performed on the log transformed values with terms for period, treatment (categorical fixed effects) and subject (random effect).

‡ Median for T_{max}. Harmonic mean for half-life.

§ Estimated slope computed from mixed-effects linear regression of log PK vs. log dose over dose range 100 to 1600 mg.

‖ Determined such that dose-adjusted ratio of high dose (1600 mg) to low dose (100 mg) is contained within the bounds 0.50 to 2.00.

¶ Dose proportionality declared over dose range from 100 to 1600 mg if 90% confidence interval for slope is contained within equivalence region for slope.

Table 3 Individual Values of MK-0518 AUC0-∞, Cmax, C12 hr and Summary Statistics Following Single Dose Administration of 100, 200, 400, 800, or 1600 mg of the Final Market Image (FMI) Formulation of MK-0518 to Healthy, Male and Female Subjects

	$AUC_{0-\infty}$ (μM·hr)					C_{max} (μM)					$C_{12\,hr}$ (nM)				
AN	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg	100 mg	200 mg	400 mg	800 mg	1600 mg
0361	3.60	16.21	34.60	23.01	115.07	0.86	8.37	10.89	8.93	38.93	46.4	34.0	121.5	172.4	218.3
0362	2.21	5.51	7.05	5.15	21.89	1.22	2.23	1.82	0.84	7.11	18.9	53.6	99.9	81.9	128.5
0363	10.11	24.50	31.50	65.26	162.02	5.22	10.15	12.20	23.63	42.08	56.9	58.5	146.9	138.8	216.2
0364	7.25	10.73	23.15	13.94	87.00	2.63	3.78	8.35	2.68	28.33	30.6	50.2	87.8	131.4	285.8
0365	5.70	6.87	19.26	32.99	36.25	1.86	1.31	6.50	7.72	10.22	19.8	46.1	101.7	342.0	164.7
0366	4.30	4.12	7.34	22.78	35.58	0.87	0.50	0.95	7.11	10.22	34.2	36.0	105.8	194.9	206.8
0367	4.04	17.76	33.41	51.45	83.97	1.62	8.93	14.67	14.45	30.60	24.1	91.4	157.3	294.8	330.8
0368	2.28	20.32	23.74	14.60	118.39	0.64	8.60	5.80	2.52	38.03	18.4	38.3	88.6	96.8	240.8
0369	4.25	6.90	15.10	26.32	35.72	1.15	1.42	3.83	5.92	7.97	26.6	119.3	117.9	214.0	303.8
0370	3.76	17.68	23.32	47.43	88.97	1.04	7.97	11.21	12.78	20.48	35.6	82.6	74.9	252.0	170.8
0371	4.20	11.08	16.77	36.65	47.96	0.71	2.68	5.06	12.53	14.60	88.4	74.5	265.5	129.6	212.2
0372	3.91	13.90	19.78	67.07	144.20	1.76	3.87	4.86	13.43	48.38	10.6	62.8	112.1	187.2	267.8
0373	5.47	5.38	27.86	15.97	130.41	0.72	0.54	6.86	2.15	48.38	53.1	79.2	104.6	288.0	364.5
0374	4.15	12.00	13.72	40.56	67.48	1.52	5.58	3.69	17.17	37.80	32.2	40.1	104.0	125.8	227.3
0375	6.04	17.29	26.25	55.23	150.66	1.69	5.33	8.24	14.29	45.00	29.5	42.3	71.6	224.1	463.5
0376	3.49	5.19	7.21	31.06	20.31	0.64	0.51	1.99	8.87	4.50	55.8	82.8	113.2	183.4	238.3
0377	3.41	15.53	19.26	53.65	102.27	0.74	8.37	5.58	14.99	30.38	34.4	114.1	87.8	190.6	283.5
0378	1.81	2.07	9.24	5.85	7.17	0.44	0.39	3.47	0.94	1.87	27.2	37.1	85.7	68.0	65.7
0379	8.48	20.31	30.62	103.11	71.71	2.90	7.16	9.38	38.03	17.62	25.0	85.1	97.0	249.8	274.5
0380	5.81	15.03	19.42	18.61	165.24	1.00	4.77	5.24	2.72	32.63	55.8	153.2	106.2	167.2	670.6
AM	4.71	12.42	20.43	36.44	84.51	1.46	4.32	6.52	10.59	28.11	36.2	68.1	112.4	186.6	266.6
SD	2.08	6.39	8.74	24.34	50.21	1.10	3.04	3.71	8.97	15.55	18.3	32.3	41.8	73.5	128.0
GM†	4.32	10.48	18.30	28.46	65.76	1.20	2.90	5.39	7.01	19.67	32.3	61.8	107.3	172.1	240.8
Med	4.18	12.95	19.60	32.03	85.47	1.10	4.32	5.59	8.90	29.93	31.4	80.6	104.3	185.3	238.6

† Least-squares geometric means from mixed-effects ANOVA performed on the log transformed values with terms for period, treatment (categorical fixed effects) and subject (random effect).

AM=Arithmetic Mean; AN = Allocation Number; SD = Standard Deviation; GM = Geometric Mean; Med = Median

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Figure 2. Predicted Mean Curve and Corresponding 95% Confidence Bands for MK-0518 AUC0-∞ Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects

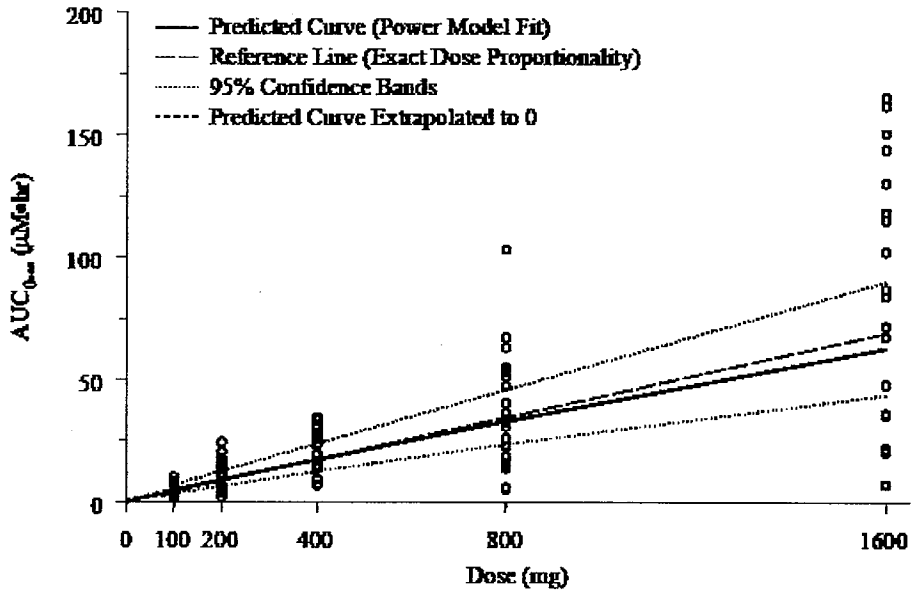


Figure 3. Predicted Mean Curve and Corresponding 95% Confidence Bands for MK-0518 Cmax Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects

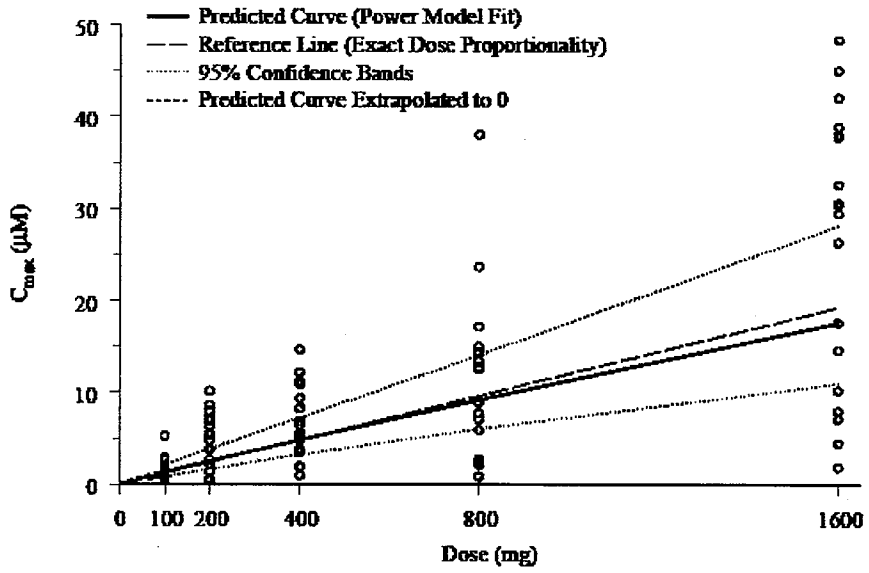
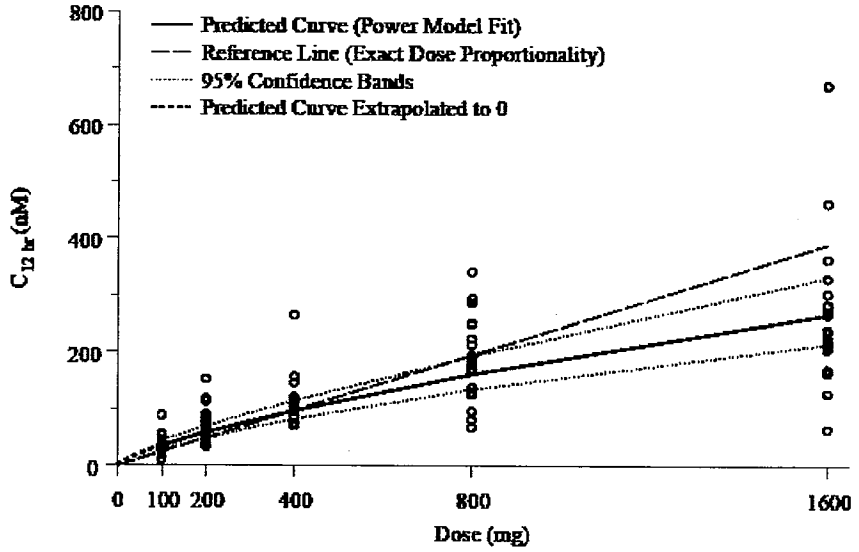


Figure 4. Predicted Mean Curve and Corresponding 95% Confidence Bands for MK-0518 C12 hr Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects



SAFETY RESULTS: MK-0518 was generally well tolerated in healthy, male and female subjects. No serious clinical or serious laboratory adverse experiences were reported, and no subject discontinued because of an adverse experience. 10 out of the 20 subjects enrolled reported a total of 34 nonserious clinical adverse experiences, 14 of which were determined by the investigator as drug related. All clinical adverse experiences reported were transient and rated mild in intensity. There were no laboratory adverse experiences reported.

DISCUSSION AND CONCLUSIONS: After administration of single oral doses of final market image MK-0518, MK-0518 $AUC_{0-\infty}$ and C_{max} were dose proportional over the dose range of 100 to 1600 mg. MK-0518 C_{12hr} was slightly less than dose proportional over the dose range of 100 to 1600 mg; however, dose proportionality was demonstrated over the dose range of 100 to 800 mg.

However, the variability is quite large (increasing with increasing dose levels), which implies a large degree of uncertainty in MK-0518 exposure level.

Protocol 026

TITLE: An Open-Label, 3-Period, Fixed-Sequence Study to Evaluate the 2-Way Interaction of MK-0518 and TMC125 in Healthy Adult Subjects

OBJECTIVES: To evaluate the effect of coadministration of TMC125 and MK-0518 on the plasma pharmacokinetic profiles of MK-0518 (e.g. $AUC_{0\text{-}12hr}$, $C_{12\ hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of TMC125 alone, MK-0518 alone, and TMC125 coadministered with multiple doses of MK-0518, and to assess the effect of MK-0518 on pharmacokinetics of TMC-125

SUBJECTS AND STUDY DESIGN: This was an open label, 3-period, fixed-sequence study in healthy adult subjects to assess the effects of co-administration of MK-0518 and TMC125. Twenty subjects each received MK-0518 and TMC125 in an open label fashion. In Period 1, all subjects were administered oral doses of 400 mg MK-0518 every 12 hours for 4 days. However, in Period 1, the Day 4 MK-0518 PM dose was not given. Period 1 was followed by a wash-out of at least 4 days. In Period 2, the same 20 subjects were administered 200-mg TMC125 q12 hours for 8 days. There was no wash-out between Periods 2 and 3. In Period 3, all 20 subjects received a combination of TMC125 (200 mg q12 hours) and MK-0518 (400 mg q12 hours) for 4 days. In Period 3, the Day 4 PM doses were not administered. All dosing was in an open label fashion.

All doses of TMC125 and MK-0518 were administered with food including days when pharmacokinetic samples were collected.

Subject Baseline Demographics

AN	Gender	Race	Age (Years)	Height (cm)	Weight (kg)
0441	Male	White	41	175.0	78.2
0442	Male	White	37	181.0	79.1
0443	Male	White	20	179.1	88.2
0444	Male	Black	33	182.0	100.0
0445	Male	White	22	173.0	58.2
0446	Male	White	38	183.7	99.6
0447	Male	White	22	175.2	67.7
0448	Male	White	34	177.4	87.7
0449	Male	White	37	176.7	88.6
0450	Male	White	24	187.0	103.2
0451	Male	Black	32	179.0	72.7
0452	Male	White	24	177.1	76.8
0453	Male	White	19	177.0	71.8
0454	Female	White	31	165.5	70.9
0455	Female	White	45	167.0	78.6
0456	Female	Black	29	164.0	83.6
0457	Female	White	29	176.5	63.6
0458	Female	White	30	166.5	60.9
0459	Female	White	23	174.5	80.0
0460	Female	Black	26	145.0	59.6

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 poloxamer formulation tablets (FMI) 400 mg, TMC125 100 mg tablets

SAMPLE COLLECTION: Serial blood samples were obtained for plasma concentrations of MK-0518 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours postdose. Serial blood samples were obtained for plasma concentrations of TMC-125 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours postdose.

ASSAYS: Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations.

The bioanalysis of TMC125 was performed by [redacted] Plasma concentrations of TMC125 were determined using a validated LC-MS/MS method. The lower limit of quantification was [redacted]

PHARMACOKINETIC DATA ANALYSIS: Plasma concentrations of MK-0518 were used to calculate pharmacokinetic parameters including AUC $_{0\text{-}12hr}$, C_{max}, $C_{12\ hr}$, T_{max}, and apparent $t_{½}$ for each subject in the presence or absence of multiple doses of TMC125. Geometric mean ratios (MK-0518 + TMC125/MK-0518) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{0\text{-}12hr}$) were calculated for treatment comparisons.

The plasma pharmacokinetic profile (e.g., $C_{12\ hr}$, $AUC_{0\text{-}12\ hr}$, C_{max}, T_{max}) of TMC125 in the presence and absence of MK-0518 was calculated for each subject. Geometric mean ratios (TMC125 + MK0518/ TMC125) and associated 90% confidence intervals (CIs) of primary plasma TMC125 PK parameters (C_{12h}, C_{max}, and $AUC_{0\text{-}12hr}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

MK-0518 Pharmacokinetics:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Multiple Doses of 400-mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Twice-Daily to Healthy Adult Subjects (Inset = Semilog Scale)

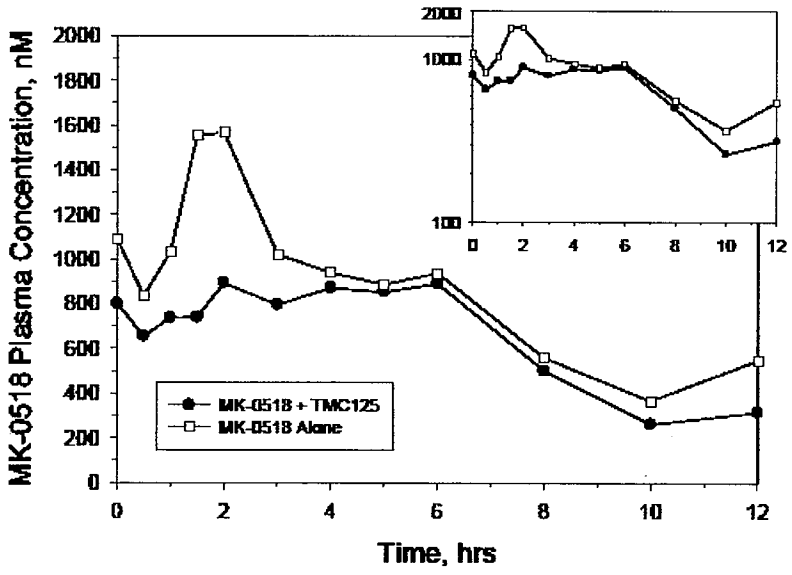


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics Following Administration of Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Daily to Healthy Adult Subjects

Pharmacokinetic Parameter	MK-0518 + TMC125			MK-0518			(MK-0518 + TMC125/ MK-0518)			MSE†
	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	
$C_{12\,hr}$ (nM)‡	19	141.6	(77.3, 259.6)	19	216.0	(117.8, 396.0)	19	0.66	(0.34, 1.36)	1.347
$AUC_{0\text{-}12hr}$ (μM·hr)‡	19	6.28	(4.49, 8.78)	19	7.01	(5.02, 9.81)	19	0.90	(0.68, 1.18)	0.348
C_{max} (μM)‡	19	1.54	(1.09, 2.18)	19	1.74	(1.23, 2.46)	19	0.89	(0.68, 1.15)	0.313
T_{max} (hr)	19	3.0§		19	1.5§		19	1.5‖	(0.3, 3.0) ‖	

† Mean square error on log-scale.

‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.

§ Median reported for T_{max}.

‖ Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Table 2. Individual MK-0518 Plasma Pharmacokinetics and Summary Statistics Following Administration of Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Twice-Daily to Healthy Adult Subjects

	C_{12hr}, nM			$AUC_{0\text{-}12hr}$, μM·hr			C_{max}, μM			T_{max}, hr		
AN	A	C	C/A	A	C	C/A	A	C	C/A	A	C	C-A
0441	39.8	587.3	14.76	4.06	9.51	2.34	1.40	1.39	0.99	0.0	0.0	0.0
0442	1032.9	130.3	0.13	9.31	11.41	1.23	2.50	2.86	1.14	0.0	4.0	4.0
0443	33.3	17.0	0.51	1.69	2.33	1.38	0.62	0.67	1.08	0.0	4.0	4.0
0444	37.8	56.7	1.50	3.46	6.88	1.99	1.40	3.76	2.69	1.5	1.0	-0.5
0445	178.4	234.0	1.31	7.98	4.71	0.59	1.42	1.27	0.89	6.0	2.0	-4.0
0446	762.8	722.3	0.95	6.56	6.94	1.06	1.17	1.34	1.15	0.5	0.0	-0.5
0447	114.3	123.8	1.08	5.40	4.63	0.86	1.29	1.16	0.90	0.0	3.0	3.0
0448	72.7	58.7	0.81	4.17	5.18	1.24	0.85	1.26	1.48	1.0	2.0	1.0
0449	402.8	479.3	1.19	2.75	3.04	1.11	0.48	0.51	1.06	0.0	5.0	5.0
0450	73.4	107.6	1.47	2.56	5.47	2.14	0.73	0.98	1.34	2.0	5.0	3.0
0451	911.3	37.8	0.04	5.70	2.59	0.45	1.32	0.96	0.73	0.0	0.0	0.0
0452	762.8	184.7	0.24	15.35	6.63	0.43	2.41	1.31	0.54	1.5	1.5	0.0
0453	64.8	33.1	0.51	3.00	3.82	1.27	0.66	1.02	1.55	1.5	4.0	2.5
0454	4207.9	142.4	0.03	16.31	10.34	0.63	4.21	2.25	0.53	12.0	0.0	-12.0
0455	185.4	61.2	0.33	30.87	5.92	0.19	9.61	1.44	0.15	1.5	2.0	0.5
0456	96.5	2452.7	25.42	12.26	8.09	0.66	4.16	2.45	0.59	5.0	12.0	7.0
0457	1039.6	288.0	0.28	18.77	25.15	1.34	5.15	7.63	1.48	2.0	6.0	4.0
0459	202.3	49.7	0.25	23.56	6.01	0.26	4.48	1.31	0.29	1.5	4.0	2.5
0460	183.4	225.0	1.23	9.01	13.00	1.44	2.30	2.90	1.26	2.0	5.0	3.0
AM	547.5	315.3	–	9.82	7.48	–	2.43	1.92	–	2.0	3.2	–
SD	957.4	554.0	–	8.04	5.19	–	2.26	1.62	–	2.9	2.9	–
Med	183.4	130.3	–	6.56	6.01	–	1.40	1.31	–	1.5	3.0	1.8†
GM‡	216.0	141.6	0.66	7.01	6.28	0.90	1.74	1.54	0.89	–	–	–

Treatment A: 400-mg MK-0518 q12h x 3.5 days

Treatment C: 400-mg MK-0518 + 200-mg TMC125 q12h x 3.5 days

AN = Allocation Number; AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean

† For T_{max} represents Hodges-Lehman estimate of median treatment difference

‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values

Figure 2. Individual MK-0518 $C_{12\,hr}$ Ratios (MK-0518 Coadministered With TMC125/MK-0518 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Twice-Daily to Healthy Adult Subjects

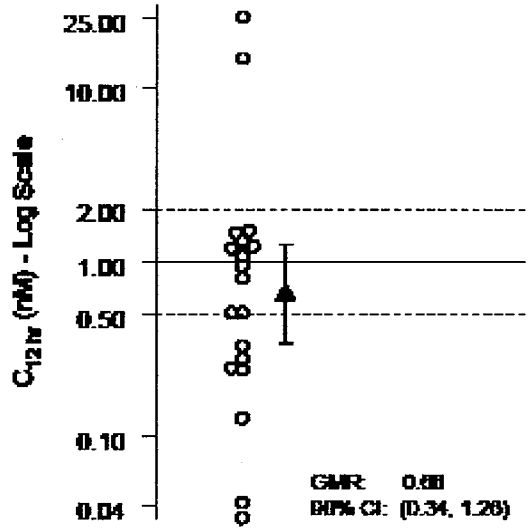


Figure 3. Individual MK-0518 $AUC_{0\text{-}12\,hr}$ Ratios (MK-0518 Coadministered With TMC125/MK-0518 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Twice-Daily to Healthy Adult Subjects

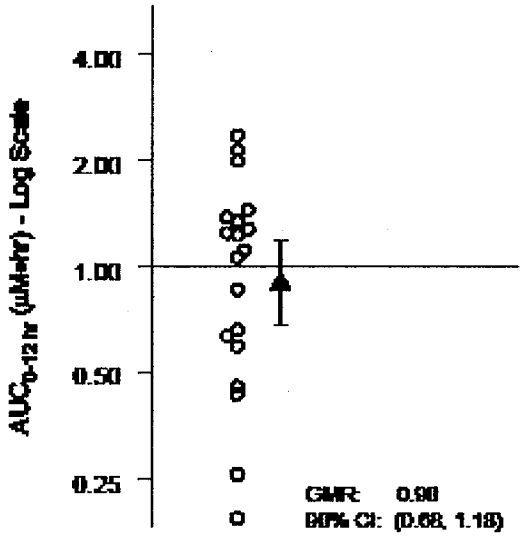
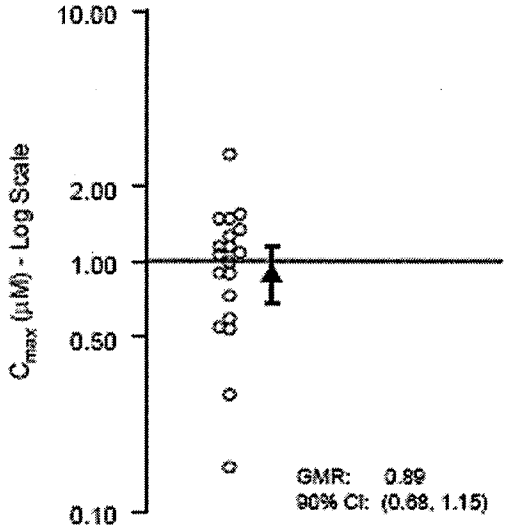


Figure 4. Individual MK-0518 C_{max} Ratios (MK-0518 Coadministered With TMC125/MK-0518 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg TMC125 Twice-Daily to Healthy Adult Subjectscts



TMC-125 Pharmacokinetics:

Figure 5. Arithmetic Mean TMC125 Plasma Concentration Profiles Following Multiple Doses of 200-mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 200 mg MK-0518 Twice-Daily to Healthy Adult Subjects (Inset = Semilog Scale)

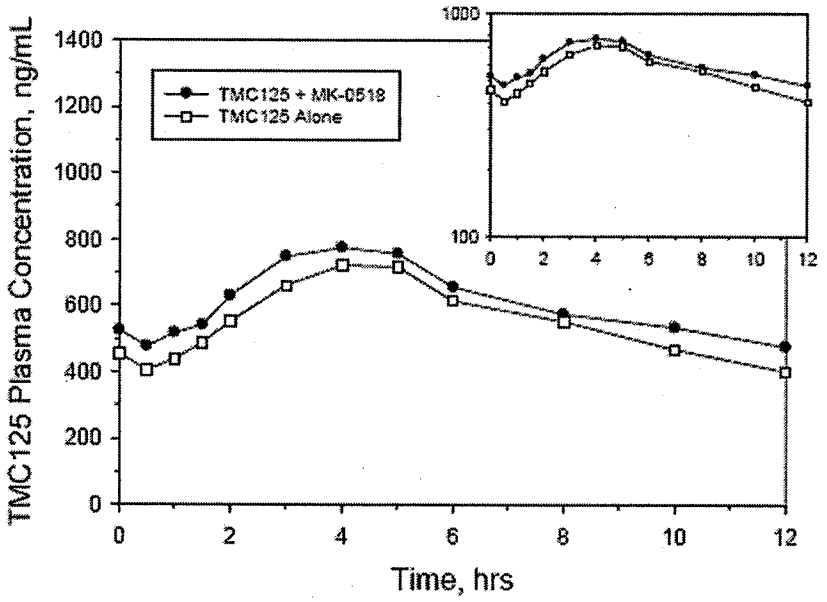


Table 3. Comparison of TMC125 Plasma Pharmacokinetics Following Administration of Multiple Doses of 200 mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice Daily to Healthy Adult Subjects

Pharmacokinetic Parameter	MK-0518 + TMC125			TMC125			(MK-0518 + TMC125/ TMC125)			MSE [†]
	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	
$C_{12\,hr}$ (ng/mL) [‡]	19	459	(359, 586)	19	373	(306, 457)	19	1.17	(1.10, 1.26)	0.015
$AUC_{0\text{-}12\,hr}$ (ng·hr/mL) [‡]	19	6813	(5633, 8240)	19	6216	(5139, 7518)	19	1.10	(1.03, 1.16)	0.011
C_{max} (ng/mL) [‡]	19	766	(633, 926)	19	734	(607, 888)	19	1.04	(0.97, 1.12)	0.017
T_{max} (hr)	19	4.0[§]		19	4.0[§]		19	-0.5[‖]	(-1.0, 0.0) [‖]	

[†] Mean square error on log-scale.
[‡] Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
[§] Median reported for T_{max}.
[‖] Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Table 4. Individual TMC125 Plasma Pharmacokinetics and Summary Statistics Following Administration of Multiple Doses of 200 mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Healthy Adult Subjects

	C_{12h}, ng/mL			AUC_{0-12h}, ng·hr/mL			C_{max}, ng/mL			T_{max}, hr		
AN	B	C	C/B	B	C	C/B	B	C	C/B	B	C	C-B
0441	369	459	1.24	6710	7394	1.10	812	782	0.96	4.0	5.0	1.0
0442	513	466	0.91	7901	7378	0.93	817	862	1.06	4.0	3.0	-1.0
0443	234	266	1.14	4193	4173	1.00	516	512	0.99	4.0	4.0	0.0
0444	355	374	1.05	5420	6173	1.14	586	646	1.10	2.0	2.0	0.0
0445	456	367	0.80	7054	5514	0.78	800	608	0.76	3.0	4.0	1.0
0446	343	436	1.27	5233	6024	1.15	612	611	1.00	5.0	5.0	0.0
0447	439	527	1.20	6907	8228	1.19	853	936	1.10	4.0	3.0	-1.0
0448	804	711	1.18	9769	11450	1.17	1030	1400	1.36	4.0	3.0	-1.0
0449	492	734	1.49	8786	10770	1.23	1080	1150	1.06	5.0	5.0	0.0
0450	214	284	1.33	3584	4863	1.36	462	642	1.40	5.0	3.0	-2.0
0451	785	994	1.27	12870	14400	1.12	1510	1700	1.13	4.0	4.0	0.0
0452	420	438	1.04	6510	7102	1.09	734	795	1.08	3.0	3.0	0.0
0453	516	513	0.99	8013	7546	0.94	924	790	0.85	5.0	4.0	-1.0
0454	325	520	1.60	6291	7584	1.21	748	904	1.21	5.0	5.0	0.0
0455	292	361	1.24	5310	5541	1.04	767	623	0.81	3.0	3.0	0.0
0456	241	368	1.53	3770	5462	1.45	435	598	1.37	5.0	5.0	0.0
0457	162	172	1.06	2550	2682	1.05	290	268	0.92	5.0	4.0	-1.0
0459	270	303	1.12	6012	5248	0.87	822	624	0.76	8.0	5.0	-3.0
0460	639	803	1.26	9732	11860	1.22	1080	1290	1.19	5.0	4.0	-1.0
AM	404	478	—	6864	7336	—	783	829	—	4.4	3.9	—
SD	162	206	—	2500	2937	—	279	345	—	1.3	0.9	—
Med	369	438	—	6510	7102	—	800	782	—	4.0	4.0	-0.5[†]
GM[‡]	373	439	1.17	6216	6813	1.10	734	786	1.04	—	—	—

Treatment B: 200-mg TMC125 q12h x 8 days

Treatment C: 400-mg MK-0518 + 200-mg TMC125 q12h x 3.5 days

AN = Allocation Number; AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean

[†] For T_{max}, represents Hodges-Lehmann estimate of median treatment difference

[‡] Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values

Figure 6. Individual TMC125 $C_{12\ hr}$ Ratios (TMC125 Coadministered With MK-0518/TMC125 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 200 mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Healthy Adult Subjects

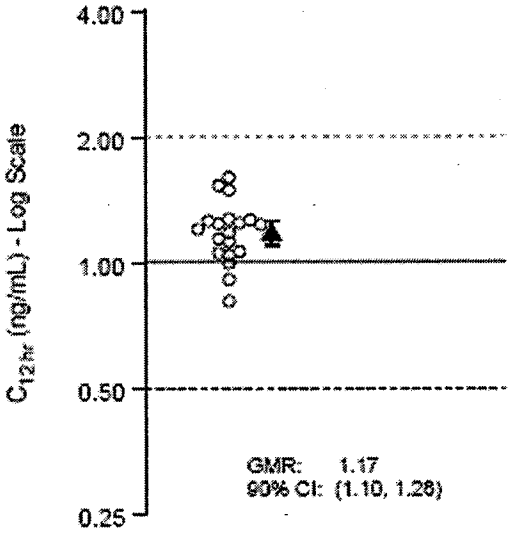


Figure 7. Individual TMC125 $AUC_{0\text{-}12\ hr}$ Ratios (TMC125 Coadministered With MK-0518/TMC125 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 200 mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Healthy Adult Subjects

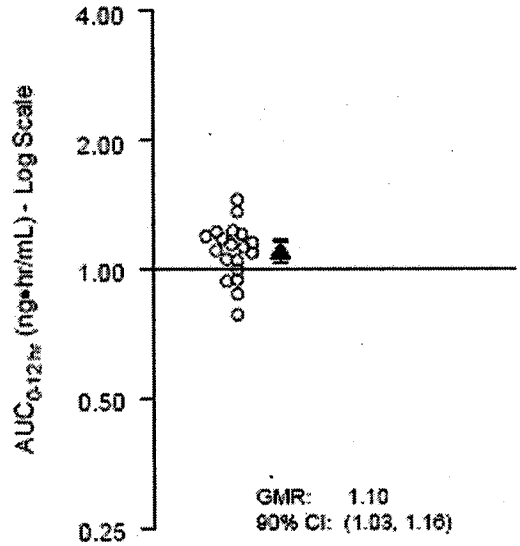
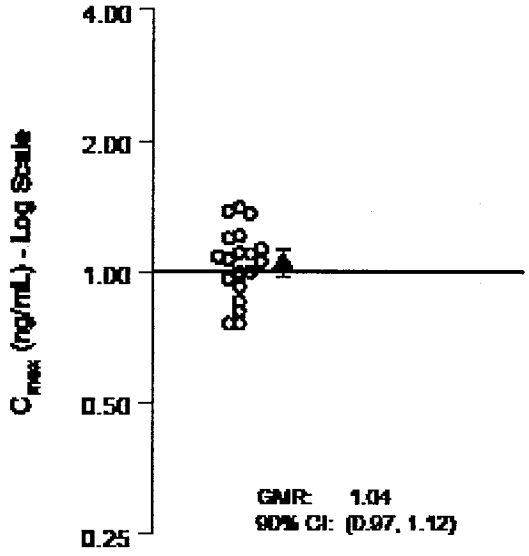


Figure 8. Individual TMC125 Cmax Ratios (TMC125 Coadministered With MK-0518/TMC125 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 200 mg TMC125 Twice-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Healthy Adult Subjects



SAFETY RESULTS: Administration of MK-0518 with concurrent administration of TMC125 was generally well-tolerated. No serious clinical adverse experiences were reported and no subject discontinued due to an adverse experience. A total of sixteen subjects reported a total of forty-four non-serious clinical adverse experiences, twenty-one of which were deemed by the investigator to be possibly related to either drug. The most common drug related adverse event was headache. There were no laboratory adverse experiences reported in this study. All adverse experiences reported were transient and rated mild to moderate in intensity.

DISCUSSION AND CONCLUSIONS: With co-administration of 200 mg TMC125 twice daily for 12 days, the MK-0518 C_{12hr} geometric mean ratio for (MK-0518 + TMC125/MK-0518) was 0.66 with a 90% CI of (0.34, 1.26). The $AUC_{0\text{-}12hr}$ geometric mean ratio (MK-0518 + TMC125/MK-0518) was 0.90 with a corresponding 90% confidence interval of (0.68, 1.18), while the C_{max} geometric mean ratio was 0.89 with a corresponding 90% confidence interval of (0.68, 1.15).

The 90% confidence interval is quite wide implying a large degree of uncertainty in the effect of TMC125 on MK-0518 $C_{12\,hr}$. This makes a definitive conclusion about the magnitude of the effect difficult.

The applicant concluded that effects up to a 2-fold increase in exposure (AUC) and a 60% decrease (equivalent to geometric mean ratio of 0.4) in trough concentration (C_{12hr}) were considered to be not clinically relevant based on available clinical experience from Phase I and Phase II studies with regard to safety and efficacy.

The lower bound of 90% CI of MK-0518 C_{12hr} ratios was 0.34 (<0.4) and a few individual MK-0518 C_{12hr} ratios were much lower than 0.4.

The effect of MK-0518 on the pharmacokinetics of TMC125 is negligible. TMC125 $C_{12\,hr}$ is unaffected when dosed in the presence of 400 mg MK-0518 with a geometric mean ratio of 1.17 and a 90% confidence interval of (1.10, 1.26). $AUC_{0\text{-}12\,hr}$ with a GMR of 1.10 and 90% CI of (1.03, 1.16), C_{max} with a GMR of 1.04 and a 90% CI of (0.97, 1.12).

Because TMC125 has not been approved, the drug interaction data described in this report will not be in the raltegravir label until TMC125 approval.

Protocol 028

TITLE: An Open-Label, Randomized, 2-Period Crossover Study to Assess the Effects of a High-Fat Meal on the Safety, Tolerability, and Pharmacokinetics of a Single Oral Dose of MK-0518 Final Market Image Tablet in Healthy Adult Subjects

OBJECTIVES: To evaluate the effect of a standard high-fat meal on the pharmacokinetics of a single 400-mg dose of MK-0518 final market image (FMI) tablet

SUBJECTS AND STUDY DESIGN: This was an open-label, randomized, 2-period crossover study to assess the effects of a high-fat meal on the safety, tolerability, and pharmacokinetics of a single oral dose of MK-0518 FMI. Twenty healthy male and female subjects (13 M/7 F) were administered a single oral dose of 400 mg MK-0518 FMI following a standard high-fat meal and in the fasted state in 2 treatment periods. The order of administration (fed or fasted) was randomly assigned. There was a minimum of a 4-day washout interval between Period 1 and Period 2 dosing.

Treatment Plan

Subjects (N=20)	Period 1†	Period 2
10	400 mg MK-0518 fed	400 mg MK-0518 fasted
10	400 mg MK-0518 fasted	400 mg MK-0518 fed

† There will be a minimum of a 4-day washout interval between Period 1 and Period 2 dosing.

Subjects received 2 treatments; 400-mg MK-0518 FMI after a high-fat meal (fed) approximately 5 minutes after consuming the meal and 400-mg MK-0518 FMI after an 8-hour fast (fasted). The caloric content of the high-fat meal followed the recommendations for food-effect bioavailability studies for the FDA and contained the following:

Total fat = 67.56 g
Total carbohydrates = 77.96 g
Total protein = 56.78 g
Total calories (kcal) = 1157.52 (613.61 in fat, 314.70 in carbohydrates, and 229.21 in protein).

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 400 mg FMI tablets

SAMPLE COLLECTION: Serial blood samples were obtained for plasma concentrations of MK-0518 at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48 and 72 hours postdose.

ASSAYS: Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations.

PHARMACOKINETIC DATA ANALYSIS:

The plasma pharmacokinetic parameters (e.g., C12 hr, AUC0-∞, Cmax, Tmax, and apparent t½) of MK-0518 were calculated for each subject after a single-dose of 400-mg MK-0518 FMI tablet in the fed and fasted states. 90% confidence intervals were constructed for the geometric mean ratios (fed/fasted) of MK-0518 $AUC_{0-\infty}$, C_{max} and C_{12hr}, respectively.

PHARMACOKINETIC RESULTS:

Table 1. Comparison of MK-0518 Plasma Pharmacokinetics in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 in the Fasted State and After a High-Fat Meal

Pharmacokinetic Parameter	400-mg Fed			400-mg Fasted			(400-mg Fed/400-mg Fasted)			MSE*
	N	Geometric Mean	95% CI for Geometric Mean	N	Geometric Mean	95% CI for Geometric Mean	N	Geometric Mean Ratio	90% CI for Geometric Mean	
$AUC_{0-\infty}$ (μM·hr)‡	20	12.27	(8.75, 17.20)	20	10.33	(7.37, 14.48)	20	1.19	(0.91, 1.54)	0.229
C_{max} (μM)‡	20	1.91	(1.18, 3.10)	20	2.91	(1.79, 4.72)	20	0.66	(0.44, 0.98)	0.526
C_{12hr} (nM)‡	20	460.3	(323.9, 654.2)	20	54.1	(38.1, 76.9)	20	8.51	(5.52, 13.12)	0.624
T_{max} (hr)	20	10.0§		20	1.8§		20	7.3‖	(5.8, 8.8)¶	
$t_{½}$ α (hr)	14	1.19§		19	0.95§		13	0.48§	(0.19, 0.87)‖	
$t_{½}$ β (hr)	20	10.2§		20	9.8§		20	1.0‖	(-2.6, 5.9)¶	

* Mean square error on log-scale.
‡ Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
§ Median reported for T_{max} and half-life.
‖ Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 400 mg of the Final Market Image (FMI) Formulation of MK-0518 to Young, Healthy, Male and Female Subjects Fasted or Following a High-Fat Meal (inset: semilog scale)

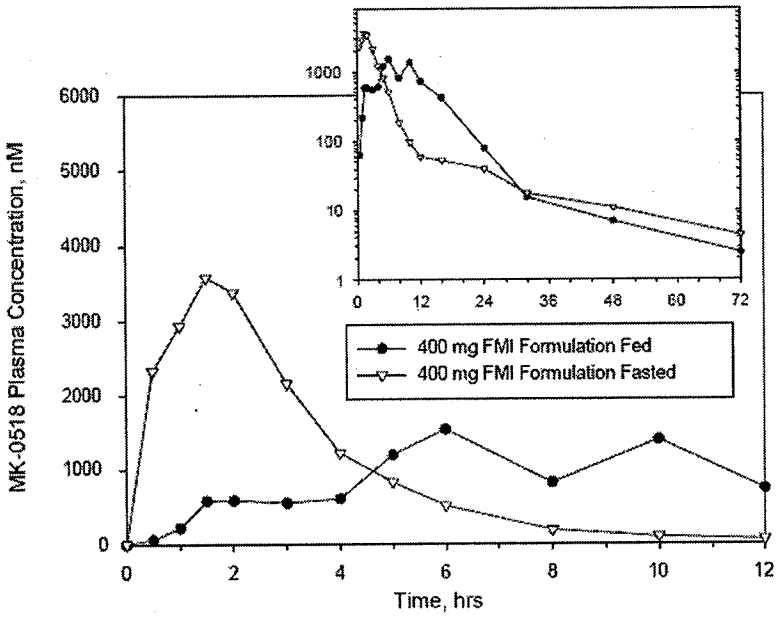


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Table 2. Individual MK-0518 Pharmacokinetic Parameter Values and Summary Statistics Following Single Dose Administration of 400 mg of the Final Market Image (FMI) Formulation of MK-0518 to Young, Healthy, Male and Female Subjects, Fasted or Following a High-Fat Meal

	AUC_{∞}, μM·hr			C_{max}, μM			C_{24hr}, nM			T_{max}, hr		
AN	Fed	Fasted	Ratio (Fed/Fast)	Fed	Fasted	Ratio (Fed/Fast)	Fed	Fasted	Ratio (Fed/Fast)	Fed	Fasted	Difference (Fed/Fast)
0421	33.71	26.98	0.80	10.79	12.30	0.88	128.1	72.7	1.69	5	1.5	3.5
0422	23.72	26.38	0.90	3.51	7.18	0.35	1258.3	72.8	17.20	16	0.5	15.5
0423	13.68	3.75	3.65	4.83	0.78	6.90	88.9	36.9	3.41	6	5	1.0
0424	6.59	7.61	0.87	0.98	5.34	0.19	203.6	48.8	4.17	10	0.5	9.5
0425	16.16	7.76	2.08	1.69	1.67	1.01	462.6	58.3	7.93	16	5	11.0
0426	12.28	5.03	2.44	1.88	1.45	1.30	1880.3	30.4	61.85	12	4	8.0
0427	6.56	8.22	0.74	0.76	2.91	0.26	169.0	33.3	5.08	6	1	5.0
0428	7.80	1.40	5.57	0.57	0.38	2.04	491.7	26.1	18.84	10	1	9.0
0429	6.13	8.34	0.74	0.71	1.77	0.40	511.9	45.9	11.15	10	2	8.0
0430	7.34	19.39	0.38	1.03	5.08	0.21	174.4	88.0	1.98	8	3	5.0
0431	22.19	21.76	1.02	3.03	7.62	0.40	3627.8	57.8	63.76	12	1.5	10.5
0432	5.42	3.60	1.51	0.51	0.86	0.59	507.0	31.7	15.99	12	5	7.0
0433	36.63	29.75	1.23	11.95	12.69	0.94	574.5	67.3	8.54	6	1.5	4.5
0434	18.86	5.20	3.61	5.74	1.08	5.31	778.1	45.2	17.21	10	6	4.0
0435	4.88	5.54	0.84	0.65	0.91	0.71	83.3	67.1	1.24	6	5	1.0
0436	13.91	23.85	0.58	3.83	9.56	0.38	1182.0	47.7	24.78	10	2	8.0
0437	18.58	18.04	1.00	1.64	5.28	0.31	642.7	70.4	9.13	16	1	15.0
0438	11.80	12.52	0.94	1.26	1.30	0.97	434.5	122.2	3.56	10	1	9.0
0439	18.92	16.24	0.67	1.09	7.17	0.15	416.5	82.8	5.03	5	0.5	4.5
0440	22.12	21.90	1.01	6.14	8.71	0.70	1088.0	62.1	17.52	10	2	8.0
AM	14.40	13.66	–	3.06	4.68	–	733.9	58.3	–	9.2	2.5	–
SD	8.52	9.14	–	3.32	3.99	–	822.5	28.4	–	3.5	1.8	–
Med	13.98	10.43	–	1.67	3.96	–	499.4	58.1	–	10.0	1.8	–

AN: Alteration Number; AM: Arithmetic Mean; SD: Standard Deviation; Med: Median; ND: Unable to calculate.
† Calculated from mono-exponential, rather than bi-exponential equation.
‡ Harmonic Mean.
§ Jackknife Standard Deviation.

Figure 2. Individual MK-0518 AUC0-∞ Ratios (Fed/Fasted) With Geometric Mean Ratio and 90% CI in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 in the Fasted State and Following a High-Fat Meal (n=20)

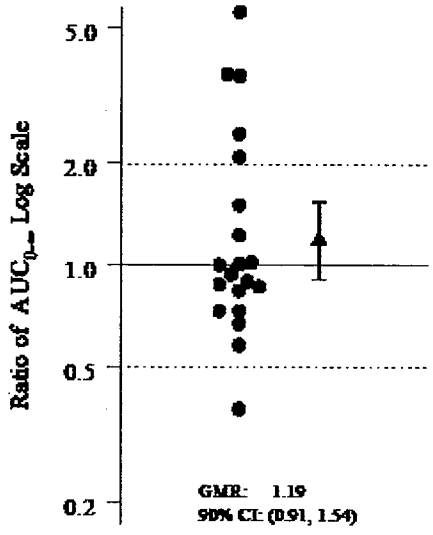


Figure 3. Individual MK-0518 Cmax Ratios (Fed/Fasted) With Geometric Mean Ratio and 90% CI in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 in the Fasted State and Following a High-Fat Meal (n=20)

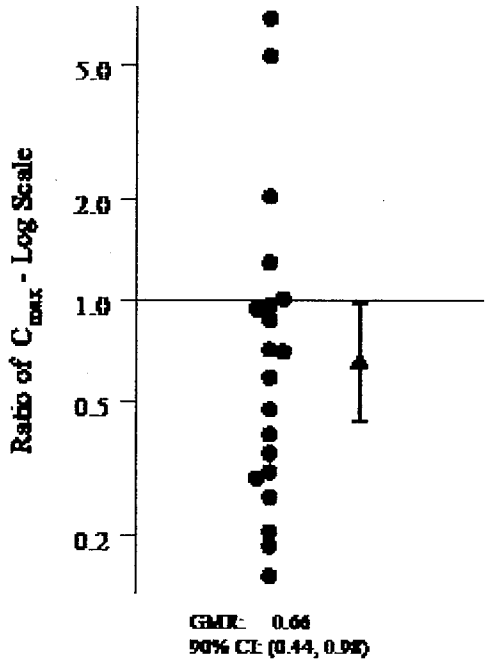


Figure 4. Individual MK-0518 C12 hr Ratios (Fed/Fasted) With Geometric Mean Ratio and 90% CI in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 in the Fasted State and Following a High-Fat Meal (n=20)

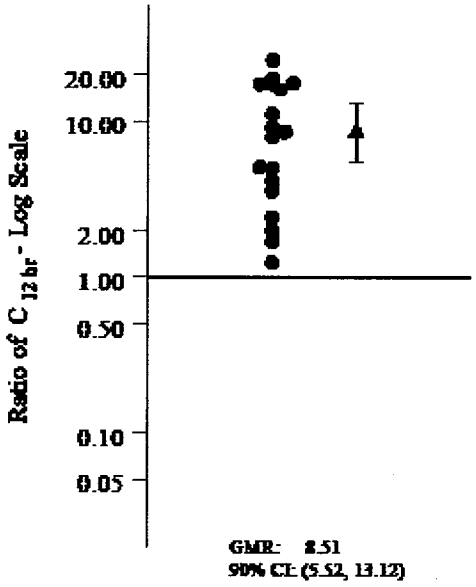
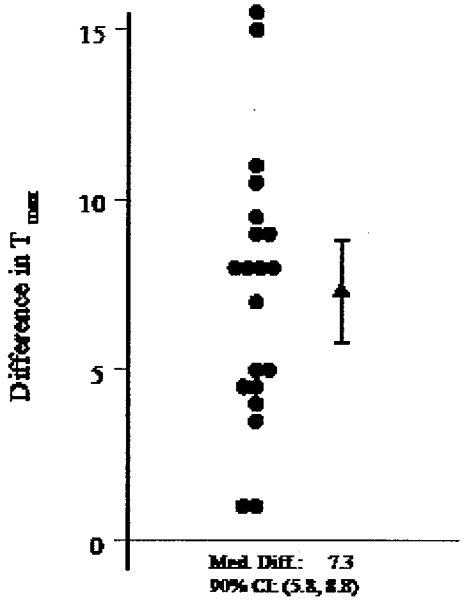


Figure 5. Individual MK-0518 Tmax Differences (Fed-Fasted) With Estimated Median and 90% CI in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 in the Fasted State and Following a High-Fat Meal (n=20)



SAFETY RESULTS: MK-0518 was generally well tolerated. No serious clinical or serious laboratory adverse experiences were reported and no subject discontinued because of an adverse experience.

DISCUSSION AND CONCLUSIONS:

The primary difference between the phase I poloxamer formulation of MK-0518 relative to the FMI formulation is the relative amount of the poloxamer excipient. There was no food effect of the phase I poloxamer formulation. The difference in poloxamer excipient may be the cause of the difference in the sensitivity of absorption rate to ingestion with a high-fat meal; though the precise cause is not known.

Phase II and III studies conducted with the Phase II/III/FMI formulation have been conducted without regard to food based on the initial food effect data from earlier formulations including the phase I poloxamer formulation.

On average, a high-fat meal resulted in 19% increase in AUC, 34% decrease in Cmax, 750% increase in C12hr and 7.3 hour delay in Tmax with MK-0518 final market image formulation. However, the variability is quite large.

In Vitro Studies

A. Metabolism in Liver Microsomes and Hepatocytes

Methods:

Incubations: Rat, dog, and human liver microsomes were obtained from

Results:

In rat, dog, and human liver microsomal incubations fortified with NADPH, no significant metabolism of MK-0518 was observed after 1-hr incubation period in all three species. The results indicated that there is little biotransformation of the compound by cytochromes P450.

The major metabolite identified in all three species in hepatocytes was the phenolic glucuronide derivative M2. Minor metabolites that were presented in all three species included the glucose conjugate of MK-0518 (M1) and the acetyl hydrazine derivative (M3).

Figure 1. HPLC-Radiochromatograms of Metabolites of [^{14}C] MK-0518 in Rat, Dog, and Human Hepatocyte Incubations (37°C, 4 hr, 50 µM)

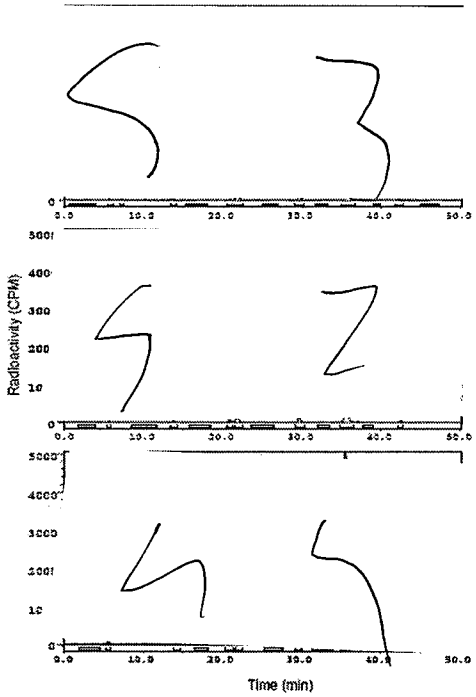
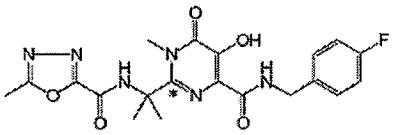
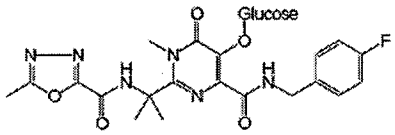


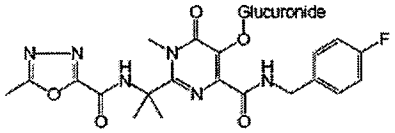
Figure 2. Structures of Metabolites of MK-0518 Identified in Rat, Dog, and Human Hepatocytes



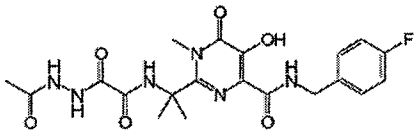
MK-0518
* C-14



M1



M2 (L-001277512)



M3 (L-001063726)

B. UGT Phenotyping

Methods:

Liver Microsomes: A pool of human liver microsomes were obtained from

Results:

A typical radiochromatogram of an extract after incubation of [^{14}C] MK-0518 with UDPGA-fortified pooled human liver microsomes is shown in Figure 3. Formation of MK-0518-glucuronide (M2) was confirmed by HPLC-MS/MS. In studies using cDNA-expressed UGTs, MK-0518 (5 and 50 µM) was converted to M2 by UGT1A1, 1A3, and 1A9 but not UGT1A4, 1A6, 1A7, 1A8, 1A10, 2B4, 2B7, 2B15, and 2B17 (Figure 4). The apparent Km for MK-0518 glucuronidation by UGT1A1 and UGT1A9 was 98 ± 16 and 296 ± 55 µM, respectively (Table 2). By comparison, the Km for pooled human liver microsomes was 205 ± 23 µM. The formation of M2 correlated highly (r = 0.88 and 0.91 at 5 µM and 50 µM MK-0518, respectively) with estradiol 3-glucuronidation (marker for UGT1A1 activity, Table 3). Correlation with other two UGT marker activities was weak i.e., r = 0.02-0.15 for trifluoperazine glucuronidation (UGT1A4) and r = 0.15-0.21 for propofol glucuronidation (UGT1A9). Formation of M2 in pooled human liver microsomes was inhibited by typical UGT1A1 substrates, bilirubin (IC_{50} = 7.1 µM) and estradiol (IC_{50} = 53 µM). In addition, atazanavir (a selective UGT1A1 inhibitor at sub-micromolar concentration inhibited the glucuronidation of MK-0518 with an IC_{50} of 0.5 µM. However, no inhibitory effect was observed with imipramine (IC_{50} >500 µM), a substrate/inhibitor for UGT1A3 and 1A4 (Figure 5).

These results demonstrated that UGT1A1 plays a major role in the glucuronidation of MK-0518 in pooled human liver microsomes.

Figure 3. A Representative Radiochromatogram of an Extract After Incubation of [^{14}C] MK-0518 (5 µM) with Pooled Human Liver Microsomes in the Presence of UDPGA

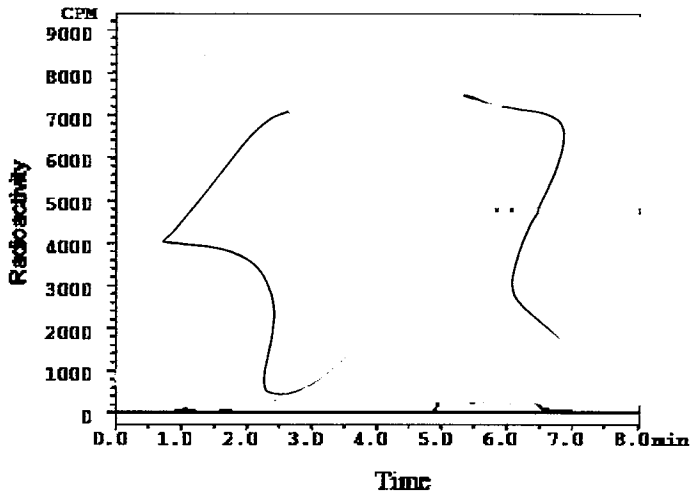


Figure 4. Metabolism of [^{14}C] MK-0518 to M2 by cDNA-Expressed Human UDP-Glucuronosyltransferases at 5 µM and 50 µM Substrate Concentrations

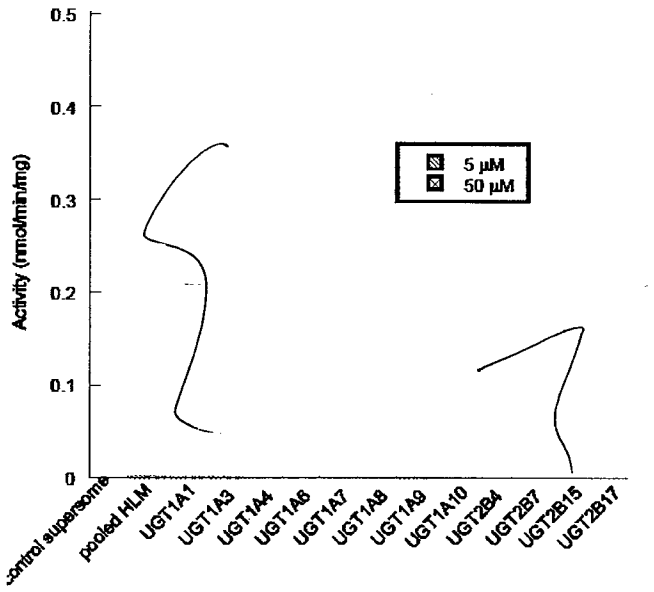


Figure 5. Inhibition of Formation of M2 by Bilirubin, Estradiol, and Imipramine in Incubations of MK-0518 (200 µM) with UDPGA-Fortified Human Liver Microsomes

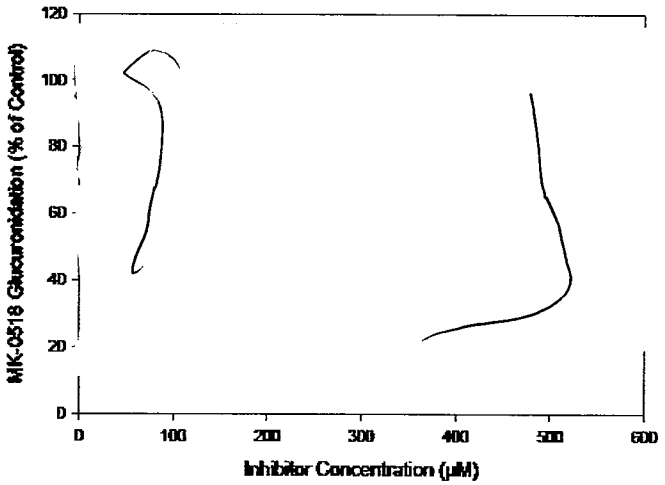


Table 1. Kinetic Parameters for Glucuronidation of [14C]MK-0518 by cDNA-Expressed UDP-Glucuronosyltransferases and Human Liver Microsomes

DNA-expressed UGT	K_m (µM)	V_{max} (nmol/min/mg)
1A1		
1A9		
Human liver microsomes[a]		

[a] Pooled human liver microsom

Table 2. Correlation of Various Human Liver Microsomal UDP-Glucuronosyltransferase Activities with the Formation of [^{14}C] MK-0518 Glucuronide (M2)

Activity	UGT	Correlation Coefficient (r)	
		5 µM	50 µM
Estradiol 3-glucuronidation	UGT1A1		
Trifluoperazine glucuronidation	UGT1A4		
Propofol glucuronidation	UGT1A9		

C. Inhibition of Human Liver Microsomal Cytochromes P450

Methods:

Results:

MK-0518 was shown to be a weak inhibitor (IC_{50} >100 μM) of all seven CYP activities.

Table 3. Evaluation of MK-0518 as a Non-Preincubation-Dependent Inhibitor of Seven CYP Activities in Pooled Human Liver Microsomes

Enzyme Involved	Reaction (Substrate concentration)	Compound Tested	Conc. Range (μM)	IC_{50} (μM)
CYP1A2	Phenacetin *O*-deethylation (100 μM)	Fluvoxamine	0.005 – 10	
		MK-0518	0.05 - 100	>100
CYP2C8	Taxol 6α-hydroxylation (15 μM)	Quercetin	0.02 - 50	
		MK-0518	0.05 - 100	>100
CYP2C9	Diclofenac 4′-hydroxylation (10 μM)	Sulfaphenazole	0.005 – 10	
		MK-0518	0.05 - 100	>100
CYP2C19	(*S*)-Mephenytoin 4′-hydroxylation (80 μM)	(R)-N-3-benzyl-phenobarbital	0.005 – 10	
		MK-0518	0.05 - 100	>100
CYP2D6	Bufuralol 1′-hydroxylation (15 μM)	Quinidine	0.005 – 10	
		MK-0518	0.05 - 100	>100
CYP3A4	Testosterone 6β-hydroxylation (60 μM)	Ketoconazole	0.005 – 10	
		MK-0518	0.05 - 100	>100
CYP2B6	Bupropion hydroxylation (100 μM)	N-(α-methylbenzyl)-1-aminobenzotriazole	0.005 – 10	
		MK-0518	0.05 - 100	>100

D. Inhibition of Human UGT1A1 and UGT2B7

Methods:

Results:

MK-0518 did not potently inhibit UGT1A1-catalyzed estradiol 3-glucuronidation and UGT2B7-catalyzed AZT glucuronidation in pooled human liver microsome. IC_{50} values were higher than 50 μM for both UGT activities.

Table 4. Evaluation of MK-0518 as an Inhibitor of Glucuronidation of β-Estradiol (UGT1A1) and AZT (UGT2B7) in Pooled Human Liver Microsomes

Inhibitor: MK-0518	Substrate: estradiol (UGT1A1)		Substrate: AZT (UGT2B7)	
Concentration (μM)	% of the control	SD	% of the control	SD
0.00	100	4	100[†]	NA
0.07	92	4	108	11
0.21	136	18	90	10
0.62	107	10	96	20
1.85	117[†]	NA	95	13
5.56	NA*	NA*	96	14
16.67	126	5	83	14
50.00	95	12	83	7
IC_{50}	>50	NA	>50	NA

[†] n = 1
NA = not applicable.
NA* = no data collected.

E. Induction of CYP3A4

Methods:

Results:

MK-0518 (up to 10 μM) did not induce CYP3A4 RNA expression or CYP3A4-dependent testosterone 6β-hydroxylase activity.

Table 5. Evaluation of MK-0518 as a Cytochrome P450 3A4 Inducer in Human Primary Hepatocytes

Human Donor #1

Compound	CYP3A4 RNA				Testosterone 6β-OH	
	24 hr		48 hr		48 hr	
	Rel Amount	P-Value	Rel Amount	P-Value	Rel Amount	P-Value
10 μM RIF		<0.001		<0.001		<.001
0.1 μM MK-0518		0.591		<0.001		0.86
1 μM MK-0518		<0.001		0.011		0.99
10 μM MK-0518		0.001		0.009		0.67

Human Donor #2

Compound	CYP3A4 RNA				Testosterone 6β-OH	
	24 hr		48 hr		48 hr	
	Rel Amount	P-Value	Rel Amount	P-Value	Rel Amount	P-Value
10 μM RIF		<0.001		<0.001		<.001
0.1 μM MK-0518		0.379		0.425		0.99
1 μM MK-0518		0.95		0.098		0.98
10 μM MK-0518		0.216		0.719		<.001

Bold values are statistically different from controls.

F. Plasma Protein Binding and Blood-to-Plasma Partitioning

Methods:

Results:

The average binding was 70, 74, 70, and 83% for mouse, rat, dog, and human, respectively. Plasma protein binding was independent of MK-0518 concentrations (2, 5, and 10 μM) in all species. The blood-to-plasma ratio of MK-0518 was independent of its concentration (0.9, 4.5, and 18 μM). MK-0518 bound minimally to the components in blood cells from rats and human, the mean blood-to-plasma ratio was 0.7 for rat and 0.6 for human. The blood-to-plasma ratio was slightly higher in the dog (0.9).

Table 6. Protein Binding of MK-0518 in Mouse, Rat, Dog, and Human Plasma

Species	Concentration (μM)	% Bound
Mouse		
Rat		
Dog		
Human		

Table 7. Blood-to-Plasma Concentration Ratios of MK-0518 in Rat, Dog, and Human

MK-0518 Concentration (μM)	Species		
	Rat	Dog	Human
0.9			
4.5			
18			
Mean ± SD	0.7 ± 0.1	0.9 ± 0.1	0.6 ± 0.0

G. P-Glycoprotein Transport

Methods:

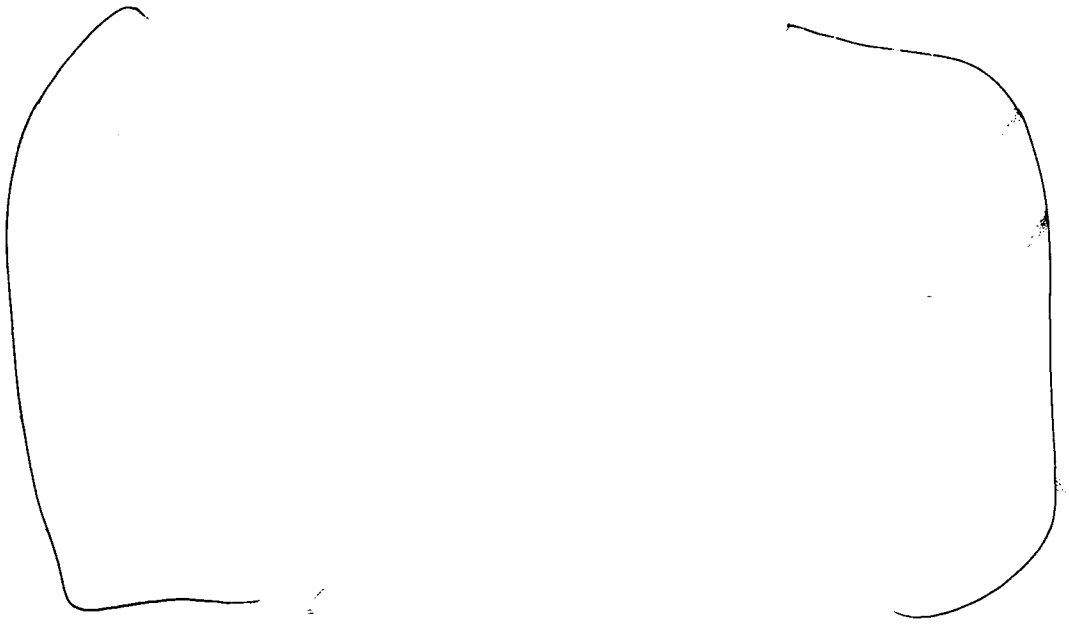
Results:

The results demonstrated that MK-0518 is a substrate for human, mouse, and rat P-gp.

Table 8. Transcellular Transport of MK-0518 and Verapamil Across L-MDR1, L-mdr1a, and L-Rmdr1a, and LLC-PK1 Cell Monolayers

Compound	B-A/A-B Ratio			
	L-MDR1	L-mdr1a	L-Rmdr1a	LLC-PK1
MK-0518				
Verapamil				

H. P-Glycoprotein Inhibition



counter.

Results:

MK-0518 over a concentration range of 1 to 100 μM did not affect [^{3}H] vinblastine (VBL) accumulation in L-MDR1 and KB-V1 cell lines. In contrast, in the presence of a typical P-gp inhibitor, cyclosporin A (CsA), cellular accumulation of [^{3}H] VBL was increased 10- and 12-fold in L-MDR1 and KB-V1 cells, respectively. These results indicate that MK-0518 is not an inhibitor of human P-gp.

Table 9. Cellular Accumulation of [^{3}H] Vinblastine in the Presence of Increasing Concentrations of MK-0518

	L-MDR1	LLC-PK1	
Treatment	Cell-Accumulation	Cell-Accumulation	Ratio* (%)
Control	0.006 ± 0.003	0.025 ± 0.001	22.6
+MK-0518 (1 μM)	0.009 ± 0.001	0.071 ± 0.001	12.2
+MK-0518 (5 μM)	0.009 ± 0.001	0.071 ± 0.001	13.1
+MK-0518 (10 μM)	0.007 ± 0.000	0.066 ± 0.007	10.8
+MK-0518 (25 μM)	0.008 ± 0.000	0.063 ± 0.006	13.3
+MK-0518 (50 μM)	0.008 ± 0.000	0.066 ± 0.001	12.1
+MK-0518 (100 μM)	0.007 ± 0.001	0.064 ± 0.006	10.2
+CsA (10 μM)	0.059 ± 0.007	0.051 ± 0.011	114.4

(b) KB-V1 and KB-3-1 Cells

	KB-V1	KB-3-1	
Treatment	Cell-Accumulation	Cell-Accumulation	Ratio* (%)
Control	0.008 ± 0.001	0.089 ± 0.003	9.4
+MK-0518 (1 μM)	0.015 ± 0.004	0.190 ± 0.004	8.1
+MK-0518 (5 μM)	0.015 ± 0.000	0.181 ± 0.010	8.3
+MK-0518 (10 μM)	0.014 ± 0.002	0.182 ± 0.017	7.4
+MK-0518 (25 μM)	0.011 ± 0.002	0.165 ± 0.022	6.9
+MK-0518 (50 μM)	0.009 ± 0.001	0.159 ± 0.005	5.6
+MK-0518 (100 μM)	0.005 ± 0.001	0.148 ± 0.014	3.2
+CsA (10 μM)	0.108 ± 0.007	0.103 ± 0.017	104.1

Results are expressed as cell-associated amounts normalized with sum of the amounts of cell-associated and in supernatant.

* Ratio represents cell-accumulation in P-gp expressing cells divided by that in control cells.

4.2 Consult Review

4.2.1 PHARMACOGENOMICS REVIEW

NDA: 22145	Submission Date(s):	April 13, 2007
Generic Name	Raltegravir (MK-0518)	
Pharmacogenomic Reviewer	Shashi Amur, Ph.D.	
Applicant	Merck	
Formulation; Strength(s)	400 mg	
Indication	In combination with other anti-retroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy	

Background: Raltegravir is metabolized by UGT1A1 with minor contributions from UGT1A3 and UGT1A9. One of the polymorphisms in the UGT1A1 gene, the variation in the number of TA repeats in the TATA box of the promoter, has been studied extensively. This polymorphism, designated UGT1A1 * 28, has 7 TA repeats instead of the 6 TA repeats observed in wild-type and results in attenuated expression of the isoenzyme. UGT1A1 plays an important role in bilirubin glucuronidation and mutations in UGT1A1 are responsible for hyperbilirubinemia. Correlation of UGT1A1*28 genotype, SN-38 exposure (AUC) and increased risk for irinotecan toxicity (diarrhea and neutropenia) has also been shown[1]. This resulted in the recommendation of lower starting doses of irinotecan in patients homozygous for UGT1A1*28 polymorphism.

Data analysis: The applicants have studied the impact of UGT1A1*28 polymorphism on pharmacokinetic parameters such as AUC, Cmax and C12hr in 48 healthy subjects that have UGT1A1 *1/*1 or UGT1A1*28/*28 genotype. At the time of review, analyzed data from seven UGT1A1 *28/*28 subjects and four UGT1A1 *1/*1 subjects was provided by the applicant.

A significant inter-individual variation was found in $AUC_{0-\infty}$ and Cmax values that made the task of finding a difference in the AUC or Cmax between the UGT1A1*1/*1 and UGT1A1 *28 subjects challenging. Given the small sample size, 7 UGT1A1 *28/*28 and 4 UGT1A1 *1/*1 subjects, and huge inter-individual variation, it is not possible to conclude whether the pharmacokinetic parameters are affected by the UGT1A1 genotype.

Suggestions for Continued Studies

Higher levels of serum bilirubin were observed in the raltegravir arm of patients who were also receiving atazanavir, an inhibitor of UGT1A1. In the presence of atazanavir, patients with UGT1A1 *28/*28 are likely to be more affected during raltegravir treatment. In support of this possibility, indinavir, an inhibitor of UGT enzyme activity[2], has been reported to induce unconjugated hyperbilirubinemia in up to 25% of patients.

UGT1A1 genotype should be tested in patients receiving raltegravir and atazanavir, especially in the patients who show elevated serum bilirubin levels and the correlation of UGT1A1*28/*28 and elevated serum bilirubin levels should be examined.

REFERENCES:

1. Ramchandani RP et al., J. Clin. Pharmacol. (2007) 47:78-86
2. Zucker et al., Proc. Natl.Acad. Sci. (2001) 98:12671-12676.

4.2.2 PHARMACOMETRICS REVIEW

Appears This Way
On Original

PHARMACOMETRICS REVIEW

NDA Number:	22145
Generic Name:	Raltegravir
Proposed Indication:	Treatment experienced subjects infected with HIV-1
Sponsor:	Merck
Type of Submission:	NME
Pharmacometrics (PM) Reviewer:	Pravin Jadhav Ph.D.
Primary Reviewer:	Derek Zhang Ph.D.
Clinical Pharmacology Team Leader:	Kellie S. Reynolds Pharm.D.
PM Team Leader:	Jogarao Gobburu Ph.D.
Proposed Dosage and Administration	400 mg BID

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Executive summary

Is there an exposure response relationship for raltegravir to support evidence of effectiveness?

Within the concentration range studied, the virologic success rate is similar (77%) for subjects with lower C_{12hr} (median C_{12hr} 76nM (~33 ng/mL)) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM (~482 ng/mL)). This relationship needs careful interpretation in the presence of high within subject variability. The lack of relationship could be due to high within subject variability leading to uncertain measure of individual exposure or it could be due to high potency (as demonstrated by maximum in vitro IC95 ~ 50nM in 50% human serum) of raltegravir such that the exposures are in the asymptotic region of the C_{12hr}-virologic success relationship.

Is there an exposure safety relationship for raltegravir?

No major adverse events of concern were found to be associated with high (top 10%) raltegravir exposures. Given the overall pharmacokinetic (PK) variability, a temporal association between raltegravir plasma concentrations and adverse events was weak. Exposure dependent safety concerns were not found; however, the safety database at high exposures is limited. The impact of these findings on the long term safety is not clear.

What are the sources of PK variability?

Raltegravir exhibits high PK variability (range of geometric mean C_{12hr} on 400 mg twice daily = 12 to 9151 nM in pivotal studies). The potential sources of variability include: food, pH dependent solubility, UGT1A1 polymorphism, UGT1A1 expression and drug interactions.

What is the impact of within-subject PK variability on effectiveness?

The overall variability in PK makes it difficult to distinguish the response rates between doses. Early short-term studies show similar response rate (~50%) at all doses (100-600 mg b.i.d.). There are early phase data available to conclude that lower doses (< 400 mg b.i.d., a proposed market dose) could be equally effective; however, in the absence of any major toxicity risks, the choice of dose is reasonable. There are no consistent data signatures to conclude effect of within subject PK variation on effectiveness. The analyses need to be repeated once the long term (48 week) data are available.

Are the labeling claims based on population PK supported?

Since the population PK model did not describe the data reasonably, the claims were assessed using observed data from multiple trials (protocols 004, 005, 018, 019, 025 and 028). PK of raltegravir is not affected by age, body weight, gender and race to an extent requiring dose adjustment.

Recommendations

1. The exposure response analyses support effectiveness of raltegravir in HIV-1 infected subjects.
2. No dose adjustments for raltegravir, when administered with tipranavir and atazanvir are recommended.
    a. Defining a clinically significant concentration threshold for potential dose adjustment is challenging because observed raltegravir plasma concentrations span over a 5-log range. It is difficult to define the maximum safe raltegravir concentration because of the size of the current safety database at high exposure levels and the high PK variability
3. The sponsor should conduct similar safety and effectiveness analyses, when data from long term (48 week) data are available.

Data

The data from two placebo controlled registration studies (018 and 019) of raltegravir (also known as MK-0518) in HIV-infected subjects with documented resistance to at least 1 drug in each of the 3 classes of licensed oral antiretroviral therapies (ART) were used in the exposure-response analyses. The supportive or further exploratory analyses included data from two dose finding studies (004, a 10-day monotherapy study in treatment naïve population and 005, a placebo controlled study in treatment experienced population) and two phase 1 studies (025 and 028).

Protocol 018 (Registration study in ART experienced subjects infected with HIV-1; Australia, Belgium, Denmark, France, Germany, Italy, Peru, Portugal, Spain, Switzerland, Taiwan and Thailand)

This was a 48-week multicenter, double-blind, randomized (2:1), placebo-controlled study of raltegravir 400 mg b.i.d. plus optimized background therapy (OBT) vs. OBT alone in HIV-infected subjects who were ≥16 years old, had failed prior antiretroviral therapy as documented by HIV RNA >1000 copies/mL, and had documented resistance to at least 1 drug in each of the 3 classes of licensed oral ARTs (NRTI, NNRTI, and PI) at screen.

- Stratification: Subjects were stratified by enfuvirtide use in OBT (yes or no) and degree of resistance to protease inhibitors (PI) at study entry (resistant to 1 PI or >1 PI).
- Virologic failure: Subjects who met the virologic failure definition[†] after Week 16 were eligible to receive open-label raltegravir 400 mg b.i.d. plus OBT (open label post virologic failure (OLPVF)).
- Pharmacodynamic sampling: HIV RNA level and CD4+ cell count were performed for all subjects at Screen, Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and at the 14-day post-therapy follow-up.
- Pharmacokinetic (PK) sampling: PK sampling was performed for all subjects in double-blind treatment arm and in the OLPVF treatment option. For subjects in the double-blind arm, samples were collected at Weeks 4, 8, 12, 16, 24, 32, 72, 96, 120, and 144. Samples at Weeks 4, 8, 16, 32, 72, 96, 120, and 144 were

[†] - a confirmed decrease from baseline plasma HIV RNA <1.0 log10 and HIV RNA >400 copies/mL starting at Week 16 or beyond; or
- virologic relapse starting at Week 16 or beyond that is defined as:
  - HIV RNA >400 copies/mL [on 2 consecutive measurements at least 1 week apart] after initial response with HIV RNA <400 copies/mL
  - >1.0 log increase in HIV RNA above nadir level [on 2 consecutive measurements at least 1 week apart]), at Week 16 or beyond

collected irrespective of time of dose, and samples at Weeks 12 and 24 were collected pre-AM dose. For subjects in the OLPVF treatment option, samples were collected at OLPVF Weeks 4, 8, 12, 16, 24, 32, 72, 96, 120, and final OLPVF visit (156 weeks of total study therapy). Samples at Weeks 4, 8, 16, 32, 72, 96, 120, and final OLPVF visit were collected irrespective of time of dose, and samples at Weeks 12 and 24 were collected pre-AM dose.

- Treatment: The raltegravir tablets were administered without regard to food.

The study is ongoing and will be fully unblinded when the last subject has completed the Week 48 visit. An interim efficacy analysis is being performed at 16 and 24 weeks. At the time of this review, week 16 data were available for all subjects.

Protocol 019 (Registration study in ART experienced subjects infected with HIV-1; United States, Puerto Rico, Canada, Brazil, Colombia and Mexico)

This study was designed identical in most respects to protocol 018 except that it recruited subjects from South, Central and North America.

Protocol 004 (Dose finding study in ART naïve subjects infected with HIV-1; United States, Canada, Latin America Thailand and Australia)

This was a 48-week multicenter, double-blind, randomized, 2-part dose-ranging study in HIV-infected subjects who were ART naïve, with baseline HIV RNA of at least 5000 copies/mL and CD4+ cell counts of at least 100 cells/mm^3. There was a 96-week double-blind extension of the original 48-week study. The antiretroviral activity, safety and tolerability of raltegravir given as 100, 200, 400 and 600 mg b.i.d. compared to placebo as monotherapy for 10 days and in combination therapy for 48 or 144 weeks was evaluated.

- Part I (monotherapy phase, 10 days)
    - Pharmacodynamic sampling: HIV RNA levels were determined at Screen, Randomization (Day 1— Predose, 6 hr, 12 hr postdose), Days 2, 3, 4, 5, 8, and 10, as well as at the 14-day postmonotherapy follow-up. CD4+ cell count was determined at Screen, Randomization (Day 1), and Day 10.
    - PK sampling: Extensive PK evaluation for raltegravir was performed for all subjects on Day 10. Samples were collected predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose.
- Part II (combination therapy phase; doses of raltegravir to be studied were contingent upon acceptable efficacy and safety data from Part I, 48 weeks)
    - Pharmacodynamic sampling: HIV RNA levels were determined at Screen, Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and at the 14-day post therapy follow-up. CD4+ cell count was determined at Screen, Randomization (Day 1); Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and at the 14-day post therapy follow-up.

- PK sampling: Extensive PK evaluation for raltegravir and lamivudine PK parameters were performed on only subjects continuing from part I at Week 2. Samples were collected predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. In addition, a 24-hour blood sample for lamivudine assay was to be taken the following day prior to the AM dose. Sparse PK sampling was performed for all subjects at Weeks 4, 8, 12, and 16. At Weeks 4, 8, and 16, the sample was collected irrespective of the time of dose. At Week 12, the sample was drawn pre-AM dose.

- Extension —Weeks 49 through 144
  - Pharmacodynamic sampling: HIV RNA levels were determined at every visit beginning with Week 60. CD4+ cell count was determined at every visit beginning with Week 60.
  - PK sampling: Sparse PK sampling was performed for all subjects at Weeks 72 and 96, the sample was drawn pre- AM dose.

Protocol 005 (Dose finding study in ART experienced subjects infected with HIV-1; United States, Europe (Belgium, France, Germany, Great Britain, Italy, Spain, and Switzerland), Americas (Brazil and Mexico), and Asia (Malaysia))

This was a double-blind, randomized (1:1:1:1), placebo-controlled, multicenter study with an open-label (OL) treatment arm after subjects completed at least 24 weeks of double-blind therapy. The antiretroviral activity, safety and tolerability of raltegravir given as 200, 400 and 600 mg b.i.d. compared to placebo was evaluated. The subject population included HIV-1 infected subjects that were failing therapy, with HIV RNA >5000 copies/mL and documented genotypic resistance to at least 1 drug in each of the 3 classes of licensed oral ARTs (NRTI, NNRTI and PI). Because preliminary PK data suggested that co-administration of raltegravir with atazanavir (ATV) increases overall drug exposure of raltegravir, in the double-blind phase, there were 2 substudies depending on whether ATV was in the OBT: subjects who received non-ATV containing OBT were enrolled in Substudy A and subjects who received ATV-containing OBT were enrolled in Substudy B. The study also had an OLPVF arm for those subjects who experienced virologic failure during the double-blind phase and decided to continue the study on this open-label treatment arm.

- Pharmacodynamic sampling: For all subjects in the double-blind treatment arms, HIV RNA and CD4+ cell count was determined at Screen, Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and at the 14-day post therapy follow up. For all subjects in the "open-label treatment post virologic failure" treatment arm, HIV RNA was determined at open-label post virologic failure Weeks 4, 8, 16, 24, 32, 40, and 48, and at the 14-day post therapy follow up. For all subjects in the "open-label raltegravir" treatment arm, HIV RNA was determined at open-label Day 1, Weeks 4, 8, 16, 24, 32, 40, 48, 60, 72, 84, and 96, and at the 14-day post therapy follow-up.

- PK sampling: Sparse sampling was performed for all subjects in the double-blind treatment arms, the open-label treatment post virologic failure treatment arm, and the open-label raltegravir treatment arm. For the blinded and open-label post virologic failure treatment arms the samples were collected at Weeks 2, 4, 8, 12, 16, and 24. Samples at Weeks 4, 8, 16, and 24 were collected irrespective of time of dose. Samples at Weeks 2 and 12 were collected pre-AM dose. For the open-label raltegravir treatment arm, samples were collected at Weeks 32, 40, 60, 84, and 96; all collected irrespective of time of dose. At open-label Weeks 48 and 72, the sample was collected pre-AM dose.

Protocol 025 (Dose proportionality study in healthy subjects)

This was an open-label, randomized, 5-period, crossover study in 20 healthy, male and female subjects. In each period, subjects received a single 100, 200, 400, 800, or 1600 mg dose of raltegravir in the fasted state. There was a 4-day washout interval separating each period. Plasma samples were collected predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hrs postdose.

Protocol 028 (Food effect study in healthy subjects)

This was an open-label, randomized, 2-period crossover study to assess the effects of a high-fat meal on the safety, tolerability, and PK of a single oral dose of raltegravir final market image (FMI) formulation. Twenty (20) healthy male and/or female subjects were administered a single oral dose of 400 mg raltegravir FMI following a standard high-fat meal and in the fasted state in 2 treatment periods. There was a minimum of a 4-day washout interval between Period 1 and Period 2 dosing. Plasma samples were collected predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hrs postdose.

Exposure response analyses

Is there an exposure response relationship for raltegravir to support evidence of effectiveness?

Univariate analyses

The data[‡] from two double-blind placebo controlled trials (Protocols 018 and 019) were used in the exposure-response analyses. These trials were conducted using the final market image (FMI) formulation, which exhibits considerable food effect on C_{12hr} (discussed later). Several binary endpoints indicating virologic success, such as

[‡] The dataset submitted with SN025 (submission date 7/10/2007) were used in the analyses. The PK information was further updated using dataset (phase3b.xpt) submitted with SN043 (submission date 8/6/2007) that had corrected time since first dose for all subjects and dosing information for subject ID#16295.

protocol defined failure at 16 weeks, viral load <50 copies/mL at 16 weeks, viral load <400 copies/mL at 16 weeks, were investigated.

Data from 673 subjects (out of 678 subjects) were available for the univariate analyses. Five subjects were excluded because of missing outcome information. Table 1 includes summary description of dataset used in the univariate analyses. A majority of the population studied were ~45 yr old white males. In these subjects the treatment options available at baseline were limited, as indicated by GSS or OSS[§] score of 0. As a standard practice, all the subjects included at least one NRTI and PI in the OBT. The concomitant administration of tipranavir, enfuvirtide and darunavir were of interest (described later).

The response rates from both trials were nearly identical (see Clinical end points in exposure response analyses (effectiveness) in Table 1). Less than 10% raltegravir subjects discontinued the treatment prior to the week-16 cut off. In other words, the high response rate achieved is complimentary to low number of subjects discontinuing on the trial medication, when ~35% placebo treated subjects discontinued from the trial. The virologic failure was the major discontinuation reason (>80%) for both dose groups.

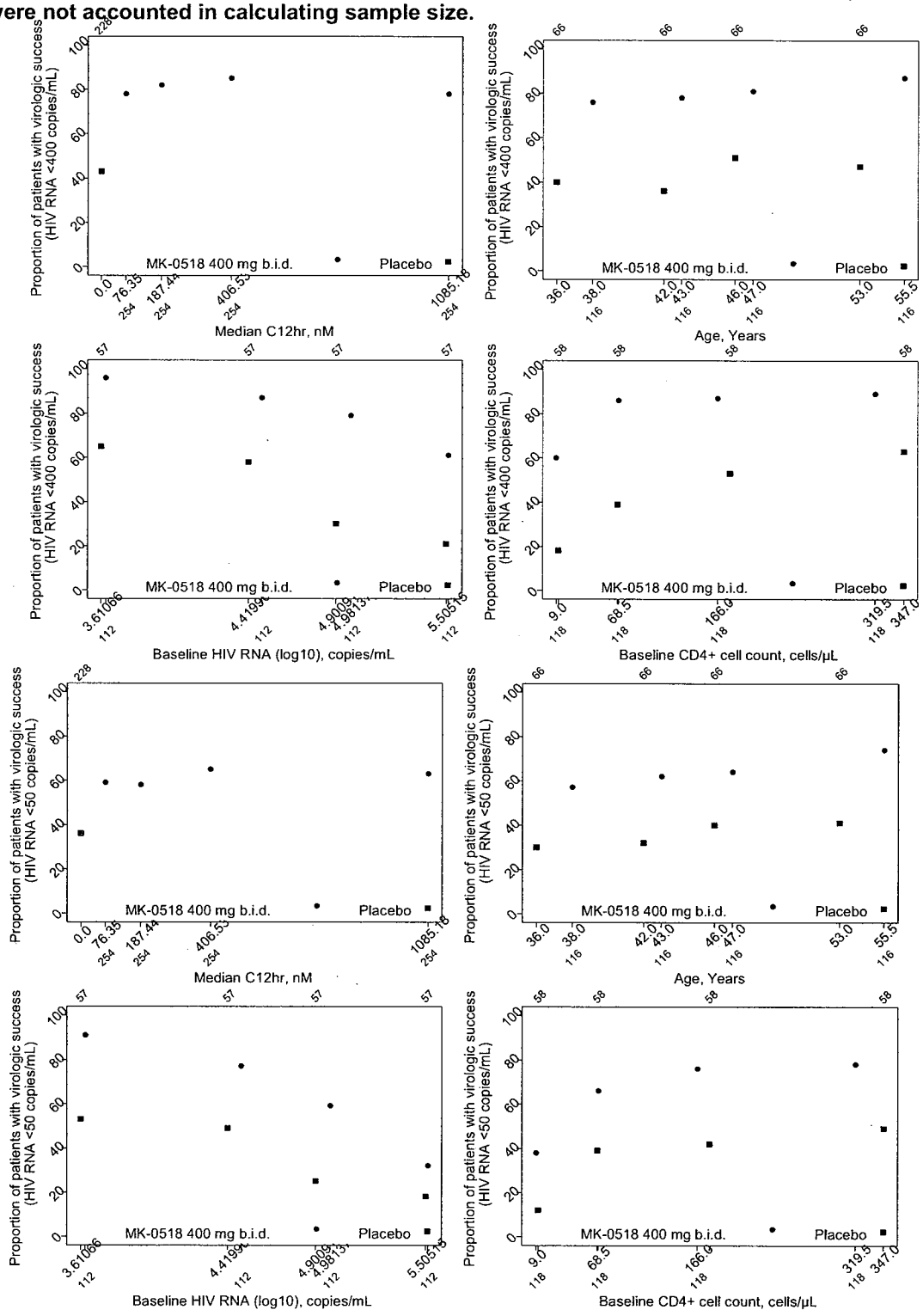
Figure 1 illustrates the relationship between continuous scale covariates (C_{12hr} (geometric mean observed C_{12hr}), age, baseline HIV RNA and baseline CD4+ cell count) and proportion of subjects with virologic success. The virologic success was higher in subjects with lower baseline HIV RNA, higher CD4+ cell count. There was a modest dependency of virologic success on C_{12hr} or age. However, with the raltegravir treated subjects, the virologic success rate is similar (77%) for subjects with lower C_{12hr} (median C_{12hr} 76nM) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM).

[§] OSS relates to number of treatment options available as predicted by genotype (GSS) and phenotype (PSS) susceptibility score. 0=No treatment options.

Table 1: Description of the database from protocols 018 and 019 used for univariate analyses

	Protocol 018		Protocol 019	
	Raltegravir	Placebo	Raltegravir	Placebo
Subject Demographic information				
Number of subjects (n)	223	113	222	115
Mean age (years)	46.3	43.4	45.3	46.5
Mean weight (Kg)	68.3	68.8	76	75.8
Male (%)	84.8	86.7	91	89.6
Race: White (n)	169	91	122	74
Black (n)	18	5	47	21
Asian (n)	13	5	2	1
Hispanic (n)	6	1	44	17
Multiple (n)	17	11	6	2
Native Americans (n)			1	
Raltegravir exposure				
Median geometric mean observed C_{12hr}, nM (Number of subjects available to calculate geometric mean observed C_{12hr}, n)	281.5 (131)		262.36 (124)	
Subject disease information				
Median baseline CD4 (cells/μL)	137	111	102	133
Median viral load (log10(RNA copies/mL))	4.8	4.63	4.75	4.67
Subject medication information				
Subjects with GSS=0 (n)	66	34	44	28
GSS=1 (n)	74	45	97	47
GSS=2 (n)	55	21	53	27
GSS=3 (n)	18	7	20	8
GSS=4 (n)	5	5	4	1
GSS=5 (n)	2			1
Subjects with OSS=0 (n)	91	42	98	57
OSS=1 (n)	76	41	73	36
OSS=2 (n)	40	22	37	14
OSS=3 (n)	15	3	10	6
OSS=4 (n)		2		1
OSS=5 (n)		1		
Subjects receiving NRTIs (%)	96.9	100	98.6	99.1
Subjects receiving NNRTs (%)	6.7	11.5	6.8	8.7
Subjects receiving PIs (%)	95.1	92	93.7	94.8
Subjects receiving tipranavir (%)	24.2	25.7	18	9.6
Subjects receiving ritonavir (%)	74	70.8	77.5	80.9
Subjects receiving enfuvirtide (%)	38.1	36.3	36.9	39.1
Subjects receiving darunavir (%)	34.1	28.3	46.8	54.8
Subjects receiving ddi (%)	17.9	12.4	13.1	13.9
Subjects with previous use of enfuvirtide (%)	47.5	44.2	44.6	45.2
Subjects with previous use of darunavir (%)	9.9	10.6	4.1	3.5
Clinical end points in exposure response analyses (effectiveness)				
Subjects with RNA copies <400 ng/mL (%)	79.8	42.5	79.7	44.3
Subjects with RNA copies <50 ng/mL (%)	63.2	34.5	64	37.4
Subjects with at least 1 log drop in RNA (%)	88.3	43.4	85.6	52.2
Subjects with at least 2 log drop in RNA (%)	83.9	42.5	81.1	47
Log10 Change from baseline RNA (copies/mL)	-1.87	-0.78	-1.92	-1.08
Change from baseline CD4+ cell count (cells/ μL)	84.15	31.29	86.09	40.38
Subject discontinuations				
Subject discontinued (%)	7.2	40.7	10.4	33.9
Virologic failure (%)	93.8	100	82.6	100
Clinical adverse event (%)	6.2	0	4.3	0
Laboratory adverse event (%)	0	0	0	0

Figure 1: Geometric mean C_{12hr}, age, baseline HIV RNA and baseline CD4+ cell count-response relationship. The mean response is plotted against the median for each quantile by dose groups. The sample size for each quantile is included: red (MK-0518) and blue (Placebo). *Missing data were not accounted in calculating sample size.



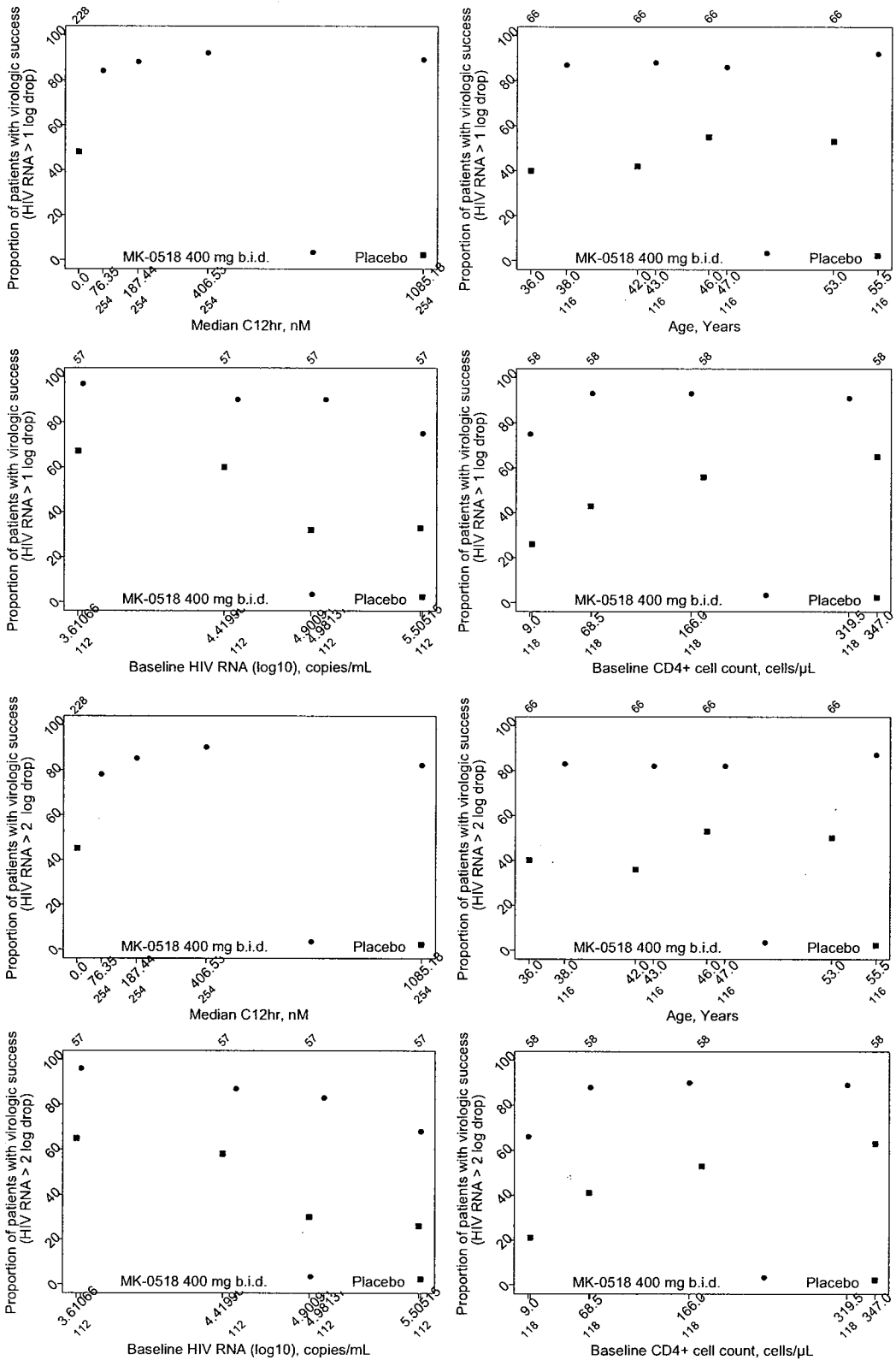

Proportion of patients with virologic success (HIV RNA > 1 log drop)
MK-0518 400 mg b.i.d.
Placebo
Median C12hr, nM
Age, Years
Baseline HIV RNA (log10), copies/mL
Baseline CD4+ cell count, cells/µL
Proportion of patients with virologic success (HIV RNA > 2 log drop)
MK-0518 400 mg b.i.d.
Placebo
Median C12hr, nM
Age, Years
Baseline HIV RNA (log10), copies/mL
Baseline CD4+ cell count, cells/µL

Table 2: Univariate analyses of response rate (number of subjects) by concomitant ARTs. Major differences in response rates are highlighted (blue: interpretable; gray: uninterpretable due to limited sample size)

	Raltegravir		Placebo	
	Without	With	Without	With
HIV RNA <400 copies/mL				
Lopinavir (Kaletra)	79.7 (369)	80.3 (76)	44.1 (195)	39.4 (33)
Enfuvirtide (T20)	77.7 (278)	83.2 (167)	36.6 (142)	54.7 (86)
Lamivudine (3TC)	80.8 (271)	78.2 (174)	42.6 (122)	44.3 (106)
Ritonavir (RTV)	77.8 (108)	80.4 (337)	34.5 (55)	46.2 (173)
Tenofovir (TDF)	80.4 (112)	79.6 (333)	43.5 (62)	43.4 (166)
Saquinavir (SQV)	80 (409)	77.8 (36)	44.4 (207)	33.3 (21)
Abacavir (ABC)	79.5 (351)	80.9 (94)	41.3 (172)	50 (56)
Emtricitabine (FTC)	80.3 (244)	79.1 (201)	42.6 (129)	44.4 (99)
Stavudine (D4T)	80 (401)	77.3 (44)	44 (207)	38.1 (21)
Zidovudine (ZDV)	79.2 (336)	81.7 (109)	42.2 (161)	46.3 (67)
Amprenavir (APV)	79.9 (432)	76.9 (13)	44.2 (224)	0 (4)
Indinavir (IDV)	79.2 (433)	100 (12)	43.6 (225)	33.3 (3)
Atazanavir (ATV)	79.9 (412)	78.8 (33)	45.6 (206)	22.7 (22)
Efavirenz (EFV)	80 (420)	76 (25)	43.6 (211)	41.2 (17)
Nevirapine (NVP)	79.7 (443)	100 (2)	43.4 (226)	50 (2)
Delavirdine (DLV)	79.6 (442)	100 (3)	43.3 (224)	50 (4)
Zalcitabine (DDC)	79.8 (445)	NA (NA)	43.6 (227)	0 (1)
Nelfinavir (NFV)	79.8 (445)	NA (NA)	43.6 (227)	0 (1)
HIV RNA <50 copies/mL				
Lopinavir (Kaletra)	62.1 (369)	71.1 (76)	36.4 (195)	33.3 (33)
Enfuvirtide (T20)	62.6 (278)	65.3 (167)	31 (142)	44.2 (86)
Lamivudine (3TC)	62.7 (271)	64.9 (174)	34.4 (122)	37.7 (106)
Ritonavir (RTV)	66.7 (108)	62.6 (337)	29.1 (55)	38.2 (173)
Tenofovir (TDF)	66.1 (112)	62.8 (333)	30.6 (62)	38 (166)
Saquinavir (SQV)	63.6 (409)	63.9 (36)	36.7 (207)	28.6 (21)
Abacavir (ABC)	62.1 (351)	69.1 (94)	35.5 (172)	37.5 (56)
Emtricitabine (FTC)	67.6 (244)	58.7 (201)	35.7 (129)	36.4 (99)
Stavudine (D4T)	62.8 (401)	70.5 (44)	36.2 (207)	33.3 (21)
Zidovudine (ZDV)	63.1 (336)	65.1 (109)	33.5 (161)	41.8 (67)
Amprenavir (APV)	63.7 (432)	61.5 (13)	36.6 (224)	0 (4)
Indinavir (IDV)	63.3 (433)	75 (12)	36 (225)	33.3 (3)
Atazanavir (ATV)	63.3 (412)	66.7 (33)	37.4 (206)	22.7 (22)
Efavirenz (EFV)	63.8 (420)	60 (25)	35.5 (211)	41.2 (17)
Nevirapine (NVP)	63.7 (443)	50 (2)	35.8 (226)	50 (2)
Delavirdine (DLV)	63.6 (442)	66.7 (3)	36.2 (224)	25 (4)
Zalcitabine (DDC)	63.6 (445)	NA (NA)	36.1 (227)	0 (1)
Nelfinavir (NFV)	63.6 (445)	NA (NA)	36.1 (227)	0 (1)

Table 2 illustrates univariate analyses of response rate by concomitant ARTs. These results need careful interpretation as a given subject had multiple ARTs as a part of the regimen and/or different OSS scores, which are not accounted in the table. For example, subjects with darunavir in the OBT had higher response rate on raltegravir (~87%) versus 60% on placebo. However, a fair comparison cannot be made for subjects without darunavir, where response rate of 75% on raltegravir versus 32% on placebo was observed because these subjects have a wide variety of PIs in the OBT leading to potential imbalance in comparison.

The response rate on adding DDI (91%) and TMC114 (87%) to raltegravir were higher than average response rate, however, the addition of FoA (63%) resulted in lower than average response rate. for other drug, such as IDV, NVP etc, (highlighted grey) the interpretation of apparent differences in response rate was limited by sample size.

Table 3: Univariate analyses of response rate (number of subjects) by gender, race, gss score and oss score. Major differences in response rates are highlighted (blue: interpretable; gray: uninterpretable due to limited sample size)

	Raltegravir	Placebo
Gender		
Females	74.1 (54)	37 (27)
Males	80.6 (391)	44.3 (201)
Race		
Asian	93.3 (15)	33.3 (6)
Black	70.8 (65)	42.3 (26)
Hispanic	72 (50)	33.3 (18)
Multi	87 (23)	69.2 (13)
Native American	100 (1)	
White	81.8 (291)	43 (165)
GSS score		
0	57.3 (110)	9.7 (62)
1	84.2 (171)	43.5 (92)
2	92.6 (108)	77.1 (48)
3	81.6 (38)	60 (15)
4	88.9 (9)	66.7 (6)
5	100 (2)	0 (1)
Missing	100 (7)	75 (4)
OSS score		
0	77.2 (189)	34.3 (99)
1	79.9 (149)	51.9 (77)
2	83.1 (77)	50 (36)
3	88 (25)	33.3 (9)
4		66.7 (3)
5		0 (1)
Missing	80 (5)	66.7 (3)

Table 3 illustrates univariate analyses of response rate by gender, race, GSS and OSS scores. As expected, higher GSS and/or OSS scores were associated with higher response rate and less difference between raltegravir and placebo treated subjects.

Based on univariate analyses results, the following covariates that could impact the virologic success were evaluated in the multivariate analysis:

- Subject disease information
  - Baseline HIV RNA (log10) (BVL)
  - Baseline CD4+ cell count (BCD4)
  - Genotypic susceptibility score (GSS) (0, 1, 2, ≥3) or
    - Overall susceptibility score (OSS) (0, 1, 2, ≥3)
  - Naïve use of enfuvirtide (naivT20: 1=Yes in naïve subject, 2=Yes in experienced subjects and 3=No)
  - Naïve use of darunavir (naiveTMC: 1=Yes in naïve subject, 2=Yes in experienced subjects and 3=No)
  - Presence of DDI (DDI: 0=No, 1=Yes)
  - Presence of fosamprenavir (FoA: 0=No, 1=Yes)
  - Presence of tipranavir (TPV: 0=No, 1=Yes)
- Subject demographic information
  - Age
  - Gender (1=male, 2=female)
  - Race (1=White, 2=Black, 3=Asian, 4=Native American and 5=Multi)
- PK information
  - Two individual exposure estimates were derived from the observed values in the sparse data set: the geometric mean observed C_{12hr} (determined from the geometric mean concentration of all samples taken between 11 and 13 hours post-dose in a given individual); and the minimum observed C_{12hr} (determined as the minimum concentration from all samples taken between 11 and 13 hours post-dose in a given individual). Due to poor predictive performance, the population PK model does not provide reliable individual exposure estimates (See Appendix 1: Population PK analyses provided by the sponsor and reviewer's assessment).

Generalized additive modeling (GAM)

The effect of raltegravir exposure and several other predictors on the viral load was analyzed as a binary variable (success) using both logistic regression and generalized additive models (GAM). A GAM model was built using the automated step-wise search developed in S-PLUS. This automated step-wise search selects the best GAM using forward selection and backwards deletion given the range of models. A series of candidate relationships (e.g. linear, log-transformation, spline, Loess smooth) that describe how each particular predictor might enter the model was defined for every

predictor and the final model was built up by evaluating all candidate forms for each predictor in a step-wise manner.

A total of 483 subjects (255 raltegravir treated and 228 placebo treated) were available for GAM analyses. Approximately 200 subjects were excluded due to lack of sufficient PK information; specifically, at least one plasma trough concentrations (C_{12hr}) was required to be included in the analyses. The geometric mean C_{12hr} or minimum C_{12hr} were used as an exposure variable. Due to collinearity in these exposure measures, the analyses described here focuses on geometric mean C_{12hr} as an exposure variable. Thirteen subjects were further deleted due to lack of covariate information. The GAM model was built using data from 470 subjects (247 raltegravir treated and 223 placebo treated). The Akaike statistic (AIC) was used to select the final model. Table 4 summarizes the final model for all endpoints and Figure 2 summarizes the change in AIC in the automated step-wise search for model predictors.

Table 4: Final GAM model for all endpoints

	Endpoint	Final model
1	HIV RNA <50 copies/mL at 16 weeks	HIVF5S ~ lo(C_{12hr}) + lo(BVL) + s(BCD4, 2) + naivT20 + naivTMC + FoA + DDI + GSS
2	HIV RNA <400 copies/mL at 16 weeks	HIVF4S ~ lo(C_{12hr}) + lo(BVL) + lo(BCD4) + naivT20 + naivTMC + FoA + GSS

Figure 2: Results of the automated step-wise search for predictors of virologic success. -> a indicates addition of variable a; a->b indicates the replacement of variable b with a, c->indicate removal of a variable.

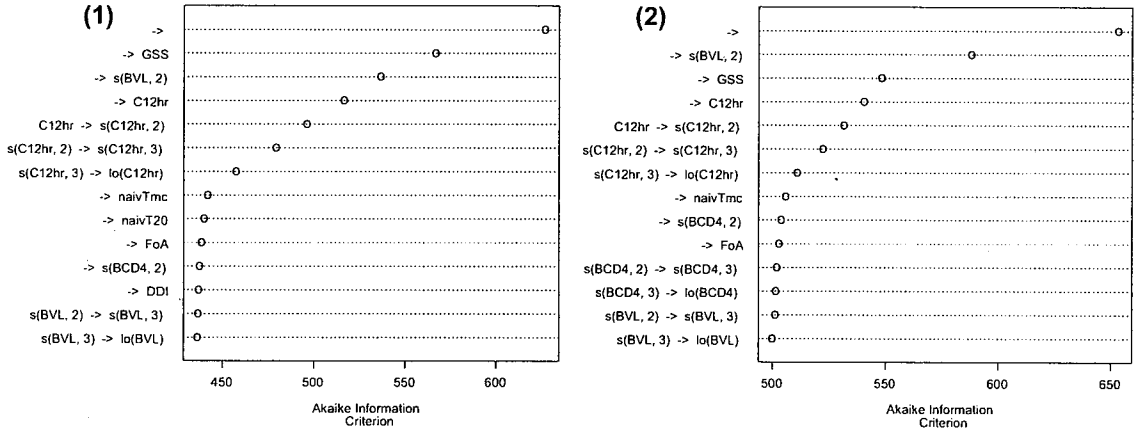


Figure 3 illustrates distribution of residuals and qqplot for residuals in the final GAM model. The residuals exhibited reasonable normal distribution. The assumption did not seem to hold at the tail ends and the central tendency is slightly farther from zero.

Figure 3: Distribution of residuals and qqplot for residuals in the final GAM model (model 1) for HIV RNA <400 copies/mL at 16 weeks

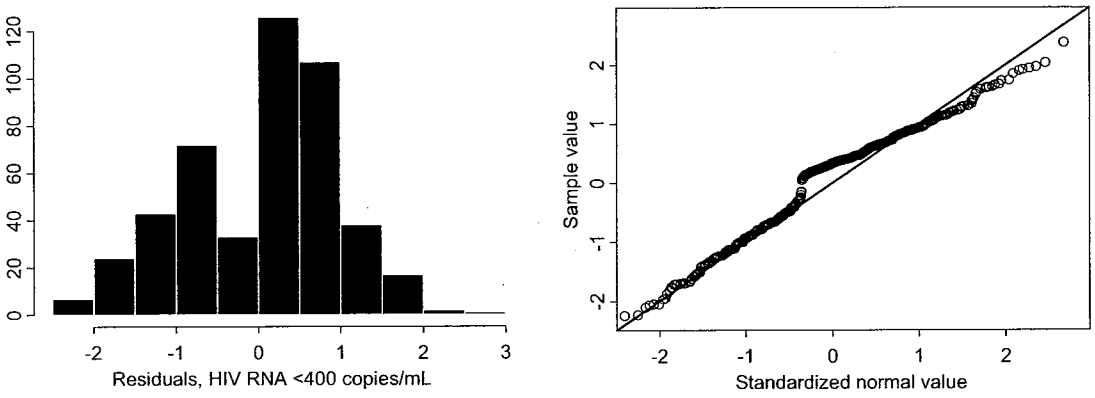
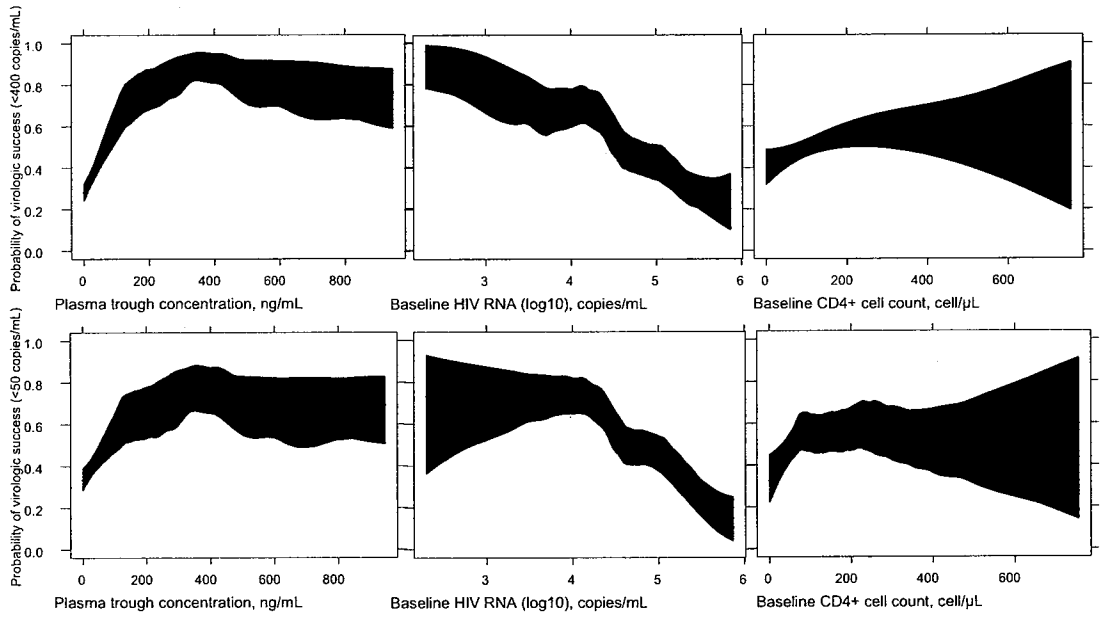


Figure 4 illustrates the relationship between the probability of virologic success (<400 copies/mL) and C_{12hr}, baseline CD4+ count and baseline viral load.

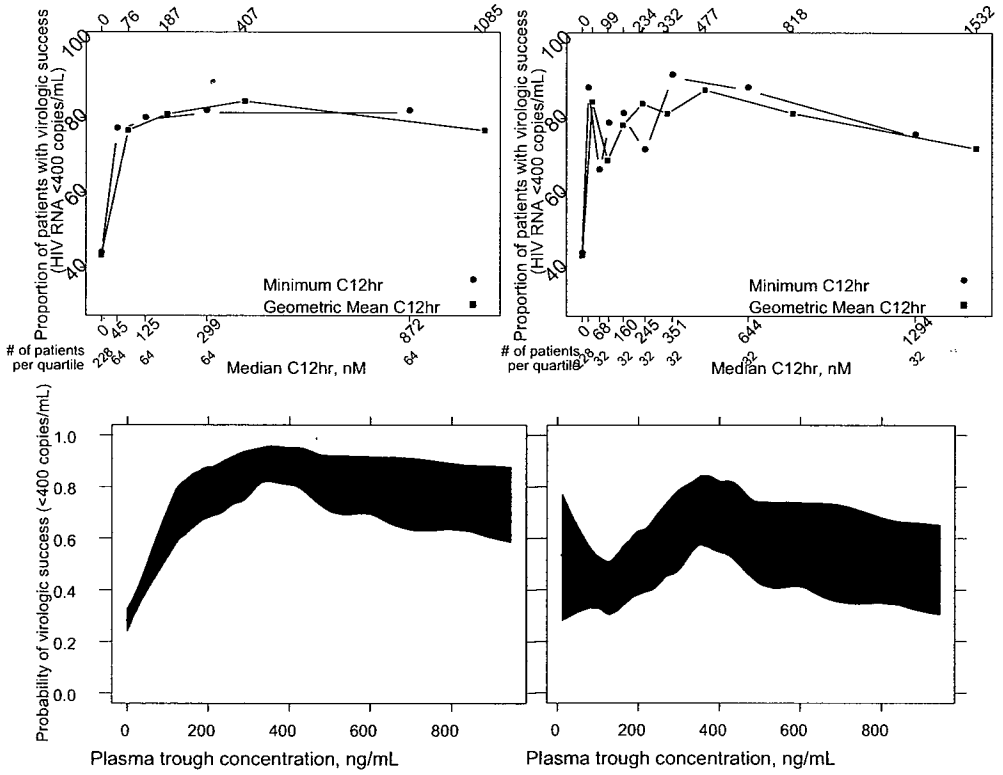
Figure 4: C_{12hr} (left panel), baseline CD4+ cell count (middle panel) and baseline HIV RNA (right panel) are important predictors of the virologic success. The line represents partial probability from the GAM model. The shaded area represents twice standard error region.



Based on the model predictions, the probability of virologic success was higher at higher C_{12hr} and/or higher baseline CD4+ cell count and/or lower baseline HIV RNA. The C_{12}-virologic success relationship needed further investigation as the model predicted relationship (Figure 4) was steeper than observed relationship (Figure 1 or Figure 5). Figure 5 illustrates local noise in the response rate by dividing raltegravir treated subjects in 8 quantiles. Clearly, the model predicted relationship ignored the

noise or nonlinearity introduced by the lowest quantile. The response was driven by the intercept (placebo treated subjects) and subjects within 25th-75th percentile. Neither the flexible GAM model nor the linear logistic regression is suitable in describing such relationships. The point was further illustrated by fitting only the raltegravir treated subjects with the final GAM model, the local noise is captured well and there seems little dependency of virologic success on the C_{12hr}, within the concentration range studied. The noise could be introduced by the high within subject variability (described later) or it could be due to high potency (maximum IC95~50nM in 50% human serum) of raltegravir such that the exposures are in the asymptotic region of the C_{12hr}-virologic success relationship.

Figure 5: C_{12hr}-response relationship demonstrating local noise in response rate. Top panel: The mean response is plotted against the median for each quantile by dose groups (Left: raltegravir treated subjects divided in 4 quantiles and Right: raltegravir treated subjects divided in 8 quantiles). The placebo response is plotted at C_{12hr}=0. Bottom panel: Partial probability from the GAM model plotted against C_{12hr} on a continuous scale (Left: full model (model 1) fitted to data including placebo treated subjects and Right: full model (model 1) fitted to data excluding placebo treated subjects



In conclusion, within the concentration range studied, the virologic success rate is similar (77%) for subjects with lower C_{12hr} (median C_{12hr} 76nM) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM). This relationship needs careful interpretation in the presence of high within subject variability.

Is there an exposure safety relationship for raltegravir?

Univariate analyses

Before conducting extensive exposure response analyses, univariate analyses were conducted to assess adverse events of concern. The rate of adverse events leading to discontinuations was low (see Table 1); therefore, the areas of concern were not clear. According to the clinical reviewer, rash and neoplasm were potential concerns. For preliminary analyses, a subset of the subjects with the top 10% exposures (observed plasma concentrations > 1230 ng/mL (2768 nM) any time during the course of the trial) was derived. A total of 176 concentrations from 124 subjects were available for these analyses. The adverse event profiles in the subset were assessed by two methods. First, the frequency of the adverse event was noted and compared to the overall frequency. Table 5 illustrates most frequent adverse event (>3% events) in subjects with the top 10% raltegravir exposure and comparison with overall frequency in raltegravir treated and placebo treated subjects.

Table 5: Most frequent adverse events in subjects with top 10% raltegravir exposure and comparison with overall frequency in raltegravir and placebo treated subjects. The data are presented as number of events (% subjects with the adverse event (total number of subjects in the database))

AE preferred term	Subjects within top 10% of raltegravir exposures	All raltegravir treated subjects	All placebo treated subjects
Alanine aminotransferase increased	16 (7.3% (124))	40 (4.8% (462))	12 (2.1% (237))
Aspartate aminotransferase increased	11 (5.6% (124))	26 (4.3% (462))	16 (3% (237))
Blood cholesterol increased	10 (4.8% (124))	23 (3% (462))	7 (1.7% (237))
Blood creatine phosphokinase increased	6 (4% (124))	16 (3% (462))	4 (1.3% (237))
Blood creatinine increased	7 (4% (124))	15 (1.9% (462))	6 (1.7% (237))
Blood triglycerides increased	8 (3.2% (124))	26 (3.9% (462))	10 (3.4% (237))
Herpes simplex	5 (3.2% (124))	23 (3.7% (462))	13 (4.2% (237))
Herpes zoster	8 (5.6% (124))	23 (4.5% (462))	4 (0.8% (237))
Hyperhidrosis	5 (4% (124))	7 (1.5% (462))	2 (0.8% (237))
Lymphadenopathy	6 (4.8% (124))	15 (3% (462))	6 (2.5% (237))
Myalgia	6 (4% (124))	9 (1.7% (462))	12 (3% (237))
Pruritus	7 (4.8% (124))	14 (2.6% (462))	5 (2.1% (237))
Rash	15 (9.7% (124))	30 (5.8% (462))	7 (2.5% (237))

Infections are common in the treated population, therefore, nasal congestions, nasopharyngitis, upper respiratory tract infections, are difficult to interpret and are not included. Most of the adverse events were similar to those reported in placebo treated subjects. The frequency of events, such as rash, pruritus, blood cholesterol increase, ALT increase and hyperhidrosis was higher in the top 10% exposure groups compared to the overall frequency.

Further analyses were done to assess the temporal association between plasma concentration and adverse events, especially, rash and pruritus. Appendix 4 includes graphs illustrating temporal association between plasma concentration and adverse

events for all subjects. Figure 6 illustrates temporal association between plasma concentration and adverse events only for subjects with reported rash and pruritus.

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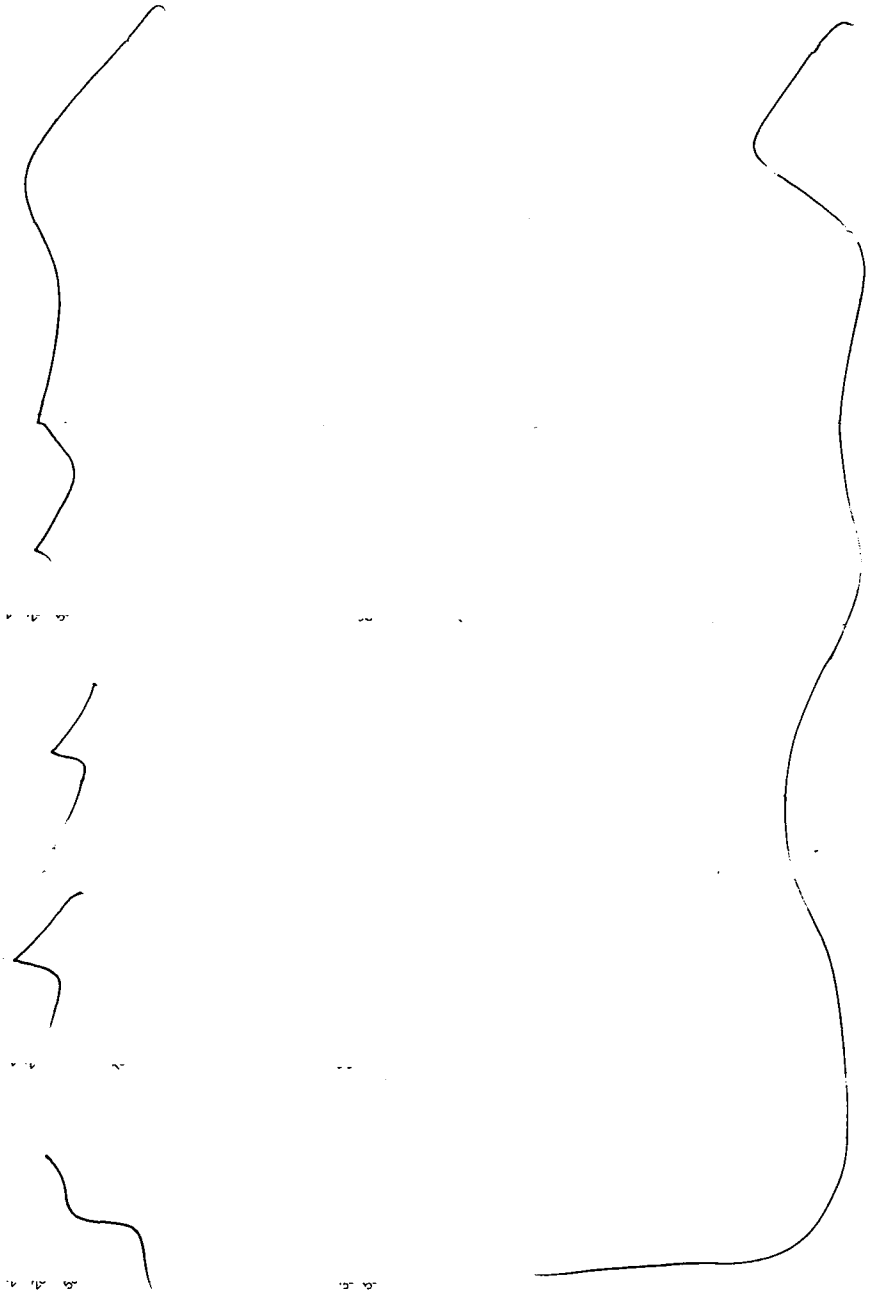
Figure 6: Temporal association between plasma concentration (green) and adverse events (red). The x-axis represents time since the start of the therapy in days. The y-axis (right side) represents raltegravir plasma concentrations, ng/mL. The horizontal line represents 1230 ng/mL cut off. The positioning of the adverse event relative to y-axis for adverse events is random.



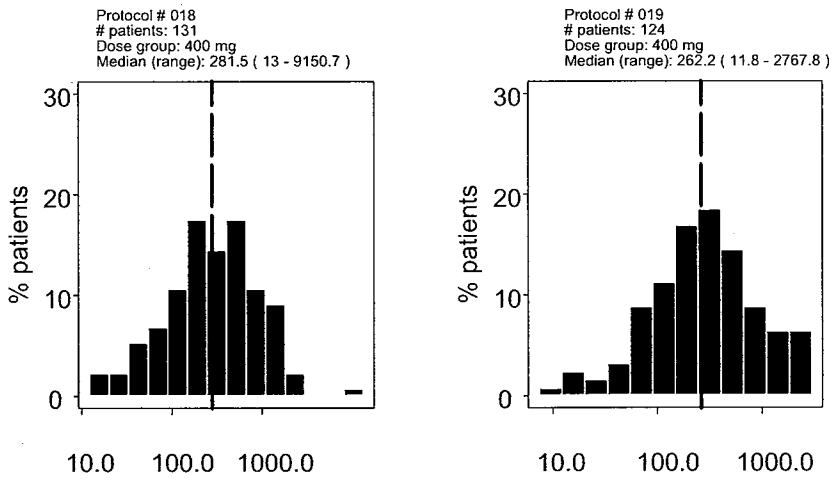
Given the overall variability (see What are the sources of PK variability?), the temporal association, if any, is weak. In conclusion, exposure dependent safety concerns were not found, however, the safety data base at high exposures is limited. The impact of these findings on the long term safety is not clear.

The sponsor did not include exposure-safety analyses with the submission.

What are the sources of PK variability?

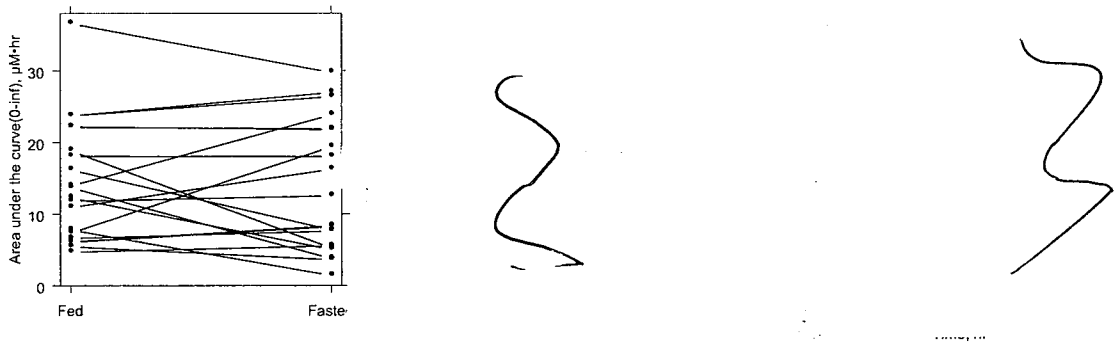
The overall variability in C_{12hr} is considerably high, with a range of 12 to 9151 nM. Figure 7 illustrates distribution of geometric mean observed C_{12hr} in registration studies.

Figure 7: Distribution of geometric mean observed C12hr (nM) in registration studies.



An attempt was made to understand the factors leading to variability in C_{12hr}. According to the clinical pharmacology review by Dr. Zhang, administration of raltegravir with a high fat meal was found to slow the rate of raltegravir absorption, causing a mean increase in C_{12hr} of 750%. Further, an approximately 34% decrease in mean Cmax, no change in mean AUC, and a median 7.3 hour delay in Tmax was observed. Figure 8 illustrates the results of a food effect study (Protocol 028) using the FMI formulation. The effect of food on raltegravir C_{12hr} was variable between subjects causing occasional double-peak phenomenon.

Figure 8: Food decreases the rate of absorption but does not affect the extent of absorption. Panel 1: Individual area under the curve under fed and fasted conditions; Panel 2: Individual C12hr under fed and fasted conditions; Panel 3: Concentration time profile of four representative subjects.



Because raltegravir dosing in pivotal studies was done without regard to food, over the course of the trials (Protocols 018 and 019) day-to-day variability was likely influenced by variability in food intake. In other words, a given subject could have 8 fold higher C_{12hr} on a day when raltegravir was taken with food compared to days when raltegravir was taken without food. In addition to food, there are other determinants of raltegravir PK, such as UGT1A1 polymorphism and drug interactions. Thus, high within subject variability is expected for raltegravir.

Figure 9 illustrates the raltegravir within-subject variability and maraviroc (for comparison) concentrations. The figure includes pre-dose and post-dose trough concentrations (C_{0hr} and C_{12hr}) for treatment-naïve HIV-infected subjects who received their assigned dose (100 to 600 mg twice daily) for 10 days as a monotherapy. The within subject variability is demonstrated by the lack of correlation between pre-dose and post-dose trough concentrations for raltegravir. A similar comparison for maraviroc demonstrates reasonable correlation between trough concentrations.

- Figure 9 NOT FOR PUBLIC DISCLOSURE-

Figure 9: Panel 1: Within subject variability in C12 hr for raltegravir on day 10 in a monotherapy study (inset: data within 0-500nM); Panel 2: Within subject variability in C12 hr for maraviroc on day 10 in a monotherapy study

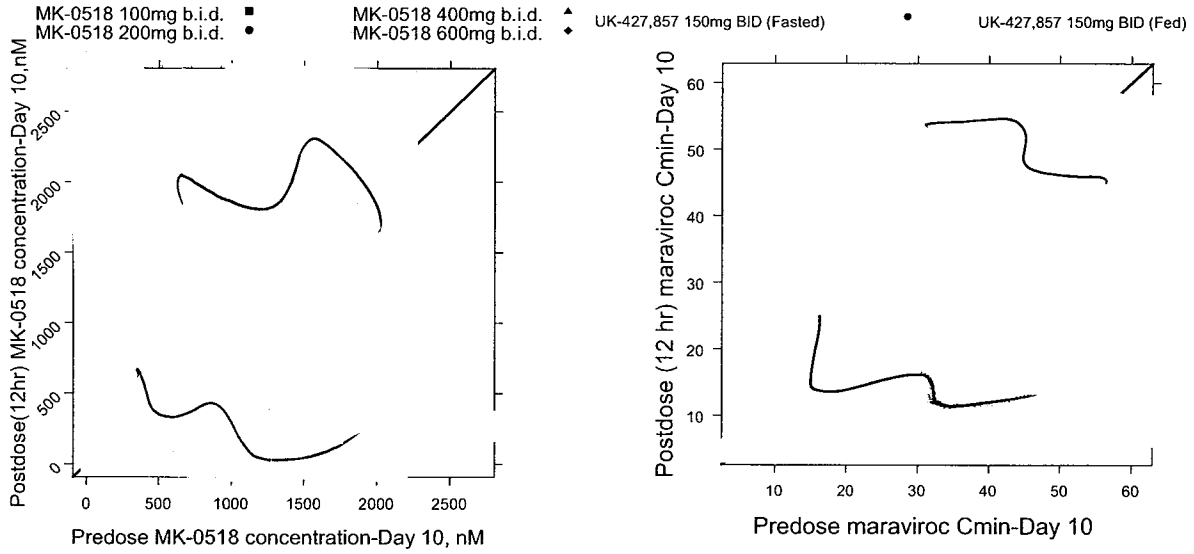


Figure 10 represents univariate analyses of drug interaction in the presence of cumulative effect of all factors that affect PK. In a prospective early phase study (Protocol 005) assessing effect of atazanavir on raltegravir PK and antiretroviral activity, the subjects were assigned 200-600 mg b.i.d. of raltegravir and were divided in 2 substudies based on whether or not the optimized background included atazanavir. The phase 1 drug interaction studies indicated atazanavir/ritonavir increased raltegravir C_{12hr} by 77%. Modest effect was seen on the mean change in raltegravir C_{12hr} due to atazanavir/ritonavir in protocol 005. Further, because of the high variability in raltegravir

concentrations, the range of raltegravir concentrations observed with or without atazanavir/ritonavir was similar. The effect was somewhat apparent on 200 mg b.i.d. dose.

Figure 11 illustrates the high variability in raltegravir concentrations observed in Protocols 018 and 019. The C_{12hr} values span a 5-log range. The figure also illustrates the impact of interactions with tipranavir and atazanavir within the context of high PK variability. The Phase 1 drug interaction studies indicated tipranavir/ritonavir decreased raltegravir C_{12hr} by 55%. The mean changes in raltegravir C_{12hr} due to atazanavir/ritonavir and tipranavir/ritonavir were similar between the Phase 1 studies and Protocols 018 and 019. However, because of the high variability in raltegravir concentrations, the range of raltegravir concentrations observed with or without either co-administered drug was similar.

Figure 10: Sparse PK sampling in a prospective study (protocol 005) assessing effect of atazanavir on raltegravir PK. (The horizontal line represents 50 nM, an in vitro IC95 using 50% human serum) The plasma concentrations are normalized to time after dose, however, the concentration were obtained over entire trial duration.

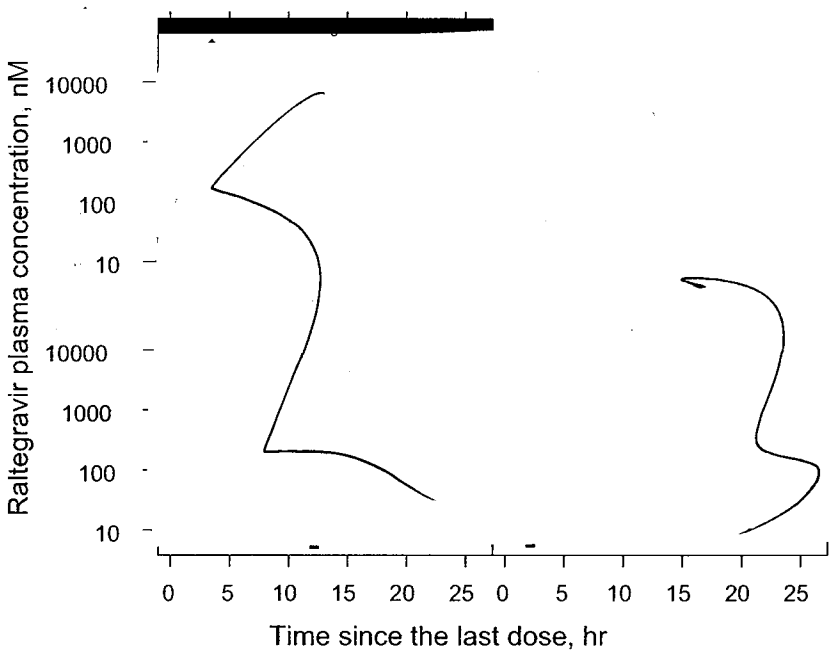


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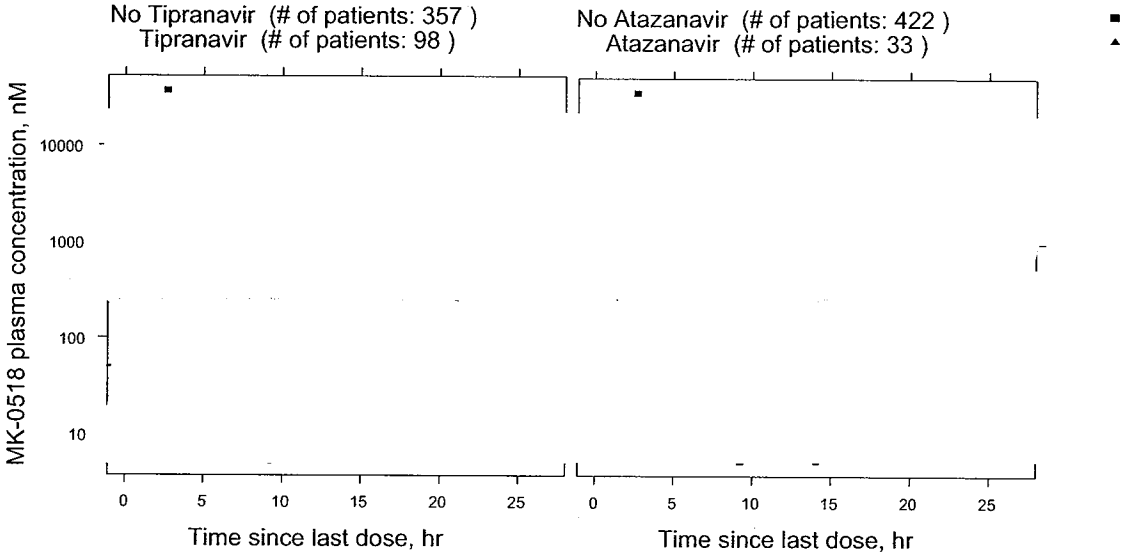
Figure 11: Effect of tipranavir and atazanavir on raltegravir plasma concentrations in Protocols 018 and 019. (The horizontal line represents 50 nM, an in vitro IC95 using 50% human serum) Plasma concentrations are normalized to time after dose, but were obtained over the trial duration



What is the impact of variability on effectiveness?

Overall variability

The overall variability in PK (described in the previous section) is contributed by several factors, such as between-subject variation, with-in subject between occasion variation (presumably constant over a given occasion) and within-subject variation at each instance of observation. This section deals with the impact of overall variation in C_{12hr} on time course of HIV-RNA response.

Figure 12: Relationship between change from baseline HIV RNA (log10), copies/mL and plasma concentration (C_{12hr}) of raltegravir. Left panel: Day 10 results of 004 study. The C_{12hr} was derived by arithmetic mean of predose and post dose (12hr) concentrations. Right panel: Results from 005, 018 and 019 studies. The C_{12hr} represents geometric mean observed C_{12hr}.

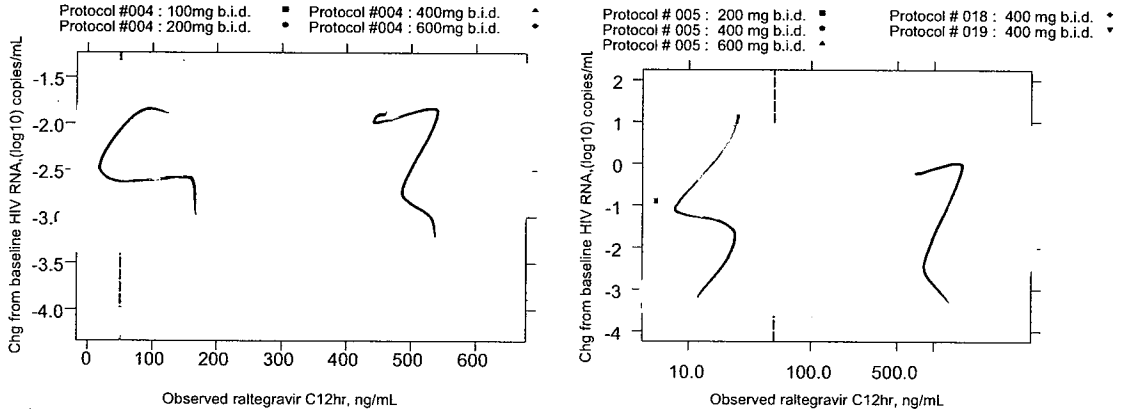
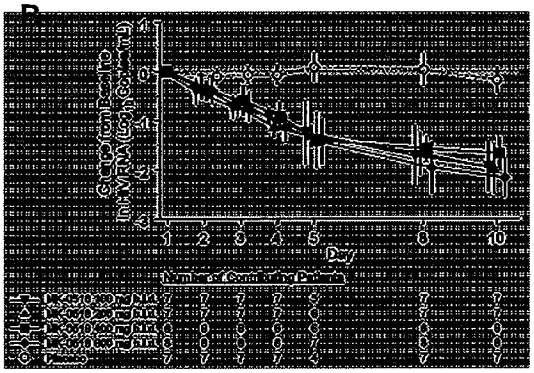


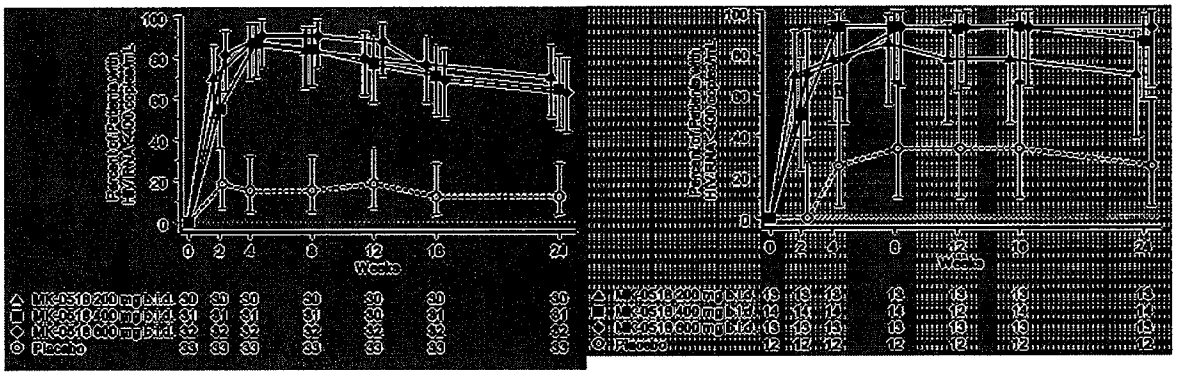
Figure 12 represents relationship between C_{12hr} and change from baseline HIV RNA (log10), copies/mL. A trend of concentration-dependent decrease in HIV RNA was not noticeable for the change from baseline endpoint or other individualized endpoint (HIV RNA<400 copies/mL) in all studies (Figure 1 and Figure 13 Panel A). Due to PK variability, all the doses exhibited overlapping exposures across doses, thus leading to similar Day 10 or long term (Week 24) antiretroviral activity (100-600 mg b.i.d.) (Figure 13 Panel B and C).

Figure 13: Protocol 004 results: Panel A: 3-dimensitonal plot of relationship between HIV RNA <400 copies/mL, (0=No and 1=Yes), Baseline HIV RNA (log10) copies/mL and raltegravir C_{12hr}. Panel B: Time course of change from baseline HIV RNA (log10) copies/mL. Panel C: Rich PK sampling data from Day 10 by dose group, with response rate (proportion of subjects with HIV RNA<400 copies/mL) indicated for each dose group. The horizontal line represents in vitro IC_{95}~25 ng/mL (50 nM) cut-off.



Similar results (Figure 14) were seen from the protocol 005, where overlapping exposures across doses (200-600 mg b.i.d.) (Figure 10) resulted in similar response rates. Small differences at higher doses between substudies could be due to limited sample size in substudy B or higher overall placebo response rate in substudy B. Such differences are not explainable by changes in PK.

Figure 14: Response rate (HIV RNA <400 copies/mL) from substudy A (without atazanavir) and substudy B (with atazanavir) over time from protocol 005.



On those lines, the mean changes in raltegravir PK (Figure 11) due to addition of tipranavir or atazanavir were not apparent in the overall response rate (Table 2), possibly due to highly overlapping exposures with and without either drug.

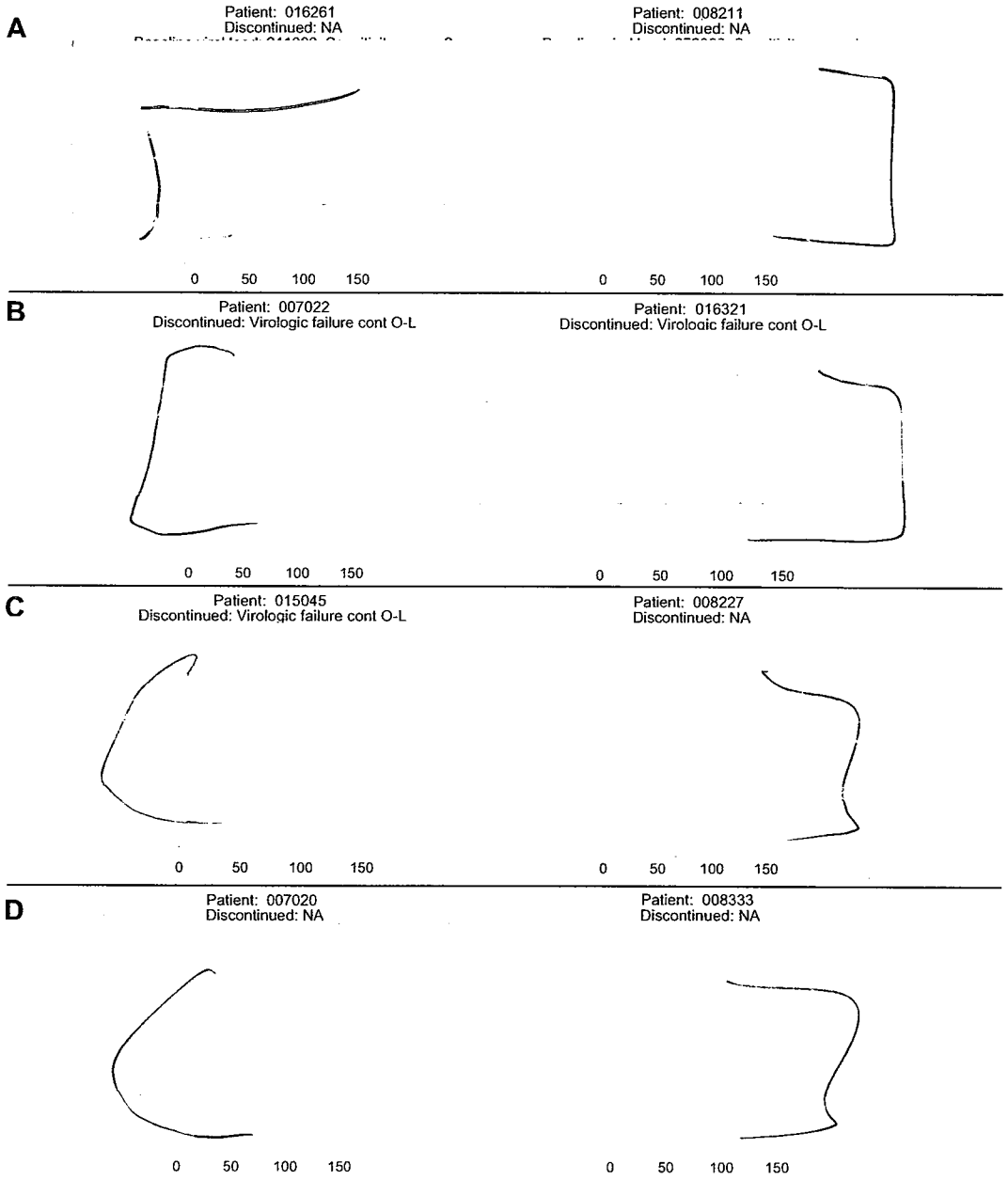
Within-subject variability

The objective was to assess the impact of day-to-day variation in C_{12hr} on time course of HIV-RNA and CD4+ cell count. To be included in the analyses, subjects from protocol 018 and 019 were required to have PK sampling on at least 3 occasions with post dose sample between 11 and 13 hrs. A time course of HIV RNA, copies/mL, CD4+ cell count, cells/μL and plasma raltegravir concentration (C_{12hr}) was plotted. Intent was to find a reflection of PK variability in time course of HIV RNA and CD4+ cell count.

Appendix 5 illustrates temporal association between plasma concentration and HIV RNA levels and CD4+ cell count for all subjects. Figure 15 illustrates temporal association between plasma concentration and HIV RNA levels and CD4+ cell count for subset of representative subjects. Panel A illustrates subjects who did not have virologic failure and had consistent high (>50nM) plasma C_{12hr}. Panel B illustrates subjects who had virologic failure and had consistent low (around 50nM) plasma C_{12hr}. Of specific interest, subject #7022 exhibited good virologic response early on in the trial with high C_{12hr}(>2000 nM), but had a rebound that seemed to match with lower C_{12hr}. Panel C matches two subjects with nearly identical baseline characteristics, but a subject (15045) with consistent low C_{12hr} failed due to virologic failure and a subject (8227) with consistent high C_{12hr} exhibited long term virologic success. Panel D illustrates two subjects with high variability in C_{12hr} and plasma levels below 50nM on at least one occasion; however, both subjects achieved long term virologic success. Subject 7020 seemed to have a rebound post week 16; however, Week 24 data for all subjects are not available at this time.

Finally, there are no consistent data signatures to conclude effect of within subject PK variation on effectiveness, however, the analyses needs to be repeated once the long term data are available.

Figure 15: A subset of subjects from appendix 5. Temporal association between plasma concentration (green symbols) and HIV RNA levels (red dotted line) and CD4+ cell count (blue solid line). The x-axis represents time since the start of the therapy in days. The y-axis (left side) represents HIV RNA, copies/mL and (right side) represents raltegravir plasma concentrations, ng/mL and CD4+ cell count, cells/μL. The horizontal line represents 25 ng/mL (~50 nM) cut off. The vertical line represents week 16 endpoint, after which the failure subjects were given an option to enroll in the open label study. The headers include subject ID, discontinuation status at week 16, baseline viral load (HIV RNA, copies/mL), sensitivity score and OBT information.



In conclusion, the size of the current safety/effectiveness database at the high raltegravir exposure levels and high variability make defining a clinically significant threshold for dose adjustment challenging. The applicant proposes that raltegravir exposures spanning a 2-fold increase in AUC for safety and a 60% decrease in $C_{12\,hr}$ for efficacy are not clinically relevant based on available clinical experience. The cut-off values are rather subjective and not based on extensive clinical experience. The effect of high day-to-day variability on long term effect is not clear at this time. Based on the applicant's rationale, a dose adjustment in the presence of atazanavir/ritonavir or tipranavir/ritonavir is not needed. Safety and efficacy data from Protocols 018 and 019 support the administration of raltegravir 400 mg twice daily with either tipranavir/ritonavir or atazanavir/ritonavir, with no dose adjustment.

Protocols 018 and 019 prohibited use of phenobarbital, phenytoin, rifabutin, and rifampin. When the protocols were amended, rifabutin (a less potent CYP3A, UGT1A1 inducer) was no longer prohibited.

Are the labeling claims based on population PK supported?

See Appendix 3: Labeling claims made by the sponsor based on population PK and reviewer's assessment

Appendices

Appendix 1: Population PK analyses provided by the sponsor

Final population PK model

The final population PK model was a two compartment model.

See population PK report provided by the sponsor (MRL Report 0437: Population PK model development and analysis of raltegravir phase 1 and phase 2 studies and MRL Report 0438: Interim population PK analysis of raltegravir phase 3 studies 018 and 019) with SN-004 for complete details.

- **Reviewer's assessment**

The goodness of fit plots for the model developed using phase 1 and 2 rich sampling data and for the phase 3 data illustrate poor predictive ability of the model (Figure 16 and Figure 17). Based on the known PK characteristics, high between and within subject variability, the poor performance was not surprising. As most of the phase 1 and 2 studies did not collect enough information on factors, such as food, pH dependent solubility, UGT1A1 polymorphism and UGT1A1 expression that could impact the variability. More importantly, the registration trials were conducted by administering raltegravir without regard to food, potentially a major source of variability. Thus, in the absence of such information, no attempt was made to further update the sponsor's model. The observed PK data were used in exposure response analyses.

Figure 16: Population (left) and individual (right) predicted raltegravir concentration versus measured raltegravir concentration from the population PK model developed using the phase 1 and 2 rich-sampling data

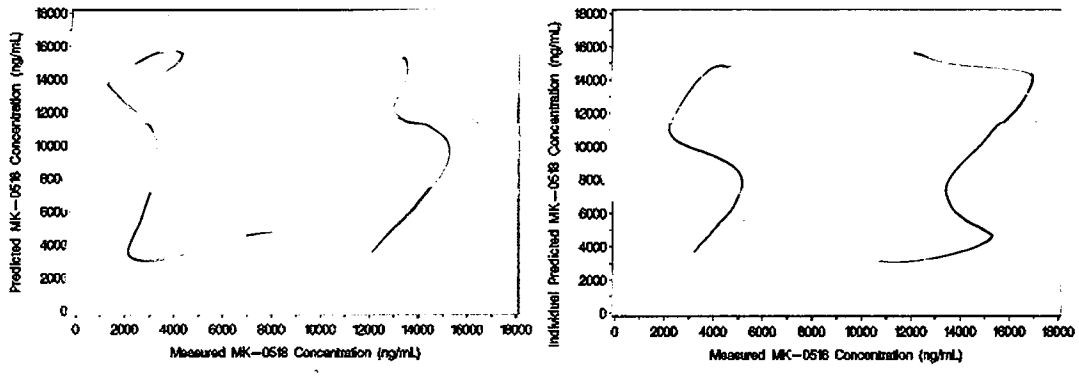
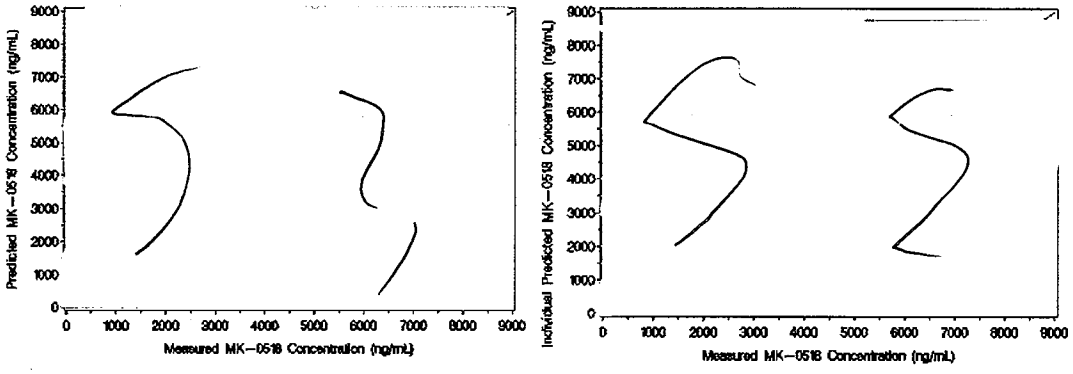


Figure 17: Population (left) and individual (right) predicted raltegravir concentration versus measured raltegravir concentration for the phase 3 data



Appendix 2: Exposure response analyses provided by the sponsor

Summary: Reference 360: MRL Report: Raltegravir PKPD associations in treatment-naïve and treatment-experienced subjects from phase II studies (Raltegravir Protocols 004 and 005).

The report describes a PK/pharmacodynamic (PKPD) analysis that was conducted in support of the HIV integrase strand inhibitor (raltegravir) development program using data from the Phase II studies (Protocol 004 and Protocol 005). All analyses were conducted using the 2-step approach; that is, individual PK parameter values were first determined and then a statistical analysis of the potential relationship between PK and a variety of efficacy response parameters was performed. Population PK data from 150 out of 198 treatment-naïve subjects enrolled in Protocol 004 and 124 out of 178 treatment-experienced subjects enrolled in Protocol 005 were included in this analysis. The antiretroviral efficacy responses used in these assessments included: HIV RNA <400 copies/mL; HIV RNA <50 copies/mL; occurrence of virologic failure; and development of integrase mutations at amino acid 148 and/or 155. These efficacy responses were based on Week 24 or 48 data and, therefore, these PKPD analyses represent longer term, and potentially more clinically relevant, concentration-response assessments than the 10-day monotherapy PKPD analyses included in the clinical study report for Protocol 004. The potential association between PK parameter values and efficacy response measures was assessed through logistic regression models, where an odds ratio (95% CI) was determined. The change from baseline in log10 HIV RNA was also examined; however, the high proportions of subjects with HIV RNA below the limit of quantitation limited the utility of these assessments.

The geometric mean of the observed C_{12hr} values for each individual subject was defined as the primary population PK exposure estimate for this PKPD association analysis. In addition, secondary population PK exposure estimates, including minimum

of observed C_{12hr}, model-predicted steady-state AUC_{0-12hr} and C_{12hr} (fasted and fed), were examined.

The model-based predicted PK summary measures were considered exploratory due to a potential bias to underestimate the highest exposures and the requirement of assumptions including food status.

The PK data from subjects in Phase II demonstrate a general trend of increasing concentrations with increasing dose with considerable, but not complete overlap of the PK values among the doses evaluated in Phase II. The individual population PK values from the sparse data from Protocol 005 were examined with respect to concomitant use of atazanavir and the results indicated that raltegravir trough concentrations and AUC were modestly elevated (30-40%) in the presence of atazanavir. This modest elevation is unlikely to be clinically meaningful.

In the PKPD association analysis for Phase II treatment naïve study (Protocol 004), efficacy responses at Week 48 in treatment naïve subjects receiving raltegravir twice daily (at doses of 100, 200, 400, and 600 mg) in combination with tenofovir and lamivudine were evaluated. There were insufficient numbers of failure subjects in most categories (HIV RNA ≥400 copies/mL; occurrence of virologic failure; and development of integrase mutations) to allow a formal association analysis for the primary PK parameter, observed geometric mean C_{12hr}. Formal statistical analyses for the occurrence of HIV RNA <50 copies/mL did not show association with any of the observed trough PK parameters. The exploratory PK parameters, model-predicted AUC and C12hr, were available for most subjects which allowed a formal association analysis with HIV RNA <400 copies/mL and occurrence of virologic failure. There was no evidence to suggest any PKPD association. This result is consistent with a lack of meaningful PKPD association over the range of PK values tested in the treatment naïve population.

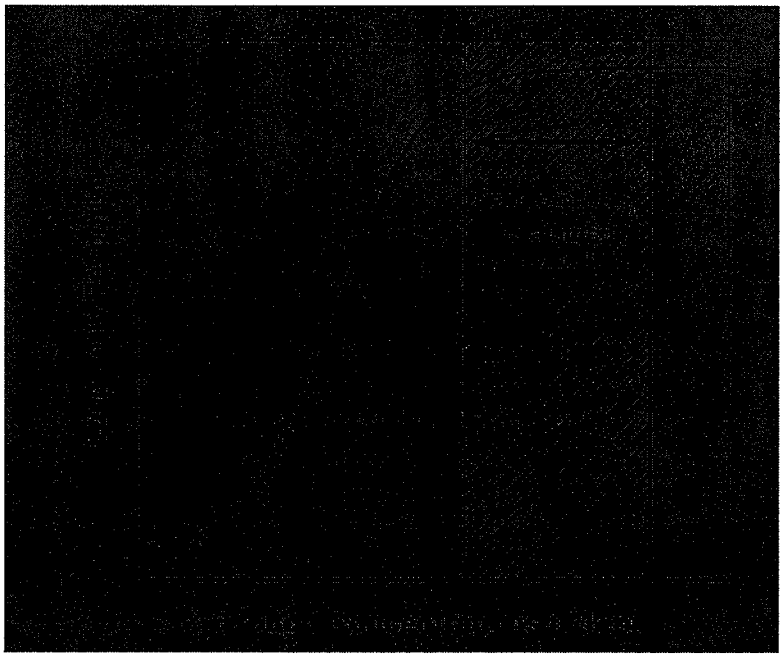
In the Phase II treatment experienced analysis (Protocol 005), efficacy responses at Week 24 in treatment experienced subjects receiving raltegravir twice daily (at doses of 200, 400, and 600 mg) in combination with optimized background therapy (OBT) were evaluated. A greater proportion of subjects (Protocol 005) compared to ART naïve subjects in protocol 004 did not achieve a favorable viral response, which allowed formal association analyses for all 6 targeted efficacy response parameters. There was no evidence to suggest a presence of PKPD association for any efficacy response compared to any PK parameter. Although one test of correlation between PK and change from baseline in log10 HIV RNA at Week 24 had a small nominal p-value, it was demonstrated that this result was driven by a single subject with an extreme PK value and, therefore, may not represent a meaningful association. This result is consistent with a lack of meaningful PKPD association over the range of PK values tested in the treatment experienced population.

Given the high percentage of favorable efficacy responses obtained in both Protocol 004 and Protocol 005, the lack of meaningful association between PK and efficacy response measures suggests that the range of raltegravir concentrations obtained from

100 - 400 mg doses falls near the top of the concentration-response curve, where treatment response has, at most, only a modest concentration dependency.

In conclusion, the analyses in this report indicate that:

(1) There is no clinically meaningful difference in the antiretroviral efficacy response measures (HIV RNA <400 copies/mL at week 48; HIV RNA <50 copies/mL at week 48; and occurrence of virologic failure) across the range of PK obtained in the Phase II study (Protocol 004) of treatment-naïve subjects in a setting of a high percentage of favorable efficacy responses. There was insufficient information to evaluate the potential association with development of integrase mutations at amino acid 148 and/or 155 in this population.



(2) There is no clinically meaningful difference in the antiretroviral efficacy response measures (HIV RNA <400 copies/mL at week 24; HIV RNA <50 copies/mL at week 24; occurrence of virologic failure; development of integrase mutations at amino acid 148 and/or 155, and change from baseline in log10 HIV RNA at week 24) across the range of PK exposure values obtained in the Phase II study (Protocol 005) of treatment-experienced subjects in a setting of a high percentage of favorable efficacy responses.

(3) The PK data from subjects in Phase II demonstrate a general trend of increasing concentrations with increasing dose, with considerable overlap of the PK values among the doses evaluated in Phase II.

(4) Raltegravir trough concentrations and AUC are modestly elevated (30-40%) in the presence of concomitant atazanavir. This modest elevation is unlikely to be clinically meaningful.

See population PKPD report provided by the sponsor (MRL Report 360 and MRL Report 375) with SN-004 for complete details.

Summary: Reference 375: MRL Report: Preliminary analysis- raltegravir PKPD associations in heavily pretreated HIV-infected subjects (raltegravir Protocols 005, 018, and 019), 29-Mar-2007.

The report describes a PKPD analysis that was conducted in support of the novel human immunodeficiency virus (HIV)-1 integrase strand transfer inhibitor (raltegravir) development program using data from the Phase II and III studies of antiretroviral treatment-experienced subjects (Protocols 005, 018, and 019). All analyses were conducted using the 2-step approach; that is, individual PK parameter values were first determined and then a statistical analysis of the potential relationship between PK and a variety of efficacy response parameters was performed. Population PK data from 579 of the 595 treatment-experienced subjects treated with raltegravir in Protocols 005, 018, and 019 were included in this analysis. The antiretroviral efficacy responses used in these assessments included: HIV RNA <400 copies/mL; HIV RNA <50 copies/mL; occurrence of virologic failure; and development of integrase mutations at amino acid 148 and/or 155. These efficacy responses were based on Week 16 data, which was the primary time point for efficacy analysis, and therefore, these PKPD analyses represent longer term, potentially more clinically relevant, concentration-response assessments than the 10-day monotherapy PKPD analyses (using full PK profile sampling) included in the clinical study report for Protocol 004. The potential association between PK parameter values and efficacy response measures were assessed through logistic regression models. The change from baseline in log10 HIV RNA was also examined; however, the high degree of data below the limit of quantitation limited the utility of these assessments.

The geometric mean of the observed C_{12hr} values for each individual subject was defined as the primary population PK exposure estimate for this PKPD association analysis. In addition, secondary population PK exposure estimates, including minimum of observed C_{12hr}, and exploratory model-predicted steady-state $AUC_{0\text{-}12hr}$ and C_{12hr} (fasted and fed), were examined. The model-based predicted PK were considered exploratory due to a potential bias to underestimate the highest exposures and the requirement of an assumption regarding food status.

Tipranavir use was allowed in the Phase 3 studies 018 and 019 with no dose adjustment to raltegravir. The individual population PK values from the sparse data from Protocol 018 and 019 were examined with respect to concomitant use of tipranavir. The results indicate that raltegravir trough concentrations and AUC are modestly reduced (51-56% in the observed trough values and 13-35% in the model-predicted values) in the presence of concomitant tipranavir.

In the pooled analysis of Week 16 responses in the treatment-experienced subjects from Protocols 005, 018, and 019, there was no evidence to suggest a PKPD association for any efficacy response compared to the observed C_{12hr} parameters, including the primary PK parameter, geometric mean observed C_{12hr}. Smaller p-values were obtained for some, but not all, efficacy responses when compared to exploratory model-predicted AUC and C_{12hr} (Fed). However, characterizations of these potential associations indicate that the magnitude of the potential associations is not substantial, i.e., there may be just a modest increase in the percentage with favorable response with higher PK values. Further, in a quantile analysis, a generally similar high-level of favorable response was seen across a wide range of PK values for all the PK parameters evaluated. Given the lack of associations based upon the primary PK parameter, and lack of substantial and clinically meaningful PKPD associations based upon all PK parameters including model-predicted PK values, these results are consistent with a lack of substantial and clinically meaningful PKPD association over the range of PK values tested in the treatment-experienced population.

Given the high percentage of favorable efficacy responses obtained in the treatment-experienced subjects from Protocols 005, 018, and 019, the lack of clinically meaningful associations between PK and longer term response measures at Week 16 suggests that the range of raltegravir concentrations obtained from 200 to 600 mg doses falls near the top of the concentration-response curve, where treatment response may only have a modest concentration dependency.

In conclusion, the analyses in this report indicate that:

(1) There is no clinically meaningful difference in the antiretroviral efficacy response measures (HIV RNA <400 copies/mL; HIV RNA <50 copies/mL; occurrence of virologic failure; development of integrase mutations at amino acid 148 and/or 155; and change from baseline in log10 HIV RNA at Week 16) across the range of observed PK values obtained in treatment-experienced subjects in a setting of a high percentage of favorable efficacy responses.

(2) There is no clinically meaningful difference in the antiretroviral efficacy response measures (HIV RNA <400 copies/mL; HIV RNA <50 copies/mL; occurrence of virologic failure; development of integrase mutations at amino acid 148 and/or 155; and change from baseline in log10 HIV RNA at week 16) across the range of model-predicted PK values obtained in treatment-experienced subjects. Although a few comparisons suggested a potential association of response with model-predicted PK, these associations were not substantial in magnitude.

(3) Raltegravir trough concentrations and AUC are modestly reduced (51-56% in the observed trough values and 13-35% in the model predicted values) in the presence of concomitant tipranavir. The C_{12hr} values (geometric mean observed, minimum observed, and the model-predicted (Fed and Fasted) in the group receiving concomitant TPV exceeded the in vitro IC95 of 33 nM for raltegravir against HIV integrase.

- **Reviewer's assessment**

See section "Is there an exposure response relationship for raltegravir to support evidence of effectiveness?" for reviewer's assessment.

Appendix 3: Labeling claims made by the sponsor based on population PK

Age

The effect of age on the PK of raltegravir was evaluated in the composite analysis and the population PK (PK) analysis.

Race

The effect of race on the PK of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Gender

A study of the PK of raltegravir was performed in young healthy males and females. Additionally, the effect of gender was evaluated in a composite analysis of PK data from 103 healthy subjects and 28 HIV subjects receiving raltegravir monotherapy with fasted administration.

No dosage adjustment is necessary.

- **Reviewer's assessment**

Since the population PK model did not provide reasonable goodness of fit, the claims were assessed based on observed data from multiple trials (004, 005, 018, 019, 025 and 028). Two time windows (2-4 hrs and 11-13 hrs) were selected with reference to reported time since the last dose. The rationale was to capture the differences, if any, around the Tmax (mean ~3 hrs) and around predose time (dosing interval 12 hrs). Only 400 mg b.i.d. data were used from the above trials. A total of 1212 concentration measurements (2-4hrs: 509 and 11-13 hrs:703) from 467 subjects (2-4hrs: 224 and 11-13 hrs:358) were available.

Table 6 summarizes demographics of the subjects used in the analyses. Figure 18 illustrates distribution of raltegravir concentrations by body weight, BMI, age, race and gender.

Table 6: Demographics of the subjects used in the analyses.

Age (mean± SD)		43.8 ± 9.9
Weight (mean± SD)		72.6 ± 14.3
BMI (mean± SD)		23.8 ± 3.9
Males (%)		85
Race	**White (n)**	306
	Black	57
	Hispanic	60
	Others	24
	Asian	20

In conclusion, PK of raltegravir are not affected by age, body weight, gender and race to an extent requiring dose adjustment.

8 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1A

Appendix 5: Temporal association between plasma concentration (green symbols) and HIV RNA levels (red dotted line) and CD4+ cell count (blue solid line). The x-axis represents time since the start of the therapy in days. The y-axis (left side) represents HIV RNA, copies/mL and (right side) represents raltegravir plasma concentrations, ng/mL and CD4+ cell count, cells/μL. The horizontal line represents 25 ng/mL (~50 nM) cut off. The vertical line represents week 16 endpoint, after which the failure subjects were given an option to enroll in the open label study. The headers include subject ID, discontinuation status at week 16, baseline viral load (HIV RNA, copies/mL), sensitivity score and OBT information.

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-2

4.3 OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA Number	022-145	Brand Name		Isentress
OCP Division	4	Generic Name		Raltegravir
Medical Division	DAVP	Drug Class		HIV Integrase Inhibitor
OCP Reviewer	Derek Zhang	Indication(s)		HIV-1 Infection
OCP Team Leader	Kellie Reynolds	Dosage Form		400 mg tablets
Date of Submission	04/13/2007	Dosing Regimen		400 mg twice daily
Estimated Due Date of OCP Review	09/30/2007	Route of Administration		oral
PDUFA Due Date	10/12/2007	Sponsor		Merck
Division Due Date		Priority Classification		P1
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies being 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	1	
Isozyme characterization:	x	2	2	
Metabolic profiling	x	1	1	
In vitro effect on metabolism	x	1	1	
P-gp	x	2	2	
Blood/plasma ratio:	x	1	1	
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2	2	
multiple dose:	x	1	1	
Patients-				
single dose:				
multiple dose:	x	2	2	
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	9	9	
In-vivo effects of primary drug:	x	4	4	
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	1	1	
hepatic impairment:	x	1	1	
PD:				
Phase 1:				
Phase2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	2	2	
Phase 3 clinical trial:	x	2	2	
Population Analyses -				
Data rich:	x	1	1	
Data sparse:	x	3	3	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	x	1	1	
solution as reference:	x			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food effect studies:	x	1	1	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	x	1	1	
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	
Comments sent to firm ?		
QBR questions (key issues to be considered)		

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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/s/

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10/1/2007 03:01:42 PM
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