CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-145	Submission Date(s): April 13, 2007
Brand Name	ISENTRESS
Generic Name	Raltegravir
Primary Reviewer	Derek Zhang, Ph.D.
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OCP Division	Division 4
OND Division	DAVP
Applicant	Merck Inc.
Relevant IND(s)	IND 69928
Submission Type	Priority
Formulation; Strength(s)	400 mg tablets
Indication	In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients ~~~~~ evidence of HIV-1 replication despite ongoing antiretroviral therapy

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1. EXECUTIVE SUMMARY

Raltegravir, in combination with other antiretroviral agents, is proposed for treatment-experienced adult patients infected with HIV-1.

The consideration for accelerated approval of this NDA is based on safety and efficacy data of 16-24 weeks duration from two identical double-blinded, placebo-controlled Phase III trials in treatment-experienced patients. The studied 400 mg dose, given twice daily, when dosed in combination with optimized background therapy (OBT), demonstrated safety, tolerability, and superior efficacy in patients with previous antiretroviral experience and advanced HIV infection.

Overall, the cumulative clinical pharmacology data for raltegravir support the proposed use of this drug in combination with other antiretroviral agents for treatment-experienced patients infected with HIV-1.

1.1 Recommendation

The Clinical Pharmacology information provided by the applicant is acceptable.

1.2 Phase IV Commitments

We are considering the following post marketing commitments because these studies will provide information that will improve the safe and effective use of raltegravir in the target population.

1. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin and rifampin using raltegravir as a probe substrate.

2. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.

Note: Not counted as phase IV commitments: We acknowledge that the applicant is going to conduct a drug interaction study between raltegravir and rifabutin. A drug interaction study between raltegravir (800 mg) and rifampin is ongoing.
The applicant also conducted a drug interaction study of raltegravir with omeprazole. The preliminary results showed that coadministration of omeprazole increases raltegravir concentrations. The results are expected because the solubility of raltegravir increases as increasing pH. The impact of the study is unknown until the final study report is submitted and reviewed.

1.3 Summary of Important Clinical Pharmacology Findings

The clinical pharmacology of raltegravir has been characterized in healthy and HIV-1 infected subjects, as well as in vitro studies using human biomaterials. The clinical pharmacology characteristics of raltegravir observed in these studies are summarized in the following sections.

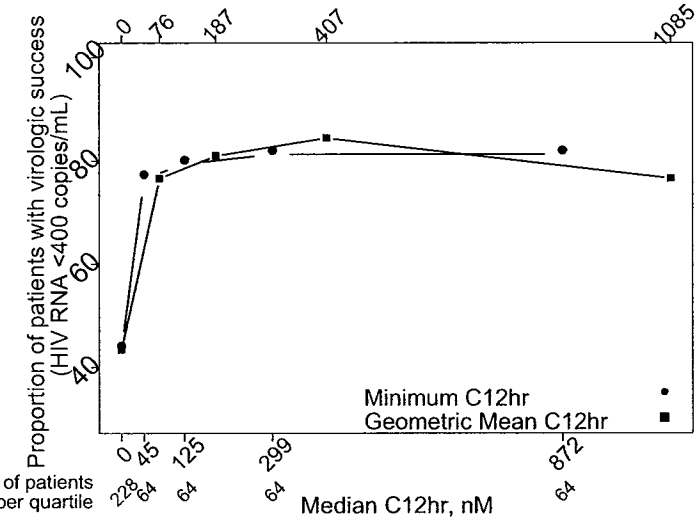
Exposure-Response Analysis

The data from two large double-blind placebo controlled trials (Protocols 018 and 019) in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral antiretroviral therapies were used in the exposure-response analysis. These trials were conducted using the to-be-marketed formulation, which exhibits considerable food effect on C_{12hr}. A total of 483 subjects (225 raltegravir treated and 228 placebo treated) were included in the analyses. Approximately 200 subjects were excluded due to lack of sufficient PK information. Plasma trough concentrations (C_{12hr}) were used as an exposure variable. 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 postdose in a given individual); and the minimum observed C_{12hr} (determined as the minimum concentration from all samples taken between 11 and 13 hours postdose in a given individual).

Within the concentration range studied, the virologic success rate is similar (77%) for patients 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 IC_{95} ~ 50nM in 50% human serum) of raltegravir such that the exposures are in the asymptotic region of the C_{12hr} -virologic success relationship.

Figure 1 illustrates the relationship between the probability of virologic success (<400 copies/mL) and C_{12hr} (geometric mean observed C_{12hr} and minimum observed C_{12hr}). Within the concentration range studied, the C_{12hr}-virologic success relationship is shallow.

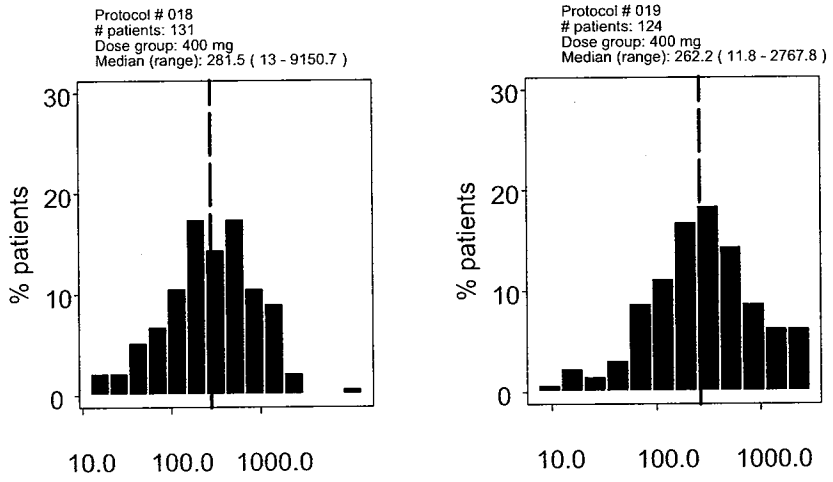
Figure 1. C_{12hr}-virologic success relationship. The C_{12hr}=0 represents placebo-treated patients; raltegravir-treated patients were divided into four quartiles.



The overall variability in C_{12hr} is considerably high, with a range of 12 to 9151 nM.

Figure 2 illustrates distribution of geometric mean observed C_{12hr} in the pivotal studies.

Figure 2. Distribution of geometric mean observed C_{12hr} (nM).



Pharmacokinetic Variability

1. Raltegravir exhibits high pharmacokinetic variability (range of geometric mean C_{12hr} on 400 mg twice daily = 12 to 9151 nM in pivotal studies).
2. The potential sources of variability include: food, pH dependent solubility, UGT1A1 expression levels, UGT1A1 polymorphism, and drug interactions.
3. Defining a clinically significant threshold for dose adjustment is challenging because observed raltegravir plasma concentrations span over a 5-log range.
    a. Within the concentration range studied, the virologic success rate is similar (77%) for patients 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.
    b. 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 pharmacokinetic variability

Pharmacokinetics (Absorption, Distribution, Metabolism, Excretion)

After oral administration of single doses of raltegravir in healthy subjects in the fasted state, raltegravir $AUC_{0-\infty}$ and C_{max} is dose proportional over the dose range of 100 to 1600 mg. However, the variability is quite large (increasing with increasing dose levels), which implies a large degree of uncertainty in raltegravir exposure level. In treatment naïve HIV-1 infected patients who received raltegravir 400 mg twice daily monotherapy, raltegravir drug exposures were similar to exposure in healthy subjects.

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

	AUC_{0-12hr} (μM·hr)					C_{max} (μM)					C_{12hr} (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	84.53	1.45	4.32	6.52	10.59	26.11	36.2	68.1	113.4	186.6	368.6
SD	2.08	6.39	8.74	24.34	50.21	1.10	3.04	5.71	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

Table 2. Summary Statistics for Raltegravir Intensive PK Parameters on Day 10 in Treatment Naïve HIV-1 Infected Patients (Cohort I; Monotherapy Phase)

Treatment	N	Arithmetic Mean (SD)	Geometric Mean (90% CI)	Median (Range)
AUC_{0-12hr} (μM·hr)				
MK-0518 100 mg b.i.d.	7	6.0 (2.1)	5.8 (4.6, 7.3)	5.3 (4.2 to 10.2)
MK-0518 200 mg b.i.d.	7	10.2 (4.2)	9.4 (5.8, 13.1)	11.3 (4.8 to 15.9)
MK-0518 400 mg b.i.d.	6	17.3 (9.7)	14.3 (7.6, 26.7)	18.5 (3.8 to 28.8)
MK-0518 600 mg b.i.d.	8	19.3 (15.4)	14.6 (8.3, 25.8)	16.4 (2.9 to 53.9)
C_{max} (μM)				
MK-0518 100 mg b.i.d.	7	2.3 (1.1)	2.1 (1.4, 3.0)	2.2 (1.1 to 4.2)
MK-0518 200 mg b.i.d.	7	4.2 (2.6)	3.3 (1.9, 5.9)	3.9 (1.1 to 8.3)
MK-0518 400 mg b.i.d.	6	6.2 (4.1)	4.5 (2.0, 10.2)	6.6 (0.8 to 10.2)
MK-0518 600 mg b.i.d.	8	5.5 (5.7)	3.8 (2.0, 7.1)	4.0 (0.7 to 19.1)
C_{12hr} (nM)				
MK-0518 100 mg b.i.d.	7	55.2 (46.1)	42.6 (24.2, 75.0)	54.9 (14.3 to 151.9)
MK-0518 200 mg b.i.d.	7	123.3 (51.5)	112.4 (78.4, 161.1)	148.7 (50.2 to 179.1)
MK-0518 400 mg b.i.d.	6	161.6 (83.4)	141.7 (87.6, 229.1)	162.4 (65.7 to 265.5)
MK-0518 600 mg b.i.d.	8	290.3 (245.5)	204.9 (108.9, 385.7)	202.6 (42.3 to 771.8)

N = Number of patients in the treatment group.

The apparent terminal $t_{½}$ of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. The median time to maximum plasma concentration (T_{max}) is ~3 hours in the fasted state. Steady-state is achieved after two days of dosing at all dose levels.

Raltegravir is approximately 83% bound to human plasma proteins and is minimally distributed into red blood cells (blood-to-plasma partitioning ratio of 0.6). No data are available regarding human central nervous system (CNS) or brain penetration. Raltegravir is a substrate of human P-gp *in vitro*, which may limit CNS penetration in humans.

The results from a single dose study of 200 mg [^{14}C] raltegravir given to young healthy subjects indicate hepatic clearance via glucuronidation plays a major role in the clearance of raltegravir in humans, while renal clearance of unchanged drug is a minor pathway of elimination of raltegravir.

The *in vitro* metabolism of raltegravir was studied in human hepatic microsomes and hepatocytes. Data indicate glucuronidation of the parent compound to M2 is the major metabolic pathway in humans. Raltegravir is not a substrate of cytochrome P450 enzymes. Correlation and specific chemical inhibition studies in pooled human liver microsomes confirm the glucuronidation of raltegravir is mainly catalyzed by UGT1A1, with a minor contribution from UGT1A9 and 1A3.

UGT1A1 is a polymorphic enzyme. A single-dose, open-label study in healthy subjects with UGT1A1*1/*1 and UGT1A1*28/*28 genotypes is ongoing.

Food Effect

A high-fat meal, on average, resulted in a 19% increase in AUC, 34% decrease in C_{max}, 750% increase in C_{12hr} and 7.3 hour delay in T_{max} with raltegravir final market image (FMI) formulation. However, the food effect is variable between subjects.

Based on the results from the high-fat meal study and the fact that raltegravir was dosed with or without food in Phase 2 and Phase 3 trials, raltegravir can be taken with or without food.

A study to investigate the effects of low, moderate, and high-fat meals on multiple dose pharmacokinetics of raltegravir in healthy volunteers is ongoing.

Special Populations

The effects of HIV status, age, gender, weight, and race on raltegravir pharmacokinetics were assessed by evaluation of raltegravir plasma trough concentrations in Phase 2 and 3 trials. The data indicate age, gender, weight, race and HIV status do not have an impact on raltegravir exposure. No clinically important effect of moderate hepatic insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with Child Pugh scores of 7 to 9. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency. No clinically important effect of severe renal insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with 24-hour creatinine clearance of <30 mL/min/1.73 m^2. No dosage adjustment is recommended for patients with renal insufficiency.

Drug-Drug Interactions

In Vitro Results: Drug-Drug Interaction Potential

- Raltegravir is a UGT1A1 substrate.
- Raltegravir is an avid P-gp substrate.
- Raltegravir is not an inhibitor (IC_{50} >100 µM) of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6. Raltegravir (up to 10 µM) has no potential to induce CYP3A4.
- Raltegravir is not a potent inhibitor of UGT1A1 or UGT2B7 (IC_{50} >50 µM).
- Raltegravir is not an inhibitor of P-gp.
- No study was conducted to evaluate other transporter pathways.

In Vivo Effects of Other Drugs on Raltegravir

Raltegravir is a UGT1A1 and P-gp substrate. Because raltegravir will be coadministered with drugs that affect UGT1A1 and P-gp activity, the effects of drugs on raltegravir pharmacokinetics were studied in Phase I clinical trials. Table 3 summarizes the effect of other drugs on raltegravir.

Table 3. Summary of the Effect of Other Drugs on Raltegravir					
Co-administered drug and dose	N	Study Design	Ratio (90% CI) of raltegravir pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC_{tau}	Cmax
UGT1A1 Inhibitors					
Atazanavir 400 mg QD	10	SD/MD	1.95 (1.30, 2.92)	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)
Atazanavir/ritonavir 300/100 mg QD	10	MD/MD	1.77 (1.39, 2.25)	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)
UGT1A1 Inducers					
Ritonavir 100 mg BID	10	SD/MD	0.99 (0.70, 1.40)	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)
Efavirenz 600 mg QD	10	SD/MD	0.79 (0.49, 1.28)	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)
Rifampicin 600 mg QD	10	SD/MD	0.39 (0.30, 0.51)	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)
Tipranavir/ritonavir 500/200 mg BID	18	MD/MD	0.45 (0.31, 0.66)	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)
TMC125 200 mg BID	20	MD/MD	0.66 (0.34, 1.26)	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)
Other Drugs					
Tenofovir 300 mg BID	10	MD/MD	1.03 (0.73, 1.45)	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)

SD/MD=Single dose administration of raltegravir and multiple dose administration of the other agent; MD/MD=Multiple dose administration of raltegravir and the other agent.

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.

As anticipated, raltegravir plasma levels were increased with coadministration with atazanavir alone and in combination with ritonavir, which is consistent with inhibition of UGT1A1. However, concomitant use of raltegravir and atazanavir was well tolerated in the Phase II and Phase III studies. Based on these data, atazanavir may be coadministered with raltegravir without dose adjustment of raltegravir. The current intended treatment population for raltegravir, treatment experienced patients, should only receive atazanavir/ritonavir.

Tipranavir/ritonavir decreased raltegravir C_{12hr} by 55%, $AUC_{0\text{-}12hr}$ by 24% and C_{max} by 18%. Approximately 100 patients received raltegravir 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 raltegravir without dose a adjustment of raltegravir.

Rifampicin decreased raltegravir C_{12hr} by 61%, $AUC_{0\text{-}12hr}$ by 40% and C_{max} by 38%. Rifampicin, phenytoin and phenobarbital were prohibited in raltegravir Phase 2 and 3 trials thus no clinical

experience is available with regards to co-administration of raltegravir with rifampicin, phenytoin and phenobarbital. Therefore, caution should be used when coadministering raltegravir with rifampin or other potent inducers of UGT1A1. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used with the recommended dose of raltegravir.

Effects of Raltegravir on Other Drugs

Raltegravir is unlikely to significantly alter plasma exposure of co-administered drugs that are metabolized by cytochrome P450 enzymes, UGT enzymes and P-gp.

Drug interaction studies demonstrated that raltegravir did not alter pharmacokinetics of midazolam (a CYP3A probe substrate), tenofovir and etravirine (TMC125).

Potential sources that contribute to pharmacokinetic variability of raltegravir

The high pharmacokinetic variability observed across the clinical studies could be due to the combination of the following factors:

1. High variability in hepatic UGT1A1 protein expression levels (>50-fold) from human liver samples.
2. UGT1A1 polymorphism
3. High variability in intestinal P-gp expression levels
4. pH-dependent solubility. Solubility increases with increasing pH.
5. Food effect on $C_{12\ hr}$ values (Raltegravir was administered with or without food in Phase 2 and 3 trials)
6. Drug interactions affecting UGT1A1 and/or P-gp

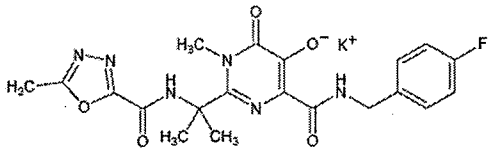
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The structure and physical properties of raltegravir are shown below:

Structural formula: $C_{20}H_{20}FKN_6O_5$



Chemical Name:	N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt
Molecular Weight:	482.51
pH-solubility profile:	This potassium salt form is highly soluble in water, in excess of — mg/mL, although solubility at physiological pH (between pH 2 to 7) is substantially lower than that in water (— mg/mL).
Apparent Permeability:	—

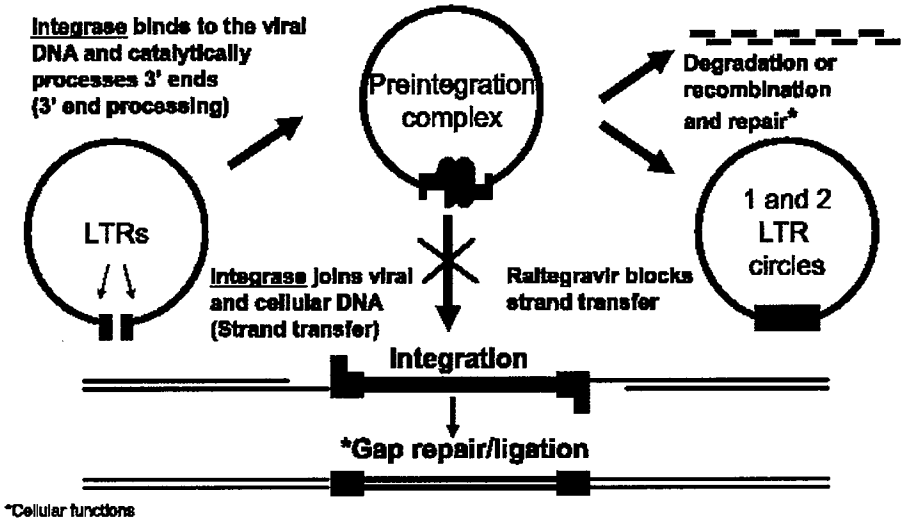
Table 2.1.1.1. The quantitative composition of the to-be-marketed raltegravir tablets

Component	Reference	Function	mg/tab	% (w/w)
Core Tablet				
MK-0518[†] (equivalent free phenol)	--	Active		
Microcrystalline Cellulose	NF, Ph. Eur.	Diluent		
Lactose Monohydrate	NF, Ph. Eur.	Diluent		
Calcium Phosphate Dibasic, Anhydrous	USP, Ph. Eur.	Diluent		
Hypromellose 2208	USP, Ph. Eur.	Binder / Stabilizing Agent		
Poloxamer 407[‡]	NF, Ph. Eur.	Surfactant		
Sodium Stearyl Fumarate	NF, Ph. Eur.	Lubricant		
Magnesium Stearate	NF, Ph. Eur.	Lubricant		
Total Core Tablet Weight				
Film Coating:				
Purified Water[‖]	USP, Ph. Eur.	Film Coating Solvent		
Total Film Coated Tablet Weight				

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Raltegravir inhibits the catalytic activity of HIV integrase. Integrase is 1 of 3 HIV-1 enzymes required for viral replication. Integrase catalyzes the stepwise process that results in the integration of the HIV-1 deoxyribonucleic acid (DNA) into the genome of the host cell (see Figure 2.1.2.1). Integration is required for stable maintenance of the viral genome as well as efficient viral gene expression, so inhibiting integration prevents propagation of the viral infection.

Figure 2.1.2.1 Inhibition of Integrase Strand Transfer



Raltegravir's indication: In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients [redacted] evidence of HIV-1 replication despite ongoing antiretroviral therapy.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose of raltegravir is 400 mg administered orally, twice daily in a combination regimen with other antiretroviral agents. Raltegravir can be taken with or without food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

1. Demonstration of Efficacy (Protocols 018 and 019, total N=699): Protocols 018 and 019 are international, multi-center, double-blind, randomized, placebo-controlled trials comparing raltegravir (400 mg twice daily) in combination with optimized background therapy (OBT) to OBT alone in highly treatment-experienced HIV-infected subjects. The studies were identical except for the location of the study sites. Protocol 018 was conducted in Europe, Asia/Pacific, and South America, while Protocol 019 was conducted in North and South America. Eligible subjects were HIV-1 infected patients who had failed therapy as documented by HIV RNA >1,000 copies/mL while on stable therapy and had documented resistance to at least 1 drug in each of 3 classes of licensed oral antiretrovirals (ARVs) (NNRTI, NRTI, and PI).

2. Supportive studies included Protocol 004, a dose-finding study in treatment-naïve patients, and Protocol 005, a dose-finding study in treatment-experienced patients. Dose selection for Phase 3 was based on Week 24 study data.

Protocol 004 was a multi-center, double-blind, randomized dose ranging, controlled study with 2 parts: Part I compared raltegravir monotherapy at doses ranging from 100 to 600 mg b.i.d. with placebo for 10 days. Part II compared the same doses of raltegravir with a standard-of-care comparator, EFV 600 mg, both in combination with TFV and 3TC.

Protocol 005 evaluated 3 doses of raltegravir (200, 400, and 600 mg b.i.d.) in combination with an optimized background therapy (OBT) versus placebo in combination with OBT for at least 24 weeks. Because preliminary PK data suggested that co-administration of raltegravir with atazanavir increased overall exposure to raltegravir, 2 substudies were conducted in Protocol 005: Substudy A for patients who did not receive atazanavir in their OBT and Substudy B for patients who received atazanavir in their OBT.

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

Viral load and CD4 cell count are accepted markers for efficacy in trials with antiretroviral agents. The primary efficacy endpoint in two Phase 3 trials was the proportion of patients achieving HIV RNA <400 copies/mL at Week 16 for accelerated approval (as agreed at the End-of-Phase II meeting). Secondary endpoints included the proportion of patients achieving HIV RNA <50 copies/mL at Week 16, the proportion of patients with greater than 1 Log10 drop in HIV RNA or HIV RNA less than 400 copies/mL, mean HIV RNA change from baseline (Log10 copies/mL), mean CD4 cell count change from baseline.

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

Yes, appropriate moieties were quantified in all the clinical pharmacology studies. Raltegravir was quantified using a sensitive and validated HPLC/MS/MS method. It was not necessary to measure concentrations of raltegravir metabolites, except for in the mass balance study, since in vitro data indicate the principal metabolites did not have any pharmacological activity predicted to be biologically relevant.

2.2.4 Exposure-response

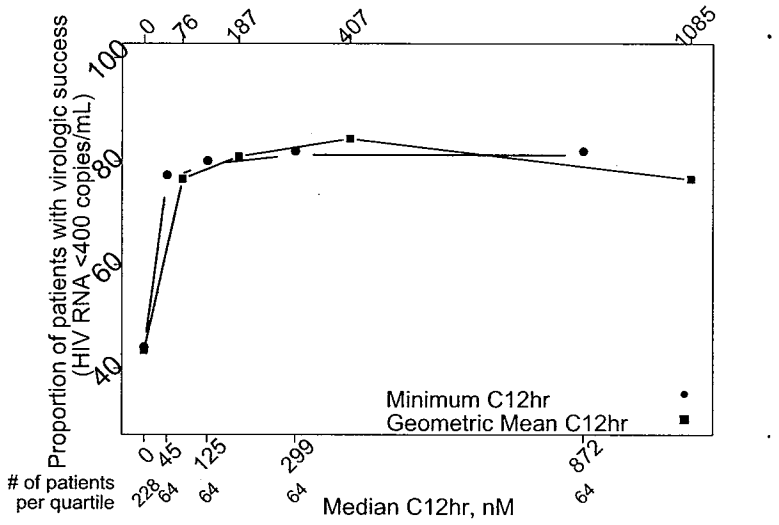
2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The data from two large double-blind placebo controlled trials (Protocols 018 and 019) in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral antiretroviral therapies were used in the exposure-response analysis. These trials were conducted using the FMI formulation, which exhibits considerable food effect on C_{12hr} (described later). A total of 483 subjects (225 raltegravir treated and 228 placebo treated) were included in the analyses. Approximately 200 subjects were excluded due to lack of sufficient PK information. Plasma trough concentrations (C_{12hr}) were used as an exposure variable. 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 postdose in a given individual); and the minimum observed C_{12hr} (determined as the minimum concentration from all samples taken between 11 and 13 hours postdose in a given individual).

Within the concentration range studied, the virologic success rate is similar (77%) for patients 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 IC_{95} ~ 50nM in 50% human serum) of raltegravir such that the exposures are in the asymptotic region of the C_{12hr} -virologic success relationship.

Figure 2.2.4.1.1 illustrates the relationship between the probability of virologic success (<400 copies/mL) and C_{12hr} (geometric mean observed C_{12hr} and minimum observed C_{12hr}). Within the concentration range studied, the C_{12hr}-virologic success relationship is shallow.

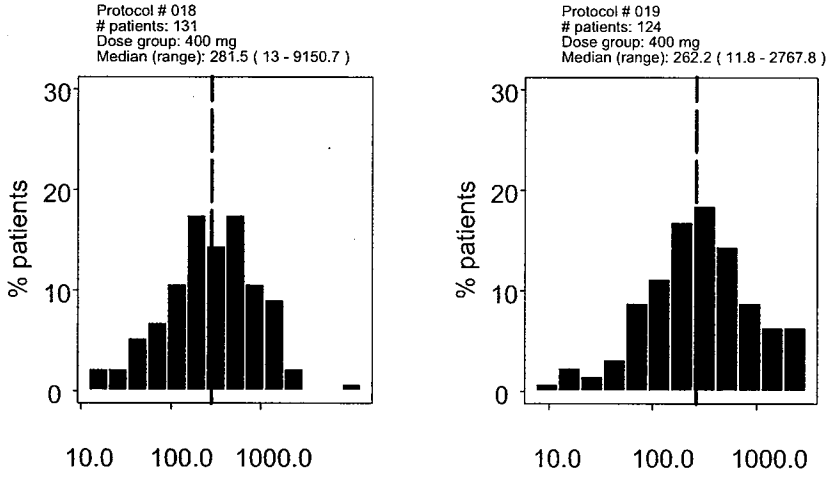
Figure 2.2.4.1.1. C_{12hr}-virologic success relationship. The C_{12hr}=0 represents placebo-treated patients; raltegravir-treated patients were divided into four quartiles.



The overall variability in C_{12hr} is considerably high, with a range of 12 to 9151 nM.

Figure 2.2.4.1.2 illustrates distribution of geometric mean observed C_{12hr} in the pivotal studies.

Figure 2.2.4.1.2. Distribution of geometric mean observed C_{12hr} (nM).



See more details in Pharmacometrics review.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In the dose-finding treatment-naïve Protocol 004 and the dose-finding treatment-experienced Protocol 005, no relationship with dose and any adverse event was observed. Safety analyses of common adverse events (AE) and laboratory abnormalities included the pooled population from the Phase 2 and Phase 3 treatment-experienced studies receiving 400 mg raltegravir twice daily or placebo in combination with an optimized background regimen (OBT). The majority of AEs were mild to moderate in intensity. The most common AEs occurring in > 10% were diarrhea, injection site reactions (due to enfuvirtide use), nausea, and headache, and were observed with similar frequency in each study arm. Adverse events that occurred at a higher frequency in raltegravir-treated subjects included: rash (5.3% versus 2.5%) and blood creatine phosphokinase increase (3.7% versus 1.1%).

See more details in Pharmacometrics review.

2.2.4.3. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed oral dose of 400 mg twice daily is consistent with the known exposure-response relationship. However, caution should be used when coadministering raltegravir with rifampin or other potent inducers of UGT1A1.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

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

After oral administration of single doses of raltegravir in healthy subjects in the fasted state, raltegravir $AUC_{0-\infty}$ and C_{max} were dose proportional over the dose range of 100 to 1600 mg (Protocol 025). Raltegravir C_{12hr} was slightly less than dose proportional over the dose range of 100 to 1600 mg. However, the variability is quite large (increasing with increasing dose levels), which implies a large degree of uncertainty in raltegravir exposure level. The apparent terminal $t_{½}$ of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. The median time to maximum plasma concentration (T_{max}) is ~3 hours in the fasted state. Typical concentration-time profiles following single dose administration of raltegravir are shown in Figure 2.2.5.1.1.

Figure 2.2.5.1.1. 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)

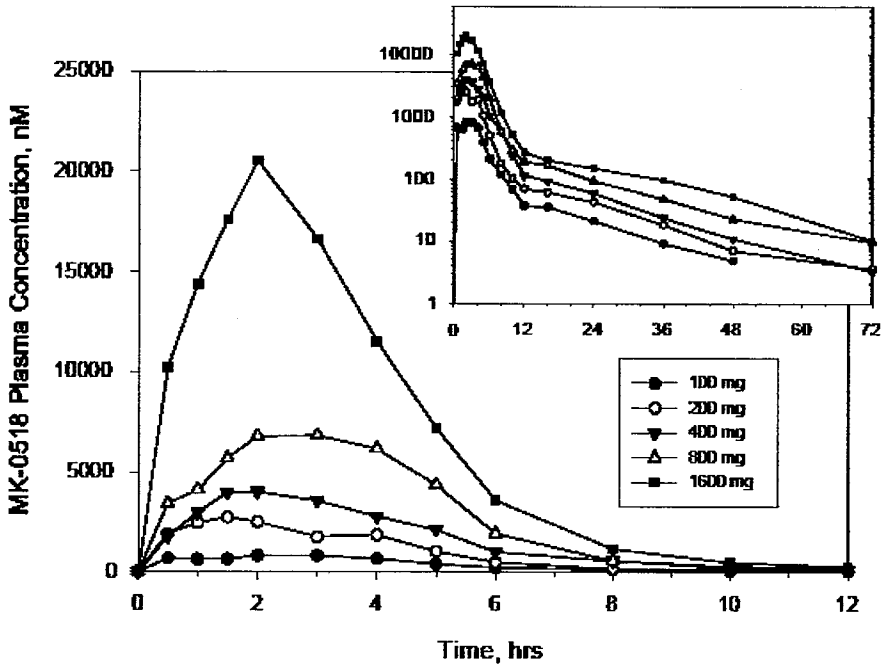


Table 2.2.5.1.1. Summary Statistics Following Single Dose Administration of 100, 200, 400, 800, or 1600 mg of the Final Market Image (FMI) Formulation of MK-0518 to Healthy, Male and Female Subjects

[redacted]

AN	T_{max} (hr)					$t_{1/2}\alpha$ (hr)					$t_{1/2}\beta$ (hr)				
	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[†]	0.88[†]	0.90[†]	0.93[†]	0.92[†]	9.0[‡]	8.7[†]	9.5[†]	10.5[†]	11.3[†]
SD	1.9	1.5	1.9	1.2	1.3	0.18[‡]	0.22[‡]	0.25[‡]	0.25[‡]	0.19[‡]	3.4[‡]	3.8[‡]	3.6[‡]	4.7[‡]	3.5[‡]
GM	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Med	3.0	3.0	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.
† Harmonic Mean; ‡Jackknife Standard Deviation.
‖ Value determined from a monoexponential rather than biexponential equation.

Figure 2.2.5.1.2. Predicted Mean Curve and Corresponding 95% Confidence Bands for MK-0518 $AUC_{0-\infty}$ Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects

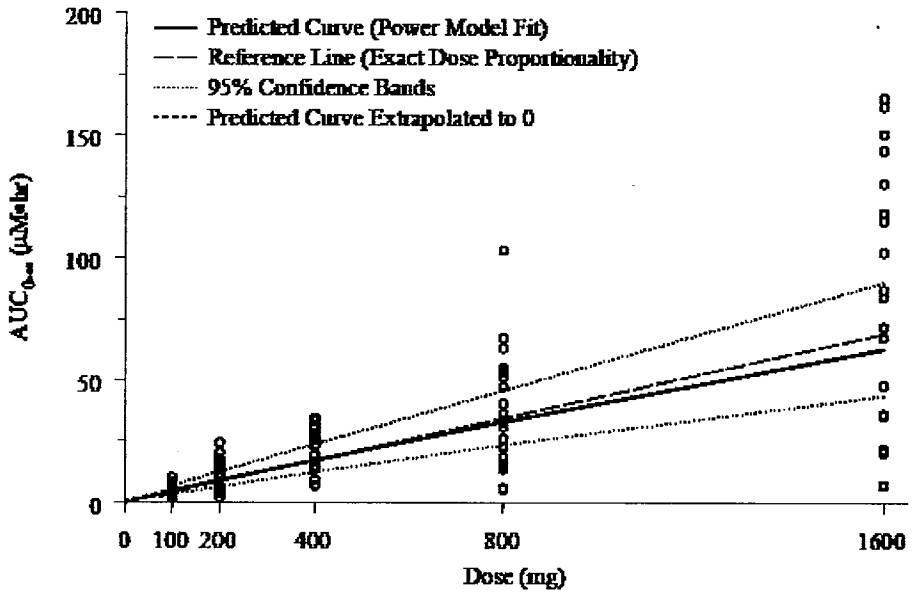


Figure 2.2.5.1.3. Predicted Mean Curve and Corresponding 95% Confidence Bands for MK-0518 C_{max} Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects

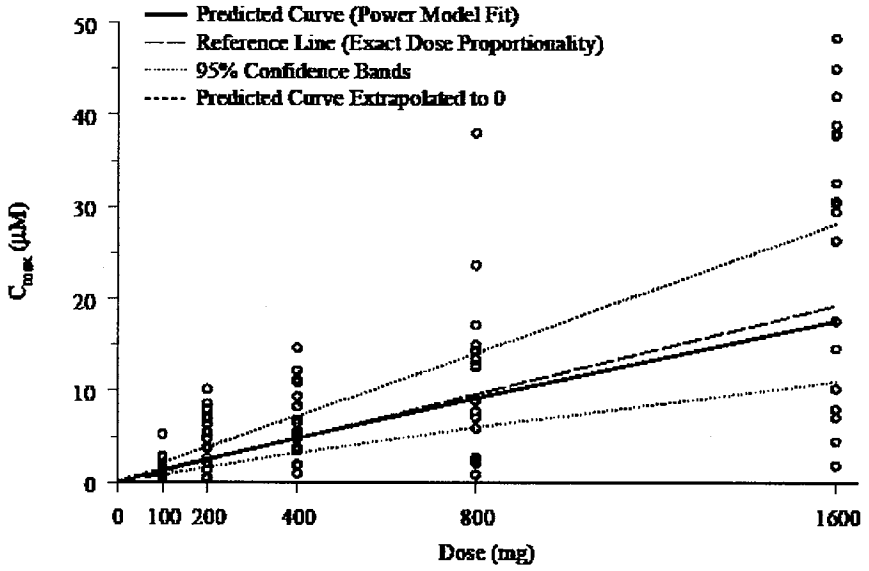
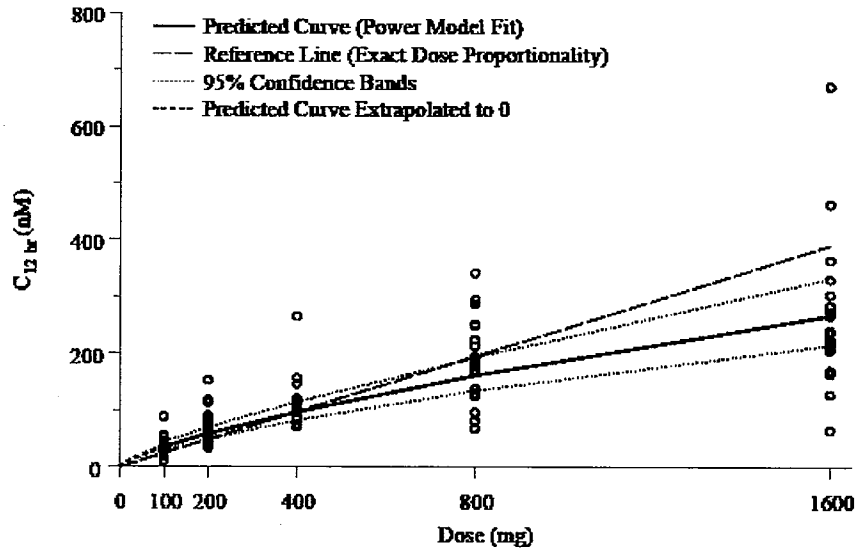


Figure 2.2.5.1.4. Predicted Mean Curve for MK-0518 $C_{12\,hr}$ Following Single Oral Dose Administration of 100 to 1600 mg MK-0518 to Healthy, Male and Female Subjects



The average accumulation ratios (steady state versus single dose) for $AUC_{0\text{-}12hr}$ and C_{max} across the dose range studied ranged from approximately 0.7 to 1.2. The average accumulation ratio for C_{12hr} ranged from approximately 1.2 to 1.6 (Protocol 001). Steady is achieved after two days of dosing at all dose levels.

2.2.5.2 How does the PK of the drug in healthy volunteers compare to that in patients?

In treatment naïve HIV-1 infected patients who received raltegravir 400 mg twice daily monotherapy (Protocol 004), raltegravir drug exposures were characterized by a geometric mean $AUC_{0\text{-}12hr}$ of 14.3 μM•hr, C_{max} of 4.5 μM and C_{12hr} of 142 nM, which are similar to exposure in healthy subjects.

Table 2.2.5.2.1. Composite Analysis of MK-0518 Pharmacokinetics Between HIV Infected and Non-HIV Infected Subjects Following Administration of MK-0518

Pharmacokinetic Parameter	Geometric Mean (95% CI) †		Geometric Mean Ratio (90% CI) †
	Patient with HIV (P)	Subject (S)	(P/S)
AUC (μM•hr)	17.1 (9.83, 29.78)	16.7 (11.06, 25.14)	1.03 (0.77, 1.36)
SD $C_{12\,hr}$ (nM)	NA	133.9 (98.76, 181.42)	
MD $C_{12\,hr}$ (nM)	196.6 (125.99, 306.66)	178.1 (109.52, 289.51)	1.10 (0.67, 1.81)
C_{max} (μM)	4.2 (2.02, 8.76)	3.7 (2.17, 6.43)	1.13 (0.78, 1.64)

2.2.5.3 What are the characteristics of drug absorption?

Raltegravir T_{max} occurs at ~3 hours at the dose of 400 mg in the fasted state. A definitive bioavailability study was not conducted.

A high-fat meal, on average, resulted in a 19% increase in AUC, 34% decrease in C_{max}, 750% increase in C_{12hr} and 7.3 hour delay in T_{max} with raltegravir final market image formulation (Protocol 028) (See General Biopharmaceutics section).

Raltegravir is an avid P-gp substrate, which can decrease drug absorption.

2.2.5.4 What are the characteristics of drug distribution?

Raltegravir is approximately 83% bound to human plasma proteins and is minimally distributed into red blood cells (blood-to-plasma partitioning ratio of 0.6). No data are available regarding human central nervous system (CNS) or brain penetration. Raltegravir is a substrate of human P-gp in vitro, which may limit CNS penetration in humans.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Following administration of a single dose of 200 mg [^{14}C] raltegravir to young healthy subjects (Protocol 011), approximately 83.0% of the radioactivity dose was recovered, with 51.1% in feces and 31.8% in urine over a 10-day period. Raltegravir accounted for approximately 69% of the radioactivity in plasma. Parent compound and the glucuronide derivative M2 were the only radioactive species detected in plasma. In fecal extracts, the only detectable radioactive peak represented the parent compound (51% of the radioactive dose); however, fecal radioactivity may represent excreted glucuronide that was back-converted to parent after biliary excretion. In urine, M2 was the primary species detected (23% of radioactive dose) in addition to 9% of radioactive dose from parent compound. The data collectively indicate hepatic clearance via glucuronidation plays a major role in the clearance of raltegravir in humans and renal clearance of unchanged drug is a minor pathway of elimination of raltegravir.

2.2.5.6 What are the characteristics of drug metabolism?

Metabolism via glucuronidation is the major pathway of elimination of raltegravir. In humans, raltegravir is metabolized via a single pathway, which results in the formation of the phenolic hydroxyl glucuronide derivative of the parent compound (See Section 2.4.2.1). In a human ADME study, the major circulating entity in plasma was the parent compound (69% of the total drug related material in plasma), while most of the drug related material in urine was accounted for by the glucuronide derivative (72% of the drug related material in urine). In feces, only parent compound was detected, but it is likely a good fraction of the raltegravir detected in feces is derived from hydrolysis of the glucuronide derivative secreted in bile, as observed in preclinical species.

Data from in vitro studies using human biomaterials indicated UGT1A1 is the main enzyme responsible for formation of the glucuronide derivative of raltegravir. Therefore, it can be concluded that the major mechanism of clearance of raltegravir in humans is glucuronidation mediated by UGT1A1.

2.2.5.7 What are the characteristics of drug excretion?

See Section 2.2.5.5. The ADME results indicate that renal clearance of unchanged drug is a minor pathway of elimination of raltegravir (9% of total dose). The observed renal clearance values (60.9 ± 10.6 mL/min, arithmetic mean ± SD) for raltegravir are somewhat higher than the value that would be anticipated based on filtration alone (fu x GFR = 0.17 x 120 mL/min = 20 mL/min), implying raltegravir may be actively excreted into urine.

2.2.5.8 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Considerable variability was observed in the pharmacokinetics of raltegravir. For observed $C_{12\ hr}$ in Phase 3 trials, the coefficient of variation (CV) for inter-subject variability = 212% and the CV for intra-subject variability = 122%.

Table 2.2.5.8.1. Pooled Variability Estimates (Log-Scale) for MK-0518 AUC (μM•hr) and C_{12hr} (nM) From Phase 1 Studies Using the Phase II/III/FMI Poloxamer Formulation

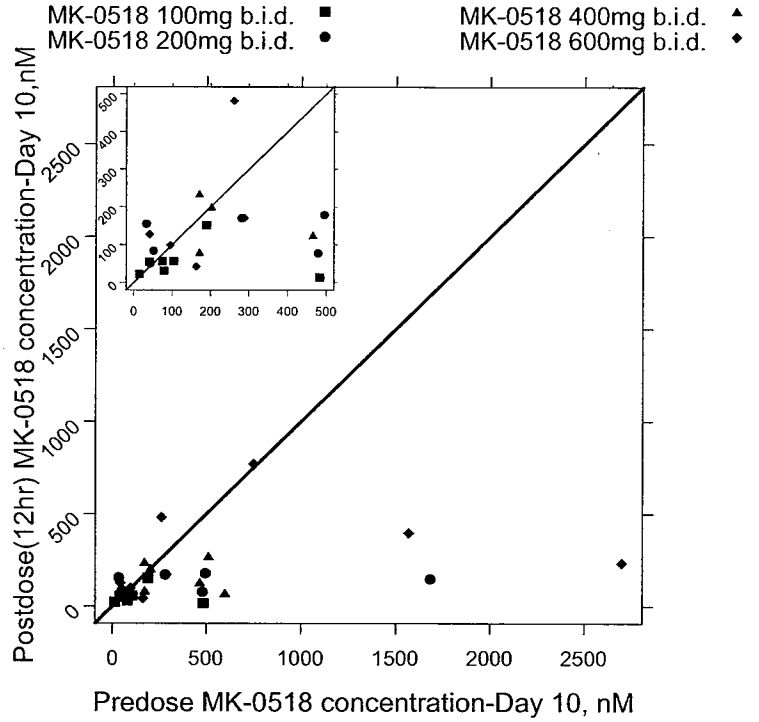
Dosing Regimen	Food Status	N	AUC[†] Between-Subject Variances	C_{12hr} Between-Subject Variance
Single Dose	Fed	20	0.350	1.016
	Fasted	162	0.439	0.179
Multiple Dose	Fed	19	0.681	1.873
	Fasted	15[‡]	0.715	0.405

[†] $AUC_{0-\infty}$ for single dose and AUC_{0-12hr} for multiple dose regimens.
[‡] N=14 for C_{12hr}

The high pharmacokinetic variability observed across the clinical studies could be due to the combination of the following factors: high variability in hepatic UGT1A1 protein expression levels (>50-fold) from human liver samples, UGT1A1 polymorphism, high variability in intestinal P-gp expression levels, pH-dependent solubility and food effect.

Figure 2.2.5.8.1 illustrates the within-subject variability in raltegravir 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. The diagonal line in the graph represents the "line of unity". If low within subject variability was observed, data points would fall on or near the line. High within subject variability is demonstrated by the lack of correlation between pre-dose and post-dose trough concentrations.

Figure 2.2.5.8.1. Within subject variability in raltegravir trough concentrations
(Inset: Data within 0–500 nM)



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2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? What dosage regimen adjustments are recommended for each of these groups?

The effects of HIV status, age, gender, weight, and race on raltegravir pharmacokinetics were assessed by evaluation of raltegravir plasma trough concentrations in Phase 2/3 trials. The data indicate age, gender, weight, race and HIV status did not have an impact on raltegravir exposure.

UGT1A1 Polymorphysm

Protocol 013 is a single-dose, open-label study in healthy subjects with UGT1A1*1/*1 and UGT1A1*28/*28 genotypes. A total of 57 subjects are to receive a 400-mg single oral dose of MK-0518 Phase II/III/FMI poloxamer formulation in a fasted state. There were 30 subjects in the UGT1A1 *28/*28 group and 27 subjects in the UGT1A1*1/*1 group. The applicant did not submit the final study report yet. The preliminary analysis indicates the geometric mean ratio and corresponding 90% confidence intervals for the comparison of UGT1A1*28/*28/UGT1A1*1/*1 for MK-0518 AUC was 1.41 (0.96, 2.09), for C_{max} was 1.40 (0.86, 2.28), and for C_{12hr} was 1.91 (1.43, 2.55). These data indicate that individuals who are homozygous for the UGT1A1*28 polymorphism have a modest increase in MK-0518 plasma concentrations relative to wild-type. However, considerable variability was observed in both UGT1A1*28/*28 and UGT1A1*1/*1 groups. We will review the impact of UGT1A1 polymorphism on raltegravir pharmacokinetics when the final study report is submitted by the applicant.

Hepatic Insufficiency

In an open-label, single-dose study (Protocol 014), 8 subjects with moderate hepatic insufficiency (a score of 7 to 9 on the Child Pugh scale) and 8 healthy matched control subjects were enrolled. Each subject received a single 400-mg dose of raltegravir in the fasted state. Overall, there was no clinically important effect of moderate hepatic insufficiency on the raltegravir pharmacokinetic profile. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.

Table 2.3.1.1 Mean MK-0518 Plasma Pharmacokinetic Parameter Values Following Administration of Single Oral Doses of 400-mg MK-0518 Phase II/III/FMI Formulation to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects (Protocol 014)

Pharmacokinetic Parameter	N	Hepatic Insufficiency		Healthy Subjects		Hepatic Insufficiency / Healthy Subjects	
		GM	95% CI for GM	GM	95% CI for GM	GMR	90% CI for GMR
$AUC_{0-\infty}$ (μM·hr)†	8	17.67	(8.93, 34.99)	20.66	(10.29, 41.47)	0.86	(0.41, 1.77)
C_{max} (μM)†	8	4.41	(1.74, 11.20)	6.99	(2.70, 18.09)	0.63	(0.23, 1.70)
$C_{12\,hr}$ (nM)†	8	143.4	(77.3, 266.1)	113.8	(60.6, 213.8)	1.26	(0.65, 2.43)
T_{max} (hr)	8	2.5‡	N/A	1.5‡	N/A	0.4§	(-1.0, 1.5)§
$t_{½}$ α (hr)	8	1.49‡	N/A	1.12‡	N/A	0.26§	(-0.15, 0.74)§
$t_{½}$ β (hr)	8	7.0‡	N/A	9.3‡	N/A	-1.9§	(-7.7, 6.8)§

† Geometric mean computed from least squares estimate from an ANCOVA performed on the natural-log transformed values, with fixed effect terms for hepatic status, age, gender, and Body Mass Index.
‡ Median reported for T_{max}. Harmonic mean reported for half-life.
§ Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference.
GM=Geometric Mean. GMR=Geometric Mean Ratio. CI=Confidence Interval. N/A=Not applicable.

Renal Insufficiency

In an open-label, single-dose study (Protocol 015), the applicant compared raltegravir pharmacokinetics in 10 subjects with severe renal insufficiency (defined as 24-hour creatinine clearance of <30 mL/min/1.73 m^2) to pharmacokinetics in 10 healthy matched control subjects (race, age, gender, and BMI). Each subject received a single 400 mg dose of raltegravir in the fasted state. The geometric mean ratio (renally impaired/healthy controls) for raltegravir $AUC_{0-\infty}$ was 0.85, with a corresponding 90% confidence interval of (0.49, 1.49). Overall, there was no clinically important effect of severe renal insufficiency on the raltegravir pharmacokinetic profile. No dosage adjustment is recommended for patients with renal insufficiency.

Table 2.3.1.2 Mean MK-0518 Plasma Pharmacokinetic Parameter Values Following Administration of Single Oral Doses of 400-mg MK-0518 Phase II/III/FMI Formulation to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects (Protocol 015)

Pharmacokinetic Parameter	N	Renally Impaired		Healthy Subjects		Renally Impaired / Healthy Subjects	
		Geometric Mean	95% CI for GM	Geometric Mean	95% CI for GM	Geometric Mean Ratio	90% CI for GMR
$AUC_{0-\infty}$ (μM·hr)†	10	16.80	(9.96, 28.35)	19.70	(11.84, 32.76)	0.85	(0.49, 1.49)
C_{max} (μM)†	10	3.85	(2.06, 7.20)	5.68	(3.09, 10.43)	0.68	(0.35, 1.32)
$C_{12\,hr}$ (nM)†	10	135.0	(85.9, 211.9)	105.5	(68.0, 163.7)	1.28	(0.79, 2.06)
T_{max} (hr)	10	3.5‡	N/A	3.0‡	N/A	0.0§	(-1.5, 1.0)§
$t_{½}$ α (hr)	10	1.38‡	N/A	1.10‡	N/A	0.26§	(0.03, 0.46)§
$t_{½}$ β (hr)	10	17.2‡	N/A	11.4‡	N/A	5.8§	(1.2, 10.4)§
f_e (%)	10	0.5‡	N/A	4.1‡	N/A		
Cl_R (mL/min)	10	2.7‡	N/A	31.5‡	N/A		

† Geometric mean computed from least squares estimate from an ANCOVA performed on the natural-log transformed values, with fixed effect terms for renal status, age, gender, and Body Mass Index.
‡ Median reported for T_{max}. Harmonic mean reported for half-life. Arithmetic mean reported for percent dose in urine and renal clearance.
§ Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference.
GM=Geometric Mean. GMR=Geometric Mean Ratio. CI=Confidence Interval. CL=Clearance. N/A=Not applicable.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure -response and what is the impact of any differences in exposure on response?

See food effect in General Biopharmaceutics Section. Drug interactions are discussed below.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any in vitro basis to suspect in vivo drug-drug interactions?

Yes. The in vitro metabolism of MK-0518 was studied in human hepatic microsomes and hepatocytes. No significant metabolism of MK-0518 was observed in NADPH-fortified microsomal incubations. MK-0518 underwent metabolism in hepatocytes, with the major metabolite being the glucuronide derivative of the parent compound (M2). The data indicate glucuronidation of the parent compound is the major metabolic pathway in humans and MK-0518 is not a substrate of cytochrome P450 enzymes. In studies using cDNA-expressed UGTs, MK-0518 (5 μM and 50 μM) was converted to M2 by UGT1A1, 1A3, and 1A9 but not by UGT1A4, 1A6, 1A7, 1A8, 1A10, 2B4, 2B7, 2B15, and 2B17. The formation of M2 correlated highly with estradiol 3-glucuronidation (marker for UGT1A1 activity), while correlation with 2 other UGT marker activities was weak (UGT1A4 and UGT1A9). Formation of M2 in pooled human liver microsomes was inhibited by typical UGT1A1 substrates, bilirubin and estradiol. In addition, atazanavir (a selective UGT1A1 inhibitor) inhibited the glucuronidation of MK-0518 with an IC_{50} of 0.5 μM. However, no inhibitory effect was observed for imipramine, an inhibitor for UGT1A3 and 1A4. The data collectively demonstrate that the glucuronidation of MK-0518 is mainly catalyzed by UGT1A1 with a minor contribution from UGT1A9 and 1A3.
MK-0518 is also a P-gp substrate.

2.4.2.2. Is the drug a substrate of CYP enzymes and UGT enzymes? Is metabolism influenced by genetics?

Raltegravir is not a substrate of CYP enzymes but it is a UGT1A1 substrate. UGT1A1 is a polymorphic enzyme. A single-dose, open-label study in healthy subjects with UGT1A1*1/*1 and UGT1A1*28/*28 genotypes is ongoing.

2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes and UGT enzymes?

No. The non-preincubation-dependent inhibitory potential of MK-0518 towards 7 human liver microsomal cytochromes P450 was evaluated in vitro. At concentrations of up to 100 μM, MK-0518 was found not to be a potent inhibitor (IC_{50} >100 μM) of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6. The potential of MK-0518 to induce CYP3A4 was evaluated in cultures of primary human hepatocytes. MK-0518 (up to 10 μM) did not induce CYP3A4 RNA expression or CYP3A4-dependent testosterone 6β-hydroxylase activity, indicating that MK-0518 has no potential to induce CYP3A4 in humans.

The potential for MK-0518 to inhibit UGT1A1 or UGT2B7 was evaluated in vitro using human liver microsomes. The drug was added at various concentrations (0.07 to 50 μM) to a reaction mixture containing human liver microsomes, UDPGA and a UGT marker substrate - estradiol (UGT1A1) and AZT (UGT2B7), both of which were used at a concentration of 100 μM. The IC_{50}

values were >50 µM for both UGT activities. Therefore, MK-0518 is not a potent inhibitor of UGT1A1 or UGT2B7.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The [redacted] of MK-0518 (5 µM) was evaluated in [redacted] cells that express human P-glycoprotein (P-gp). Directional transport studies of MK-0518 yielded transport ratios (B-A/A-B ratio) of 11.1 in LLC-PK1 cells expressing human (L-MDR1) P-gp, indicating that MK-0518 is a substrate of P-gp in humans. MK-0518 was evaluated as a potential inhibitor of P-gp in humar. [redacted] cells. Over a concentration range of 1 to 100 µM MK-0518 did not affect [^{3}H]-vinblastine accumulation in [redacted] indicating MK-0518 is not an inhibitor of human P-gp.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

No study was conducted to evaluate other transporter pathways.

2.4.2.6. Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The proposed label indicates combination of raltegravir with other antiretroviral agents (optimized background therapy). Yes, the interaction potential between raltegravir and these drugs has been evaluated either in vitro and/or in vivo. See Sections 2.4.2.7 and 2.4.2.8 for details.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

In addition to other antiretroviral drugs (optimized background therapy), raltegravir is expected to be coadministered with drugs to treat opportunistic infections and side effects of antiretroviral agents, and other common medications such as statins, antidepressants, antipsychotic agents, cardiac drugs, including calcium channel blockers, antiarrhymics, hormonal contraceptives, sedative/hypnotics, warfarin, anticonvulsants, antifungals, erectile dysfunction agents, methadone, anti-diabetic agents and macrolide antibiotics. The interaction potential between raltegravir and these drugs has been evaluated either in vitro and/or in vivo. See Section 2.4.2.8 for details.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Raltegravir is unlikely to significantly alter plasma exposure of co-administered drugs that are metabolized by cytochrome P450 enzymes, UGT enzymes and P-gp. Raltegravir is a UGT1A1 and P-gp substrate. Thus coadministered drugs that affect UGT1A1 and P-gp activity could affect raltegravir pharmacokinetics.

<u>Effects of Other Drugs on Raltegravir</u>

Raltegravir is a UGT1A1 and P-gp substrate. Because raltegravir will be coadministered with drugs that affect UGT1A1 and P-gp activity, such as atazanavir, the effects of drugs on

raltegravir pharmacokinetics were studied in Phase I clinical trials. Table 2.4.2.8.1 summarizes the effect of other drugs on raltegravir.

Table 2.4.2.8.1. Summary of the Effect of Other Drugs on Raltegravir					
Co-administered drug and dose	N	Study Design	Ratio (90% CI) of raltegravir pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC_{tau}	Cmax
UGT1A1 Inhibitors					
Atazanavir 400 mg QD	10	SD/MD	1.95 (1.30, 2.92)	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)
Atazanavir/ritonavir 300/100 mg QD	10	MD/MD	1.77 (1.39, 2.25)	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)
UGT1A1 Inducers					
Ritonavir	10	SD/MD	0.99 (0.70, 1.40)	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)
Efavirenz 600 mg QD	10	SD/MD	0.79 (0.49, 1.28)	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)
Rifampicin 600 mg QD	10	SD/MD	0.39 (0.30, 0.51)	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)
Tipranavir/ritonavir 500/200 mg BID	18	MD/MD	0.45 (0.31, 0.66)	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)
TMC125 (A new NNRTI; NDA under review) 200 mg BID	20	MD/MD	0.66 (0.34, 1.26)	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)
Other Drugs					
Tenofovir 300 mg BID	10	MD/MD	1.03 (0.73, 1.45)	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)

SD/MD=Single dose administration of raltegravir and multiple dose administration of the other agent; MD/MD=Multiple dose administration of raltegravir and the other agent.

The applicant proposes 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. Our review indicates these cut-off values are acceptable.

The effect of ritonavir (100 mg twice-daily) on the pharmacokinetics of raltegravir is not significant. The observed results may be due to counteracting effects of ritonavir on UGT1A1 (induction) and on P-gp (inhibition). Ritonavir is a potent UGT1A1 inducer and a P-gp inhibitor, and raltegravir is a dual substrate of UGT1A1 and P-gp.

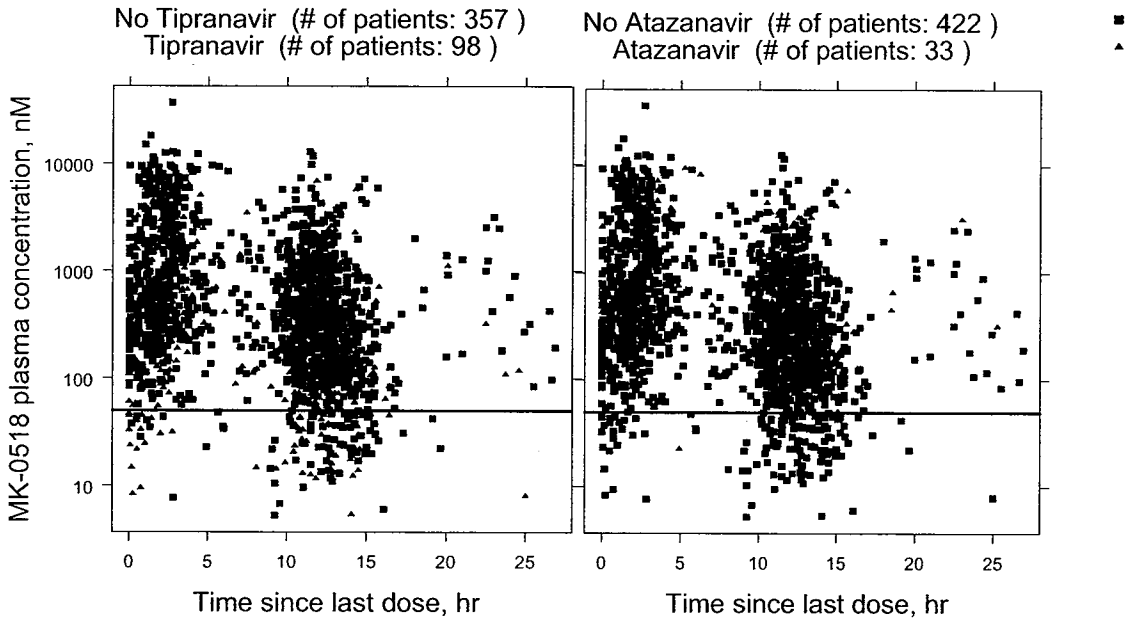
As anticipated, raltegravir plasma levels were increased with coadministration with atazanavir alone and in combination with ritonavir, which is consistent with inhibition of UGT1A1. However, concomitant use of raltegravir and atazanavir was well tolerated in the Phase 2 and Phase 3 studies. Based on these data, atazanavir may be coadministered with raltegravir without dose

adjustment of raltegravir. The current intended treatment population for raltegravir, treatment experienced patients, should only receive atazanavir/ritonavir.

Tipranavir/ritonavir decreased raltegravir C_{12hr} by 55%, $AUC_{0\text{-}12hr}$ by 24% and C_{max} by 18%. Approximately 100 patients received raltegravir in combination with tipranavir/ritonavir in Phase 3 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 raltegravir without dose adjustment of raltegravir.

Figure 2.4.2.8.1 illustrate the high variability in raltegravir C_{12hr} 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 pharmacokinetic variability. The Phase 1 drug interaction studies indicated atazanavir/ritonavir increased raltegravir C_{12hr} by 77% and 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 is similar.

Figure 2.4.2.8.1. 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 entire trial duration.



Rifampicin decreased raltegravir C_{12hr} by 61%, $AUC_{0\text{-}12hr}$ by 40% and C_{max} by 38%. Rifampicin, phenytoin and phenobarbital were prohibited in raltegravir Phase 2 and 3 trials thus no clinical experience is available with regards to co-administration of raltegravir with rifampicin, phenytoin and phenobarbital. Therefore, caution should be used when coadministering raltegravir with

rifampin or other potent inducers of UGT1A1. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used with the recommended dose of raltegravir.

Effects of Raltegravir on Other Drugs

Raltegravir is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes, UGT enzymes or P-gp based on in vitro results.

Table 2.4.2.8.2. Summary of the Effect of Raltegravir on Other Drugs					
Co-administered drug and dose	N	Study Design	Ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC_{tau}	Cmax
TMC125 200 mg BID	20	MD/MD	1.17 (1.10, 1.26)	1.10 (1.03, 1.16)	1.04 (0.97, 1.12)
Tenofovir 300 mg BID	10	MD/MD	0.87 (0.74, 1.02)	0.90 (0.82, 0.99)	0.77 (0.69, 0.85)
Midazolam 2.0 mg	10	MD/SD	ND	0.92 (0.82, 1.03)	1.03 (0.87, 1.22)

MD/SD=Single dose administration of the other agent and multiple dose administration of raltegravir; MD/MD=Multiple dose administration of raltegravir and the other agent.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No.

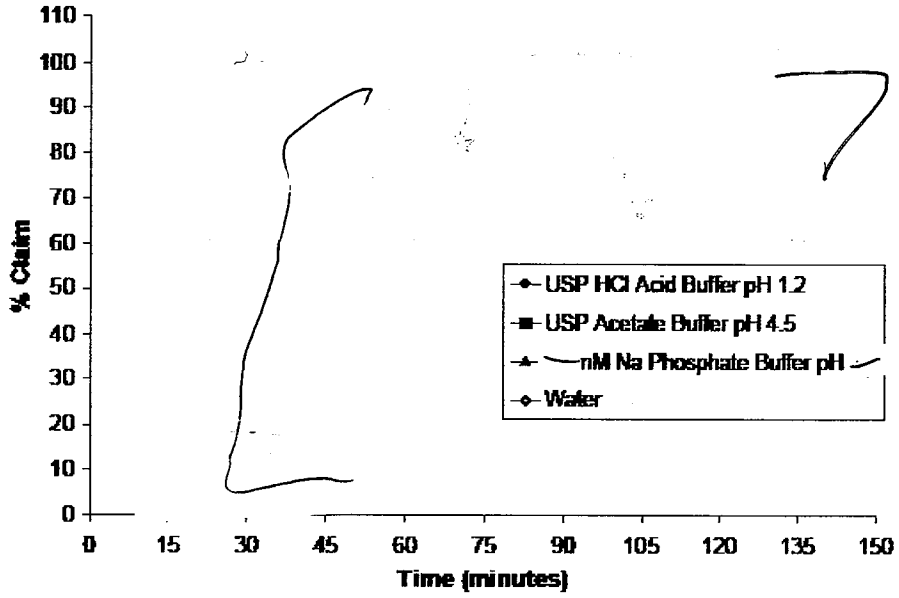
2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Raltegravir is classified as "low solubility" Although highly soluble in unbuffered water (mg/mL), MK-0518 is only sparingly soluble at a pH of and below (mg/mL at pH and mg/mL at pH . The apparent in vitro permeability (Papp) of MK-0518 across

(Papp = , and MK- 0518 is thus classified as having low permeability. The compound is therefore classified as a BCS class IV compound (low permeability and low solubility at physiological pH).

Figure 2.5.1.1. Dissolution Profiles of MK-0518 400-mg Tablets in Buffer Media at pH 1.2, 4.5, and Compared with Water Using USP Apparatus II at 100 rpm



2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The final to-be-marketed formulation was used in Phase 2 and Phase 3 trials. Thus no BA/BE study was conducted to compare the relative bioavailablity of the final to-be-marketed formulation to earlier formulations used in Phase 1 studies.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A high-fat meal, on average, resulted in a 19% increase in AUC, 34% decrease in C_{max}, 750% increase in C_{12hr} and 7.3 hour delay in T_{max} with raltegravir final market image formulation (Protocol 028). Thus, the data indicate meals decrease the rate of absorption of raltegravir for the FMI formulation, while the overall extent of absorption was relatively unchanged except for a large increase in C_{12hr}. However, the food effect is variable between subjects.

Based on the results from the high-fat meal study and the fact that raltegravir was dosed with or without food in Phase 2 and Phase 3 trials, raltegravir can be taken with or without food.

Figure 2.5.3.1. 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)

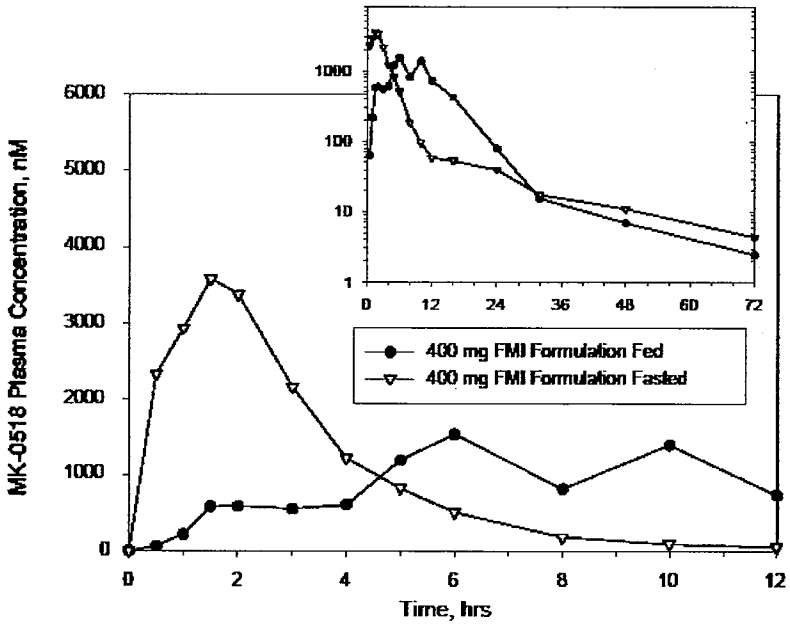


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Figure 2.5.3.2 illustrates the results of a food effect on raltegravir C_{12hr} study using the FMI formulation. As noted earlier, a high fat meal appeared to slow the rate of absorption of raltegravir, resulting in an approximately 34% decrease in Cmax, a 750% increase in C_{12hr}, and a median 7.3 hour delay in Tmax. The food effect was not observed with Phase I formulations.

Figure 2.5.3.2. Food decreases the rate of absorption but does not affect the extent of absorption. Panel 1: Individual AUC under fed and fasted conditions; Panel 2: Individual C12hr under fed and fasted conditions; Panel 3: Concentration time profile of four representative subjects.

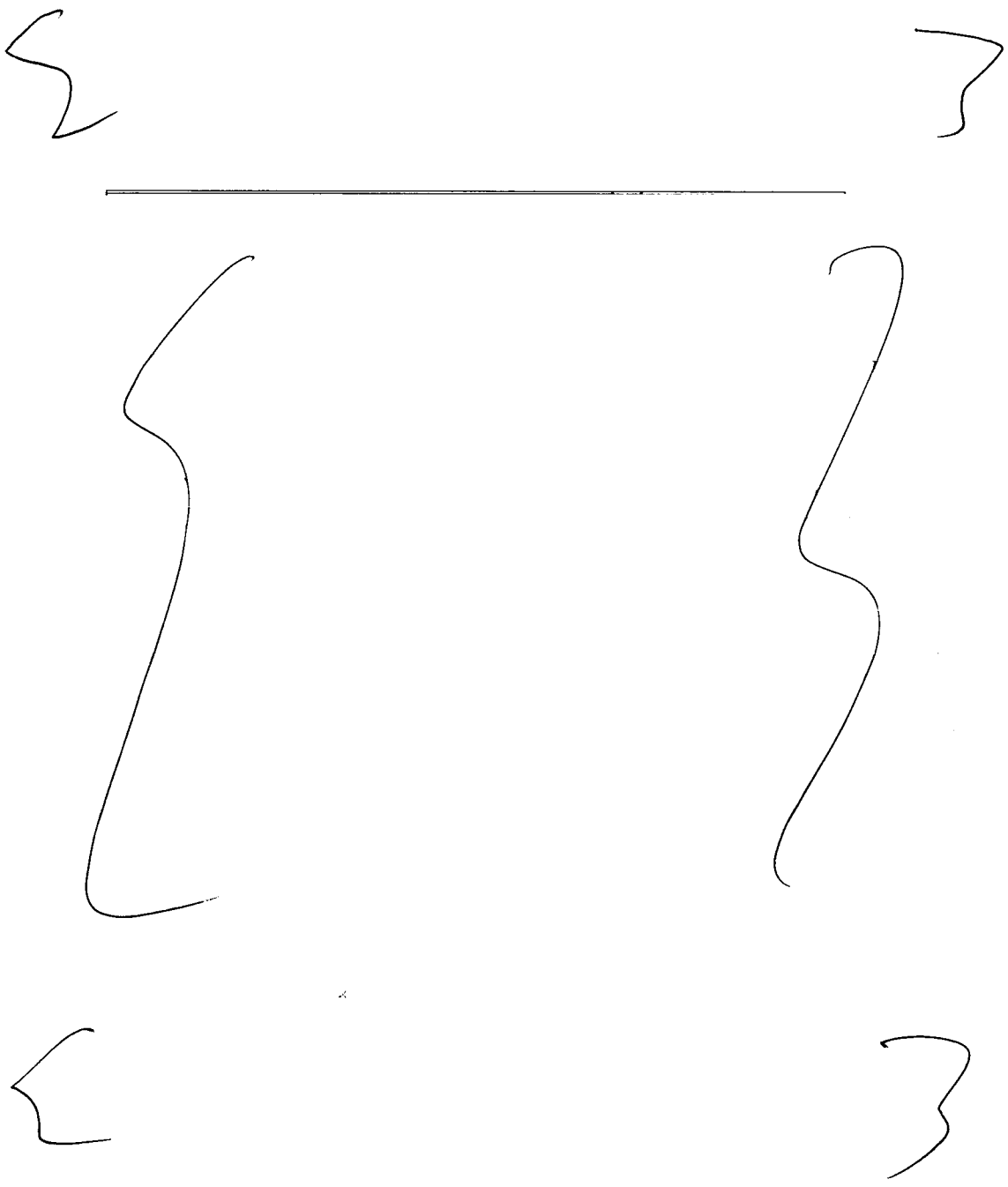
The dosing in pivotal studies was done without regard to food. Thus, over the course of the trials (018 and 019), day-to-day variability is likely influenced by variability in food intake. In other words, a given patient could have 8 fold higher C_{12hr} depending on whether the dose was taken with a meal or under fasted conditions.

A study to investigate the effects of low, moderate, and high-fat meals on multiple dose pharmacokinetics of raltegravir in healthy volunteers is ongoing. The applicant initiated the study without FDA request. The information will complete the full picture of food effects, but the study will likely not change the recommendation that raltegravir could be administered with or without food.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?

Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations. A brief overview of these assays, together with a summary of their analytical figures of merit is presented below.



2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because protein binding of raltegravir (83%) is independent of concentration, total raltegravir concentrations were measured in the clinical pharmacology studies.

13 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

4. APPENDICES

4.1 INDIVIDUAL STUDY REVIEW

Protocol 001

TITLE: A Sequential, 2-Part, Double-Blind, Placebo-Controlled, Single-Rising-Dose and Serial-Panel, Rising-Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-0518 in Healthy Male Subjects

OBJECTIVES: To evaluate the safety, tolerability and pharmacokinetics of single and multiple-rising oral doses of MK-0518 in healthy young male volunteers under fasted conditions and to evaluate food effect (a moderate-fat or standard high-fat breakfast) on a single oral dose of MK-0518.

SUBJECTS AND STUDY DESIGN: This was a sequential, 2-part study.

Fifty-eight (58) healthy male subjects between 18 and 45 years of age were enrolled into the study and 56 subjects completed the study per protocol. Two (2) subjects were discontinued, one in Part I and one in Part II of the study.

Part I was a double-blind, placebo-controlled, alternating-panel, multiple-period, single-rising-dose study in healthy young male subjects. Panels A and B alternately received single-rising oral doses of MK-0518 or placebo for Periods 1 through 5 starting with Panel A. Each panel consisted of 8 subjects. Six subjects received active drug and 2 subjects received placebo. Subjects in Panel A were given single doses of 10, 50, 200, and 800 mg of MK-0518 or placebo in the fasted state. In Period 5, Panel A, subjects were given a second oral dose of 200 mg MK-0518 or placebo following a moderate-fat breakfast in order to assess the effect of food on the plasma concentration profile of MK-0518 compared to that obtained in the fasted condition. Subjects in Panel B were given single doses of 25, 100, 400, and 1200 mg of MK-0518 or placebo in the fasted state. In Period 5, Panel B, subjects were given a second oral dose of 100 mg MK-0518 or placebo following a standard high-fat breakfast in order to assess the effect of food on the plasma concentration profile of MK-0518 compared to that obtained in the fasted condition. In each treatment period, 2 different subjects received placebo for each dose level according to a randomized allocation schedule. However, for Panel A Period 3 and Panel B Period 2, the same 2 subjects who received placebo also received placebo for their repeat dose in treatment Period 5. This permitted an intra-subject comparison of the effect of food on the pharmacokinetic profile of MK-0518. A third panel (Panel E) of 8 additional subjects followed in treatment Period 6 and received a single oral dose of 1600 mg of MK-0518 or placebo in the fasted state. Subjects who participated in Panel E for Part I went on to participate in Panel E for Part II of this study. The same 2 subjects received placebo in Panel E for both Parts I and II of this study. There was at least a 7-day washout between treatment periods for any individual subject. There was at least a 3-day washout between dose escalation.

Summary of Part I Treatment Schematic

Panel†	Period 1		Period 2		Period 3		Period 4		Period 5		Period 6
A	10 mg		50 mg		200 mg		800 mg		200 mg w/food		
B		25 mg		100 mg		400 mg		1200 mg		100 mg w/food	
E‡											1600 mg

† In each panel, 6 subjects will be randomized to receive MK-0518 and 2 subjects to receive placebo.
‡ The same 8 subjects will participate in Panel E of Part II of this study.

Part II was a double-blind, randomized, placebo-controlled, serial-panel, rising-multiple-dose study. Five panels (Panels A, B, C, D, and E) consisted of 8 subjects each who received 100, 200, 400, 600, and 800 mg of MK-0518 or placebo administered twice daily (q12 hr) for 10 consecutive days. Two out of

the 8 subjects in each panel received placebo instead of MK-0518 according to a randomized allocation schedule. The subjects in Panel E participated in both Parts I and II of this study.

Summary of Part II Treatment Schematic

Treatment Schematic					
Panel A	100 mg q12 hr X 19 doses or Placebo				
Panel B		200 mg q12 hr X 19 doses or Placebo			
Panel C			400 mg q12 hr X 19 doses or Placebo		
Panel D				600 mg q12 hr X 19 doses or Placebo	
Panel E					800 mg q12 hr X 19 doses or Placebo
In each panel, 6 subjects received active drug and 2 received placebo.					

There were no known critical Good Clinical Practices deficiencies noted during the course of the study.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 Phase I Lactose formulation: 5, 25, 100, 200 tablets and placebo 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. Urine samples were also obtained for the concentrations of MK-0518. Urine samples were collected at 0-4, 4-8, 8-12 and 12-24 hours postdose.

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

PHARMACOKINETIC DATA ANALYSIS:

The plasma pharmacokinetic profile (e.g., AUC, Cmax, C12 hr, Tmax, and apparent t½) of MK-0518 was calculated for each subject at each dose in Part I of this study. In Part II, the plasma pharmacokinetic profile (e.g., AUC, Cmax, C12 hr, Tmax, apparent t½, and accumulation ratios) of MK-0518 was calculated for each subject after multiple dose administration of MK-0518.

The urinary pharmacokinetic profile of MK-0518 was calculated for each subject at each dose level.

PHARMACOKINETIC RESULTS:

Single-Dose Pharmacokinetics of MK-0518 (Part I)

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations (nM) Versus Time (hr) Following Single-Dose Administration of 10 to 1600 mg MK-0518 in the Fasted State to Young, Healthy, Male Subjects (inset: semilog scale)

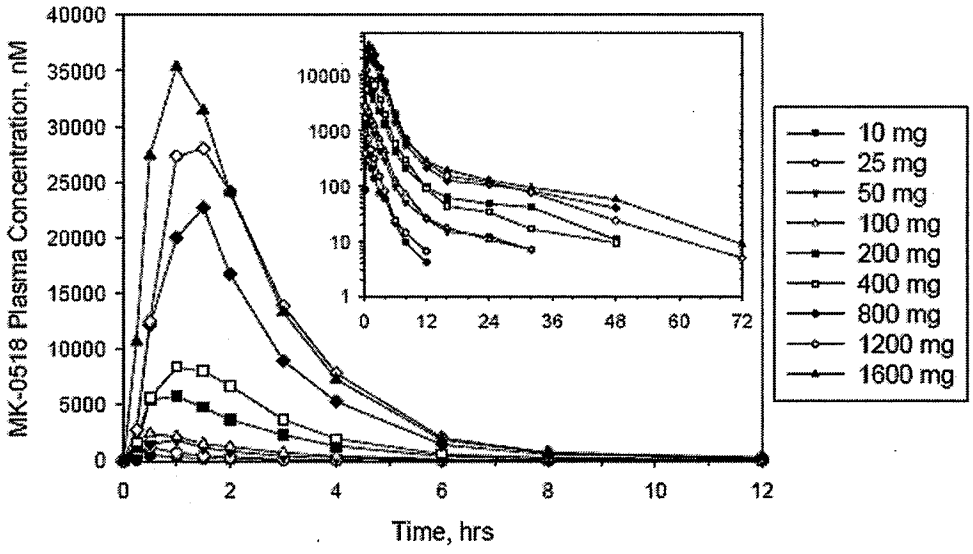


Table 1. Geometric Means and Confidence Intervals for MK-0518 C_{12hr} (nM) Following Fasted Administration of Single Oral Doses to Young, Healthy, Male Subjects

Treatment	N	Geometric [1] Mean	90% Confidence Interval [1] for Geometric Mean
10 mg	6	3.8	(2.8, 5.1)
25 mg	6	4.8	(3.6, 6.4)
50 mg	6	20.8	(15.4, 28.1)
100 mg	6	27.4	(20.3, 36.9)
200 mg	6	85.3	(63.2, 115.2)
400 mg	6	81.3	(60.3, 109.4)
800 mg	6	206.9	(153.4, 279.1)
1200 mg	6	241.7	(179.4, 325.5)
1600 mg	6	267.4	(196.2, 364.5)

[1] Based on least squares means from an ANOVA performed on the natural-log transformed values.
Mean square error arising from ANOVA equal to 0.1244.

Table 2. Geometric Means and Confidence Intervals for MK-0518 $AUC_{0-\infty}$ (μM•hr) Following Fasted Administration of Single Oral Doses to Young, Healthy, Male Subjects

Treatment	N	Geometric [1] Mean	95% Confidence Interval [1] for Geometric Mean
10 mg	6	0.82	(0.71, 0.96)
25 mg	6	1.69	(1.45, 1.96)
50 mg	6	4.49	(3.86, 5.23)
100 mg	6	6.12	(5.25, 7.13)
200 mg	6	16.90	(14.51, 19.69)
400 mg	6	24.61	(21.15, 28.64)
800 mg	6	63.11	(54.19, 73.50)
1200 mg	6	84.01	(72.18, 97.77)
1600 mg	6	95.60	(81.70, 111.86)
[1] Based on least squares means from an ANOVA performed on the natural-log transformed values. Mean square error arising from ANOVA equal to 0.0231.			

Table 3. Geometric Means and Confidence Intervals for MK-0518 C_{max} (μM) Following Fasted Administration of Single Oral Doses to Young, Healthy, Male Subjects

Treatment	N	Geometric [1] Mean	95% Confidence Interval [1] for Geometric Mean
10 mg	6	0.58	(0.43, 0.79)
25 mg	6	1.17	(0.86, 1.60)
50 mg	6	2.37	(1.74, 3.22)
100 mg	6	2.75	(2.02, 3.75)
200 mg	6	5.83	(4.28, 7.94)
400 mg	6	10.63	(7.81, 14.47)
800 mg	6	24.67	(18.13, 33.58)
1200 mg	6	30.96	(22.75, 42.14)
1600 mg	6	36.06	(26.46, 49.16)
[1] Based on least squares means from an ANOVA performed on the natural-log transformed values. Mean square error arising from ANOVA equal to 0.1239.			

Table 4. Summary Statistics for Times of Maximum Observed Plasma Concentrations (T_{max}, hr) of MK-0518 Following Administration of Single Oral Doses of 10 to 1600 mg MK-0518 to Young, Healthy, Male Subjects

Panel	AN	T_{max}, hr								
		10 mg	25 mg	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg	1600 mg
Arithmetic Mean		0.7	0.5	0.8	0.8	0.9	1.2	1.3	1.3	1.2
Standard Deviation		0.3	0.2	0.3	0.6	0.4	0.5	0.3	0.4	0.3
Median		0.5	0.5	1.0	0.5	1.0	1.0	1.3	1.3	1.0
Range [min, max]		[0.5, 1.0]	[0.3, 1.0]	[0.5, 1.0]	[0.5, 2.0]	[0.5, 1.5]	[0.5, 2.0]	[1.0, 1.5]	[1.0, 2.0]	[1.0, 1.5]

Table 5. Summary Statistics for Apparent Half-lives of the Alpha Phase (t½ α, hr) of MK-0518 Following Administration of Single Oral Doses of 10 to 1600 mg MK-0518 to Young, Healthy, Male Subjects

Panel	AN	$t_{½}$ α, hr								
		10 mg	25 mg	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg	1600 mg
Harmonic Mean		N	N	0.96	1.06	1.11	1.07	1.01	1.02	1.01
Jackknife SD		N	N	0.18	0.17	0.16	0.14	0.13	0.11	0.05
Median		N	N	1.01	1.05	1.09	1.13	1.02	1.06	0.99
Range [min, max]		N	N	[0.75, 1.18]	[0.88, 1.44]	[0.92, 1.51]	[0.90, 1.16]	[0.87, 1.28]	[0.90, 1.15]	[0.94, 1.12]

Table 6. Summary Statistics for Apparent Half-lives of the Beta Phase ($t_{½}$ β, hr) of MK-0518 Following Administration of Single Oral Doses of 10 to 1600 mg MK-0518 to Young, Healthy, Male Subjects

Panel	AN	$t_{½}$ β, hr								
		10 mg	25 mg	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg	1600 mg
Harmonic Mean		2.6	2.2	8.2	12.2	10.8	6.9	12.4	10.4	12.0
Jackknife SD		1.4	0.8	2.4	5.3	4.3	10.6	5.3	2.0	4.3
Median		3.2	2.3	7.9	11.8	10.8	10.0	12.0	9.5	12.4
Range [min, max]		[1.5, 5.5]	[1.5, 4.5]	[6.2, 10.8]	[8.0, 26.3]	[7.3, 22.0]	[2.3, 20.4]	[8.2, 42.3]	[9.3, 17.3]	[8.4, 24.7]

Table 7. Summary Statistics for Percent of MK-0518 Dose Excreted Unchanged in Urine over 24 hours Following Administration of Single Oral Doses of 10 to 1600 mg MK-0518 to Young, Healthy, Male Subjects

Panel	AN	Percent of Dose Excreted Unchanged in Urine (%)								
		10 mg	25 mg	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg	1600 mg
Arithmetic Mean		11.3	15.9	11.6	9.2	10.1	10.0	9.8	7.5	8.9
Standard Deviation		2.5	2.0	2.4	3.4	1.7	2.1	2.1	3.2	2.6
Median		10.9	14.3	11.9	8.9	10.2	9.5	9.6	6.7	8.8
Range [min, max]		[8.9, 16.1]	[10.3, 16.0]	[7.7, 14.9]	[5.4, 14.4]	[7.4, 12.4]	[7.7, 12.7]	[7.5, 13.4]	[4.4, 13.4]	[3.7, 10.3]

Table 8. Summary Statistics for Renal Clearance Values (Cl_R, mL/min) of MK-0518 Following Administration of Single Oral Doses of 10 to 1600 mg MK-0518 to Young, Healthy, Male Subjects

Panel	AN	Cl_R, mL/min								
		10 mg	25 mg	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg	1600 mg
Arithmetic Mean		51.6	78.4	53.9	59.0	46.5	60.9	48.3	42.2	43.5
Standard Deviation		9.8	15.9	16.7	17.8	9.1	10.6	7.0	23.1	12.2
Median		52.4	71.7	49.6	59.3	48.1	58.0	46.5	35.0	45.5
Range [min, max]		[36.3, 62.2]	[58.1, 109.7]	[35.6, 84.5]	[32.3, 88.7]	[38.2, 59.5]	[49.0, 79.8]	[39.5, 60.1]	[23.4, 87.9]	[24.7, 58.6]

Table 9. Assessment of Dose Proportionality Following Administration of Single Oral Doses of 10 to 1200 mg MK-0518 to Young, Healthy, Male Subjects

PK Parameter	Panel	Estimate of Slope [1]	95% Confidence Interval for Slope
$AUC_{0-\infty}$ (μM*hr)*	Pooled	0.994	(0.966, 1.021)
	A	0.990	(0.955, 1.025)
	B	1.009	(0.962, 1.057)
$C_{12\,hr}$ (nM)*	Pooled	0.944	(0.864, 1.025)
	A	0.925	(0.821, 1.030)
	B	1.003	(0.867, 1.139)
C_{max} (μM)*	Pooled	0.831	(0.767, 0.896)
	A	0.838	(0.736, 0.940)
	B	0.841	(0.746, 0.936)

[1] Slope of log(PK) versus log(Dose), with a true slope of 1 representing exact dose proportionality.

*Testing indicates similar slopes for the panels. Use Pooled results.

Figure 2. Assessment of Dose Proportionality Using the Power Model for AUC0-∞ Following Administration of Single Oral Doses of 10 to 1200 mg MK-0518 to Young, Healthy, Male Subjects

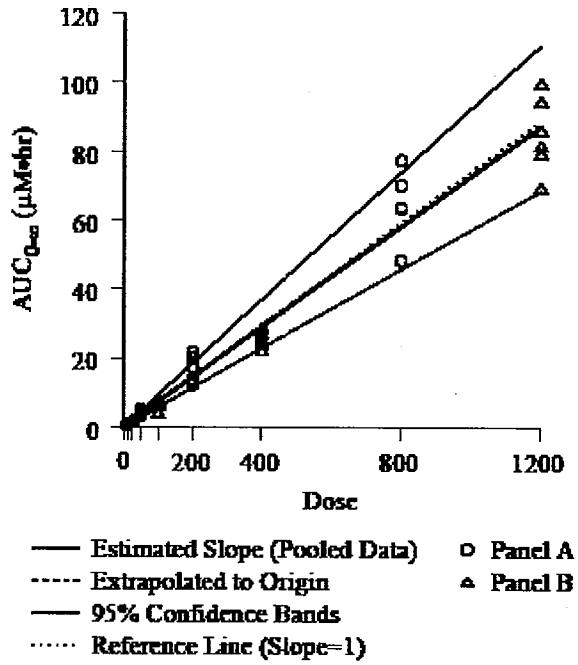


Figure 3. Assessment of Dose Proportionality Using the Power Model for C12 hr Following Administration of Single Oral Doses of 10 to 1200 mg MK-0518 to Young, Healthy, Male Subjects

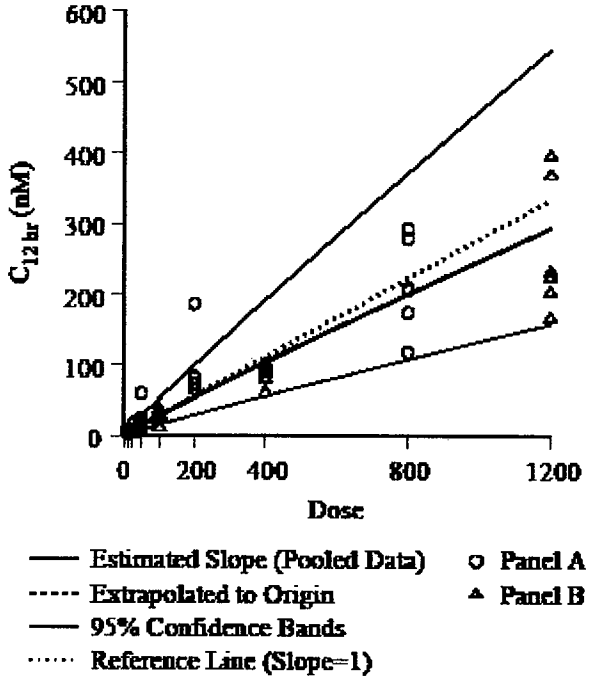


Figure 4. Assessment of Dose Proportionality Using the Power Model for Cmax Following Administration of Single Oral Doses of 10 to 1200 mg MK-0518 to Young, Healthy, Male Subjects

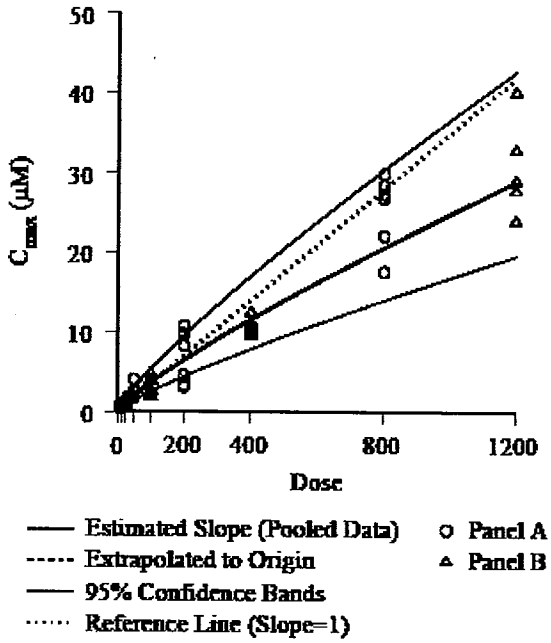


Table 10. Effect of Food on MK-0518 Pharmacokinetics Following Administration of Single Oral Doses of 100-mg or 200-mg MK-0518 to Young, Healthy, Male Subjects

PK Variable	Treatment†	N	Geometric Mean		Geometric Mean Ratio (Fed/Fasted)	90% Confidence Interval for GMR
			Fed	Fasted		
C_{12hr} (nM)	100 mg	6	39.0‡	37.4‡	1.06	(0.75, 1.49)
	200 mg	6	77.2‡	85.3‡	0.91	(0.64, 1.31)
C_{max} (μM)	100 mg	6	3.27‡	3.75‡	0.82	(0.58, 1.16)
	200 mg	6	3.82‡	5.83‡	0.66	(0.47, 0.92)
$AUC_{0-\infty}$ (μM-hr)	100 mg	6	5.99‡	6.12‡	0.96	(0.84, 1.14)
	200 mg	6	13.38‡	16.80‡	0.79	(0.68, 0.92)
T_{max} (hr)	100 mg	6	2.0§	0.5§	1.5¶	(0.5, 3.5)§
	200 mg	6	2.0§	1.0§	2.3¶	(0.5, 5.0)§
$t_{1/2}\alpha$ (hr)	100 mg	5	0.89§	1.06§		
	200 mg	3	1.89§	1.31§		
$t_{1/2}\beta$ (hr)	100 mg	6	7.3§	12.3§		
	200 mg	6	10.2§	10.2§		

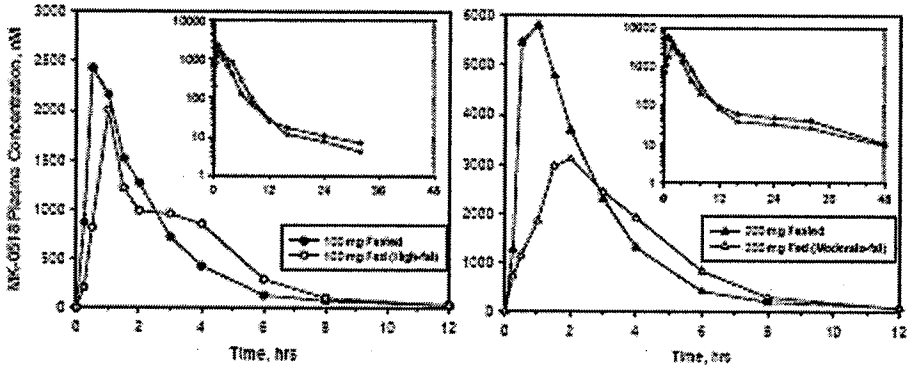
† 100 mg fed dose administered with high-fat meal. 200 mg fed dose administered with moderate-fat meal.

‡ Least squares estimate for geometric means are based on an ANOVA performed on the natural-log transformed values.

§ Medians reported for T_{max}, harmonic means reported for half-life.

¶ For T_{max}, represents Hodges-Lehman estimate of median treatment difference, with corresponding 90% CI for the true median difference.

Figure 5. Arithmetic Mean MK-0518 Plasma Concentrations (nM) Following Administration of 100 or 200 mg Single Oral Doses to Fed (High-Fat or Moderate-Fat Meal) and Fasted Young, Healthy, Male Subjects (inset: semilog scale)



Multiple-Dose Pharmacokinetics of MK-0518 (Part II)

Figure 6. Arithmetic Mean MK-0518 Plasma Concentrations (nM) Versus Time (hr) Following Multiple-Dose Administration of 100 to 800 mg MK-0518 q12 hr in the Fasted State to Young, Healthy, Male Subjects (semilog scale)

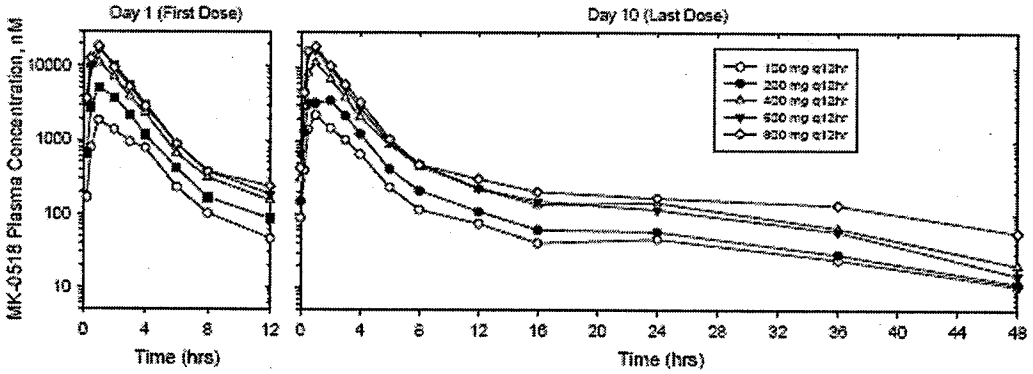


Table 11. Geometric Means and Confidence Intervals for MK-0518 C_{12hr} (nM) Following Multiple Dose (q12 hr) Administration to Young, Healthy, Male Subjects

Treatment	N	Day 1 (First Dose)		Day 10 (Last Dose)		Accumulation Ratio (Day 10 / Day 1)	
		Geometric Mean [1]	90% CI for Geometric Mean	Geometric Mean [1]	90% CI for Geometric Mean	Geometric Mean Ratio [1]	90% CI for GMR
100 mg	6	43.9	(28.8, 67.1)	70.6	(46.2, 107.7)	1.61	(1.02, 2.54)
200 mg	6	82.9	(54.3, 126.5)	107.1	(70.2, 163.5)	1.29	(0.82, 2.03)
400 mg	6	135.5	(88.8, 206.9)	200.6	(131.4, 306.1)	1.48	(0.94, 2.34)
600 mg	6	176.7	(115.8, 269.7)	213.7	(140.0, 326.2)	1.21	(0.76, 1.91)
800 mg	6	220.9	(144.7, 337.2)	300.8	(197.1, 459.2)	1.36	(0.86, 2.15)

[1] Based on least squares means from an ANOVA performed on the natural-log transformed values.
Mean square error arising from ANOVA equal to 0.2318.

Table 12. Geometric Means and Confidence Intervals for MK-0518 $AUC_{0\text{-}12hr}$ (μM•hr) Following Multiple Dose (q12 hr) Administration to Young, Healthy, Male Subjects

Treatment	N	Day 1 (First Dose)		Day 10 (Last Dose)		Accumulation Ratio (Day 10/ Day 1)	
		Geometric Mean †	95% CI for Geometric Mean	Geometric Mean †	95% CI for Geometric Mean	Geometric Mean Ratio †	90% CI for GMR
100 mg	6	5.80	(4.49, 7.26)	6.53	(5.21, 8.20)	1.13	(0.94, 1.35)
200 mg	6	13.54	(10.88, 16.90)	12.31	(9.81, 15.44)	0.91	(0.76, 1.09)
400 mg	6	27.24	(21.72, 34.17)	28.69	(22.86, 35.97)	1.05	(0.88, 1.26)
600 mg	6	36.87	(29.39, 46.25)	40.57	(32.35, 50.89)	1.10	(0.92, 1.32)
800 mg	6	36.77	(29.31, 46.09)	43.27	(34.49, 54.28)	1.17	(0.98, 1.40)

† Based on least square means from an ANOVA performed on the natural-log transformed values.
Mean square error arising from ANOVA equal to 0.0334.

Table 13. Geometric Means and Confidence Intervals for MK-0518 C_{max} (μM) Following Multiple Dose (q12 hr) Administration to Young, Healthy, Male Subjects

Treatment	N	Day 1 (First Dose)		Day 10 (Last Dose)		Accumulation Ratio (Day 10 / Day 1)	
		Geometric Mean †	95% CI for Geometric Mean	Geometric Mean †	95% CI for Geometric Mean	Geometric Mean Ratio †	90% CI for GMR
100 mg	6	2.06	(1.48, 2.85)	2.20	(1.60, 3.09)	1.08	(0.79, 1.49)
200 mg	6	5.34	(3.85, 7.42)	3.87	(2.79, 5.37)	0.72	(0.53, 1.00)
400 mg	6	11.43	(8.22, 15.85)	11.18	(8.05, 15.52)	0.98	(0.71, 1.35)
600 mg	6	16.19	(11.65, 22.48)	18.89	(13.61, 26.24)	1.17	(0.85, 1.61)
800 mg	6	18.97	(13.59, 26.21)	19.79	(14.21, 27.49)	1.05	(0.76, 1.44)

† Based on least square means from an ANOVA performed on the natural-log transformed values.
Mean square error arising from ANOVA equal to 0.106.

Table 14. Assessment of Dose Proportionality Following Multiple Dose (q12 hr) Administration of MK-0518 to Young, Healthy, Male Subjects

PK Parameter	Estimate of Slope †	95% Confidence Interval for Slope
C_{12hr} (nM)	0.684	(0.509, 0.860)
C_{max} (μM)	1.145	(0.952, 1.338)
$AUC_{0\text{-}12hr}$ (μM•hr)	0.979	(0.857, 1.101)

† Slope of log(PK) versus log(Dose), with a true slope of 1 representing exact dose proportionality.

Figure 7. Assessment of Dose Proportionality Using the Power Model for AUC0-12 hr Following Multiple Dose (q12 hr) Administration of MK-0518 to Young, Healthy, Male Subjects

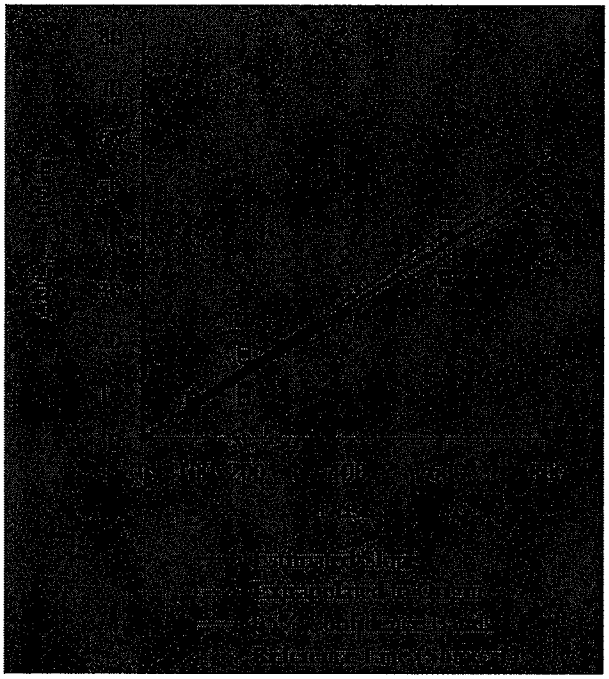


Figure 8. Assessment of Dose Proportionality Using the Power Model for C12 hr Following Multiple Dose (q12 hr) Administration of MK-0518 to Young, Healthy, Male Subjects

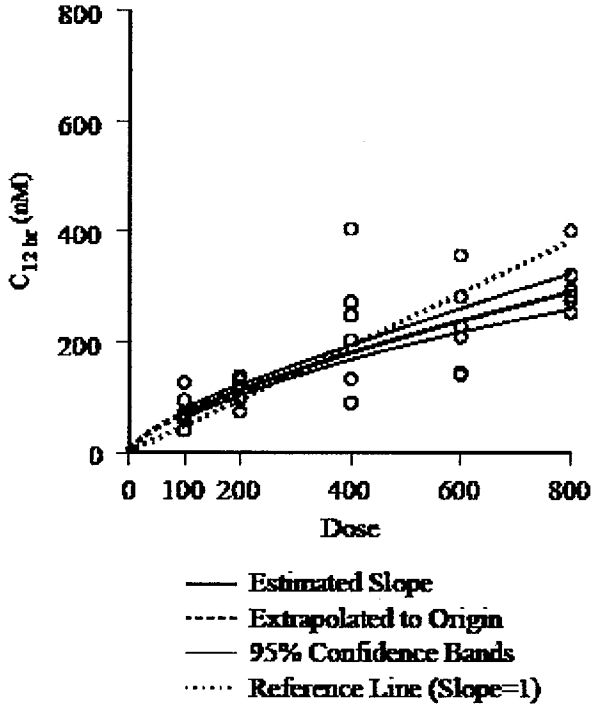


Figure 9. Assessment of Dose Proportionality Using the Power Model for Cmax Following Multiple Dose (q12 hr) Administration of MK-0518 to Young, Healthy, Male Subjects

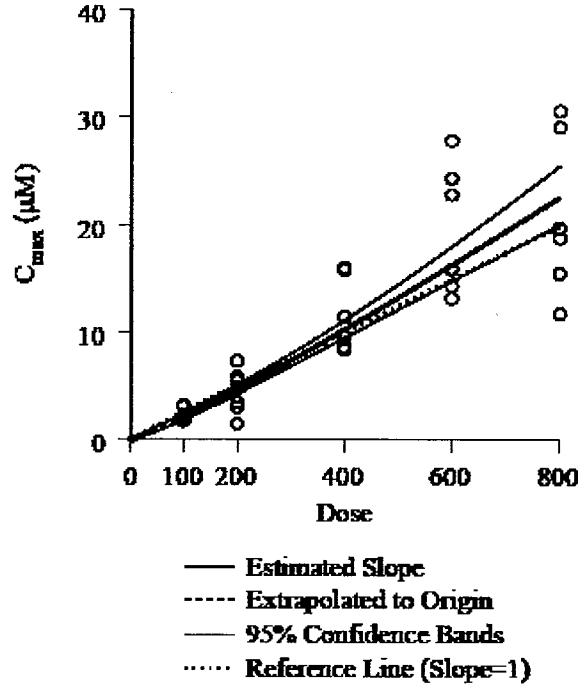
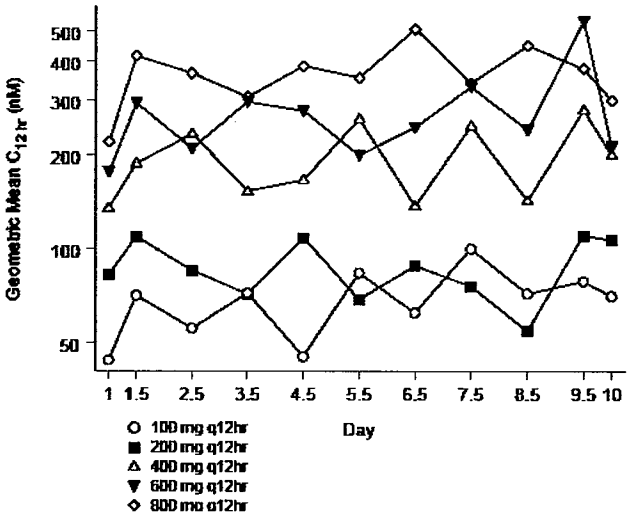


Figure 10. MK-0518 Trough Plasma Concentrations (nM) Versus Time (hr) Following Multiple-Dose Administration of 100 to 800 mg MK-0518 q12 hr in the Fasted State to Young, Healthy, Male Subjects - Assessment of Time to Steady State



SAFETY RESULTS: MK-0518 was generally well tolerated in young, healthy, male subjects. No serious clinical or serious laboratory adverse experiences were reported and no subject discontinued because of an adverse experience. See more details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS:

Following single-dose administration of MK-0518, at doses from 10 to 1600 mg, MK-0518 appears to be rapidly absorbed, with median T_{max} values in the fasted state ranging from 0.5 to 1.3 hrs. MK-0518 concentrations declined from C_{max} in a biphasic manner, with an apparent half-life of the initial (α) phase of approximately 1 hour, and an apparent half-life of the terminal (β) phase of approximately 7 to 12 hours. $AUC_{0-\infty}$ and $C_{12\,hr}$ increase approximately dose proportionally over the dose range 10 mg to 1200 mg. C_{max} appears to increase slightly less than dose proportionally over this same dose range, and T_{max} values were slightly longer at the higher doses compared to the lower doses. Approximately 7 to 14% of the oral MK-0518 dose was excreted unchanged in urine, and the renal clearance was approximately 42 to 78 mL/min.

Moderate-fat and high-fat meals appear to have no significant effect on the extent of absorption of MK-0518 Phase I Lactose formulation except that high-fat meals decrease C_{max} by 34%.

Following multiple-dose administration of MK-0518 twice daily (q12 hr) for 10 days, at doses from 100 to 800 mg, AUC_{0-12hr} and C_{max} increase approximately dose proportionally, while $C_{12\,hr}$ appears to increase moderately less than dose proportionally. The apparent terminal elimination half-lives following the final dose were approximately 1 hour for the initial (α) phase and approximately 10 to 12 hours for the terminal (β) phase. The average accumulation ratios (steady state versus single dose) for AUC_{0-12hr} and C_{max} across the dose range studied ranged from approximately 0.7 to 1.2, indicating little if any accumulation in these parameters with q12 hr dosing. The average accumulation ratio for C_{12hr} ranged from approximately 1.2 to 1.6, indicating modest accumulation in this parameter with q12 hr dosing. Approximately 8 to 11% of the oral MK-0518 dose was excreted unchanged in urine during a steady-state dosing interval, with renal clearance values of approximately 54 to 65 mL/min. After multiple-dose administration of MK-0518, steady state appears to have been achieved after two days of dosing at all dose levels.

Protocol 002

TITLE: A Randomized, Double-Blind, Placebo-Controlled, 2-Period Study to Evaluate the Influence of Ritonavir on a Single Dose of MK-0518 Pharmacokinetics in Healthy Male Volunteers

OBJECTIVES: To evaluate the effect of coadministration of ritonavir and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\,hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of ritonavir coadministered with a single dose of MK-0518

SUBJECTS AND STUDY DESIGN: This was a randomized, double-blind, placebo-controlled, 2-period study in healthy, young, male subjects. In Period 1, 12 subjects received a 400 mg single oral dose of MK-0518 (N=10) or placebo (N=2). This was followed by at least a 4-day washout prior to the start of Period 2. In Period 2, the same 12 subjects received 100 mg oral doses of ritonavir twice a day for 16 days. On Day 14, subjects received their AM dose of ritonavir in combination with a 400 mg single oral dose of MK-0518 or placebo. Ritonavir was administered in an open-labeled fashion, while MK-0518 was administered in a double-blind fashion. The same 2 subjects in each period received placebo, based on a computer-generated randomized allocation schedule.

All doses of study drug were administered following a moderate-fat meal. On days of pharmacokinetic samplings, the meal was administered ~30 minutes prior to dose and ingested within ~25 minutes. The dose was administered within ~5 minutes after completion of the meal.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518, Phase I lactose formulation tablets 100 mg, placebo MK-0518 (100 mg image) tablets, NORVIR (ritonavir) 100 mg capsules

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

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following a Single Oral Dose of 400-mg MK-0518 With or Without Multiple Oral Doses of 100-mg Ritonavir Twice-Daily to Young, Healthy, Male Subjects (Inset: Semilog Scale)

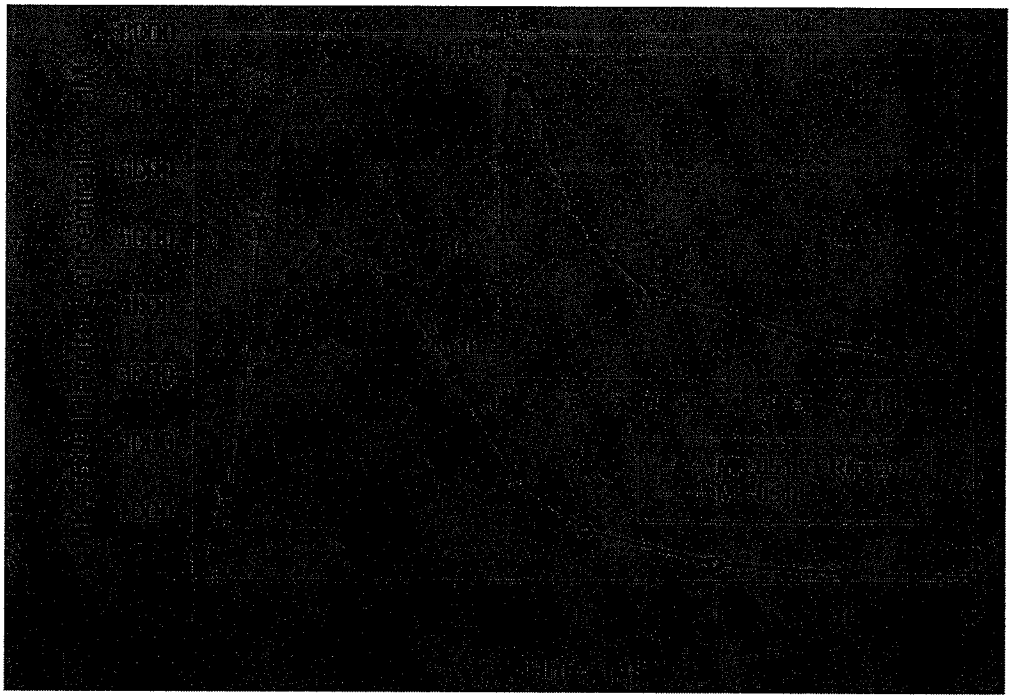


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics in Young, Healthy, Male Subjects Administered Single Oral Doses of 400-mg MK-0518 With or Without Administration of 100-mg Ritonavir Twice Daily

Pharmacokinetic Parameter	MK-0518 + Ritonavir			MK-0518			(MK-0518 + Ritonavir / MK-0518)			
	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†
C_{12hr} (nM)‡	10	76.5	(52.6, 111.3)	10	77.1	(53.0, 112.2)	10	0.99	(0.70, 1.40)	0.177
$AUC_{\phi-\infty}$ (μM·hr)‡	10	19.32	(15.69, 23.80)	10	22.88	(18.58, 28.19)	10	0.84	(0.70, 1.01)	0.049
C_{max} (nM)‡	10	7.23	(5.52, 9.46)	10	9.57	(7.31, 12.52)	10	0.76	(0.55, 1.04)	0.153
T_{max} (hr)	10	2.0§		10	1.5§		10	0.5‖	(-1.0, 2.0)‖	
$t_{1/2}$ (hr)	10	0.97¶		10	1.06¶		10	-0.11‖	(-0.16, -0.05)‖	
$t_{1/2}$ (hr)	10	10.0¶		10	10.8¶		10	0.3‖	(-2.5, 3.8)‖	

† 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 Half-Life.
N=Number of subjects.

Table 2. Individual MK-0518 Pharmacokinetic Parameters and Summary Statistics Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 100-mg Ritonavir Twice-Daily to Young, Healthy, Male Subjects

AN	$C_{12\ hr}$, nM			$AUC_{0-\infty}$, μM·hr			C_{max}, μM			T_{max}, hr			$t_{½}\ \alpha$, hr		$t_{½}\ \beta$, hr	
	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B	A	B	A	B
49	109.6	103.1	1.06	19.73	21.36	0.92	7.84	7.66	1.02	1.5	2.0	-0.5	0.88	0.94	17.2	11.1
50	130.1	59.9	2.17	14.53	28.53	0.51	3.02	19.92	0.20	4.0	1.0	3.0	1.58	1.02	18.1	8.1
51	140.9	44.3	3.18	14.03	10.05	1.49	8.42	4.47	1.44	2.0	3.0	-1.0	0.68	0.92	6.7	8.4
52	54.5	115.2	0.47	22.25	26.68	0.83	8.46	11.26	0.75	2.0	1.5	0.5	1.18	1.40	16.7	14.8
53	35.8	54.0	0.66	17.84	23.03	0.77	8.89	11.51	0.75	1.5	1.5	0.0	0.73	0.83	9.0	14.5
55	25.0	40.7	0.61	20.88	24.40	0.85	11.08	12.34	0.90	0.5	1.5	-1.0	1.05	1.09	11.4	12.4
57	132.1	107.8	1.23	25.31	37.10	0.68	7.19	11.92	0.60	4.0	2.0	2.0	0.92	1.07	11.6	12.6
60	54.5	74.3	0.73	18.23	16.53	1.10	7.39	5.65	1.31	2.0	2.0	0.0	1.08	1.17	9.8	14.7
1054	80.8	116.8	0.69	20.03	33.31	0.60	7.96	13.10	0.61	3.0	1.0	2.0	0.91	1.08	4.2	6.7
1058	120.4	115.2	1.05	22.59	20.99	1.08	5.71	6.68	0.85	1.5	3.0	-1.5	1.19	1.28	18.1	13.0
AM	88.4	83.1	—	19.59	24.20	—	7.47	10.45	—	2.2	1.9	—	0.97†	1.06†	10.0†	10.8†
SD	43.5	31.6	—	3.39	7.84	—	1.91	4.53	—	1.1	0.7	—	0.24†	0.16†	6.3†	3.4†
Med	95.2	88.7	—	19.88	23.72	—	7.62	11.39	—	2.0	1.8	0.5‡	0.99	1.08	11.5	12.5
GM§	78.5	77.1	0.99	19.32	22.88	0.84	7.23	9.57	0.76	—	—	—	—	—	—	—

A: 100-mg ritonavir q12 hr x 16 days with 400-mg MK-0518 on Day 14.
B: 400 mg single dose MK-0518.
AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean.
† Values reported for half-lives are harmonic mean and jackknife standard deviation.
‡ For T_{max}, represents Hodges-Lehmann estimate of median treatment difference.
§ Based on least squares mean from an ANOVA performed on the natural-log transformed values.

Figure 2. Individual MK-0518 C_{12hr} Ratios [MK-0518 Coadministered With Ritonavir (A) / MK-0518 Administered Alone (B)] With Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400-mg MK-0518 With or Without Multiple Oral Doses of 100-mg Ritonavir Twice-Daily to Young, Healthy, Male Subjects (n=10)

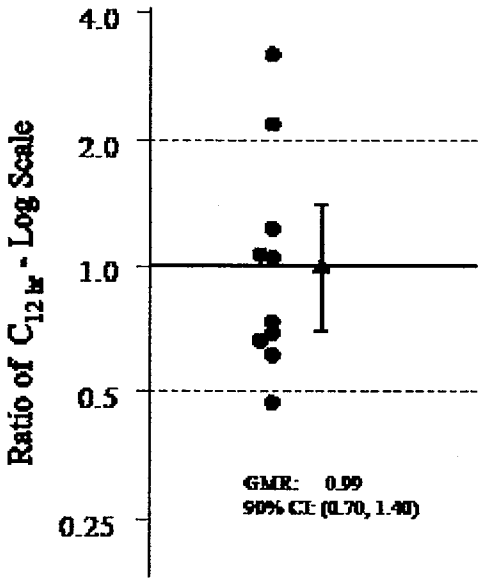


Figure 3. Individual MK-0518 $AUC_{0-\infty}$ Ratios [MK-0518 Coadministered With Ritonavir (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400-mg MK-0518 With or Without Multiple Oral Doses of 100-mg Ritonavir Twice-Daily to Young, Healthy, Male Subjects (n=10)

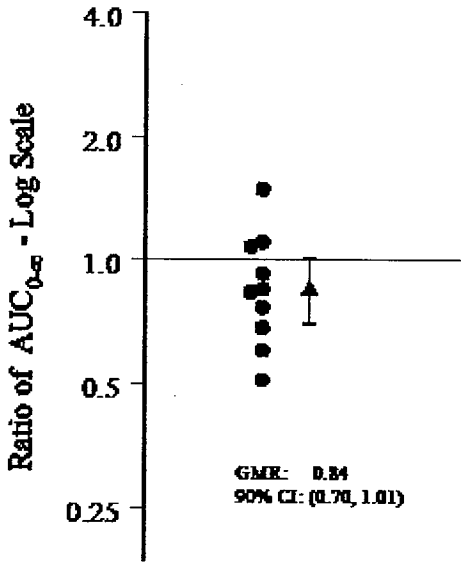
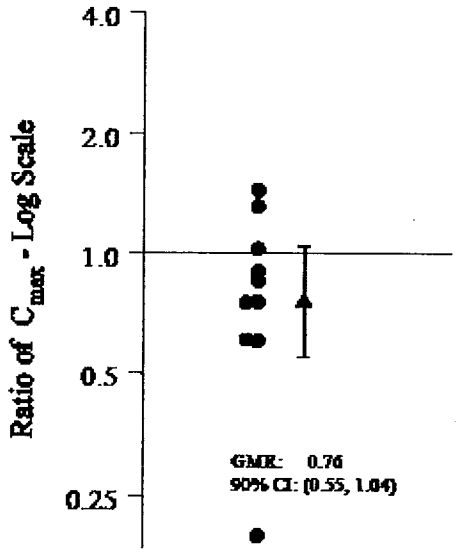


Figure 4. Individual MK-0518 C_{max} Ratios [MK-0518 Coadministered With Ritonavir (A) / MK-0518 Administered Alone (B)] With Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400-mg MK-0518 With or Without Multiple Oral Doses of 100-mg Ritonavir Twice-Daily to Young, Healthy, Male Subjects (n=10)



SAFETY RESULTS: MK-0518 was generally well tolerated in young, healthy, male subjects. No serious clinical or serious laboratory adverse experiences were reported and no subject discontinued because of an adverse experience. Five (5) subjects reported a total of 7 nonserious clinical adverse experiences, 3

of which were determined by the investigator as possibly drug related. None of the adverse experiences reported occurred in subjects treated with MK-0518 alone, MK-0518 in combination with ritonavir, or with placebo for MK-0518. The 3 possibly drug-related adverse experiences occurred when subjects were treated with ritonavir alone. There were no laboratory adverse experiences reported in this study. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

DISCUSSION AND CONCLUSIONS: With co-administration of 100 mg ritonavir twice daily for 14 days, the C_{12hr} geometric mean ratio for (MK-0518 + ritonavir/MK-0518) was 0.99 with a corresponding 90% confidence interval of (0.70, 1.40). The $AUC_{0-\infty}$ geometric mean ratio (MK-0518 + ritonavir /MK-0518) was 0.84 with a corresponding 90% confidence interval of (0.70, 1.01), while the C_{max} geometric mean ratio was 0.76 with a corresponding 90% confidence interval of (0.55, 1.04).

Individual MK-0518 $AUC_{0-\infty}$ ratios were below 2.0 and individual MK-0518 C_{12hr} ratios were above 0.4.

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.

Ritonavir has been reported to be an inducer of glucuronidation as well as an inhibitor of P-glycoprotein. Based on preclinical and in vitro data, the main route of elimination for MK-0518 is glucuronidation mediated by UGT1A1 and MK-0518 is a P-gp substrate. Results of this study support that a commonly used boosting dose of ritonavir (100 mg twice-daily) had no significant effect on the pharmacokinetics of MK-0518, despite the potential for induction of UGT1A1 by ritonavir. Due to the competing effects of ritonavir on UGT1A1 and P-gp, a balance of competing effects of induction and inhibition cannot be ruled out.

Protocol 003

TITLE: A Randomized, Double-Blind, Placebo-Controlled, 2-Period Study to Evaluate the Influence of Efavirenz on a Single Dose of MK-0518 in Healthy Male Volunteers

OBJECTIVES: To evaluate the effect of coadministration of efavirenz and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\,hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of efavirenz coadministered with a single dose of MK-0518

SUBJECTS AND STUDY DESIGN: This was a randomized, double-blind, placebo-controlled, 2-period study in young, healthy, male subjects. In Period 1, 12 subjects received a 400-mg single oral dose of MK-0518 (N=10) or placebo (N=2). This was followed by at least a 4-day washout prior to the start of Period 2. In Period 2, the same 12 subjects received 600-mg oral doses of efavirenz once daily for 14 days. On Day 12, subjects received their daily dose of efavirenz in combination with a 400-mg single oral dose of MK-0518 or placebo. Efavirenz was administered in an open-labeled fashion, while MK-0518 was administered in a double-blind fashion. The same 2 subjects in each period received placebo, based on a computer-generated randomized allocation schedule.

All doses of study drug were administered in the fasted state.

INVESTIGATORS AND STUDY LOCATIONS

FORMULATION: MK-0518, Phase I lactose formulation tablets 100 mg, placebo MK-0518 (100 mg image) tablets, efavirenz 600 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, 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: Plasma concentrations of MK-0518 were used to calculate pharmacokinetic parameters including $AUC_{0-\infty}$, C_{max}, $C_{12\,hr}$, T_{max}, and apparent $t_{½}$ for each subject in the presence or absence of multiple doses of efavirenz. Geometric mean ratios (MK-0518 + efavirenz/MK-0518) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{(0-\infty)}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Efavirenz Once-Daily to Young, Healthy, Male Subjects (Inset: semilog scale)

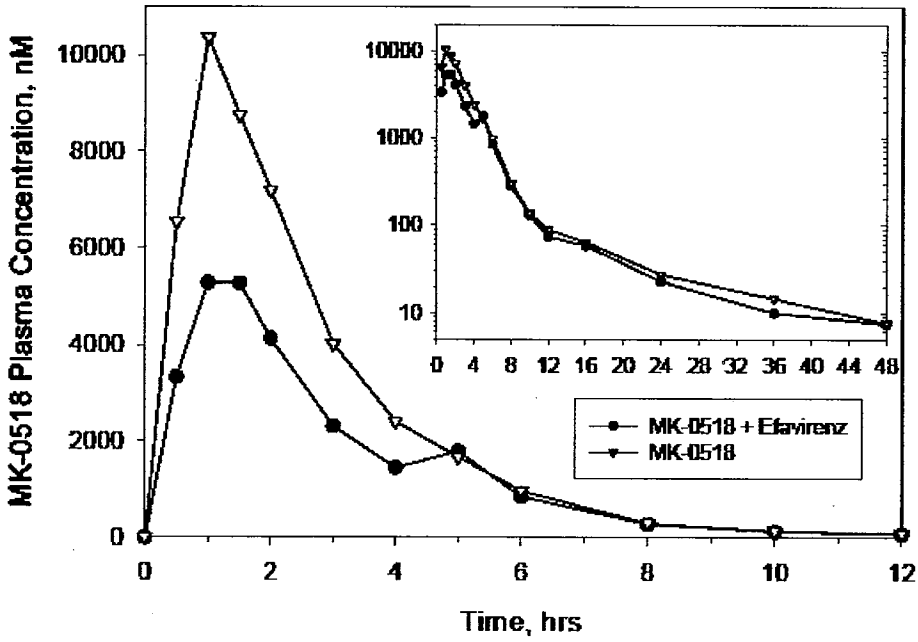


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics after Administration of a Single Oral Dose of 400-mg MK-0518 With or Without Multiple Oral Doses of 600-mg Efavirenz Once-Daily to Young, Healthy, Male Subjects

Pharmacokinetic Parameter	MK-0518 + Efavirenz N	MK-0518 + Efavirenz Geometric Mean	MK-0518 + Efavirenz 95% Confidence Interval for Geometric Mean	MK-0518 N	MK-0518 Geometric Mean	MK-0518 95% Confidence Interval for Geometric Mean	(MK-0518 + Efavirenz/MK-0518) N	(MK-0518 + Efavirenz/MK-0518) Geometric Mean Ratio	(MK-0518 + Efavirenz/MK-0518) 90% Confidence Interval for Geometric Mean Ratio	MSE†
C_{12h} (nM)‡	9	82.5	(41.4, 94.5)	9	79.1	(52.3, 119.5)	9	0.79	(0.49, 1.28)	0.397
$AUC_{\tau,ss}$ (micM*hr)‡	9	18.14	(15.14, 21.73)	9	28.15	(23.49, 33.73)	9	0.64	(0.53, 0.80)	0.062
C_{max} (micM)‡	9	8.45	(4.39, 9.71)	9	10.13	(6.73, 15.24)	9	0.64	(0.41, 0.98)	0.344
T_{max} (hr)	9	1.5§		9	1.5§		9	-0.1‖	(-1.0, 2.2)‖	
$t_{1/2}\alpha$ (hr)	9	0.95¶		9	0.98¶		9	-0.06‖	(-0.14, 0.16)‖	
$t_{1/2}\beta$ (hr)	9	9.1¶		9	10.8¶		9	-0.6‖	(-4.4, 2.7)‖	

† 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 $t_{1/2}$.

Table 2. Individual MK-0518 Pharmacokinetics and Summary Statistics Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Efavirenz Once-Daily to Young, Healthy, Male Subjects

	C_{12hr}, nM			$AUC_{0-\infty}$, μM•hr			C_{max}, μM			T_{max}, hr			$t_{1/2}$ α, hr		$t_{1/2}$ β, hr	
AN	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B	A	B	A	B
69	96.1	43.7	2.20	14.78	46.58	0.32	5.77	26.12	0.22	5.0	1.0	4.0	0.76	0.80	6.8	14.0
70	63.7	46.1	1.38	17.17	24.83	0.69	7.49	13.38	0.56	1.5	1.0	0.5	0.80	0.89	8.9	9.4
72	32.2	73.1	0.44	21.21	27.32	0.78	10.68	7.12	1.50	1.0	2.0	-1.0	0.87	1.00	8.8	15.9
74	44.3	91.4	0.48	19.27	58.78	0.50	9.06	13.19	0.69	1.0	1.5	-0.5	0.84	1.06	5.6	7.2
76	154.6	56.7	2.73	17.14	19.37	0.88	3.33	7.87	0.42	1.0	1.5	-0.5	1.65	1.11	11.0	15.9
77	48.8	132.8	0.37	18.07	19.41	0.93	5.06	3.92	1.55	1.5	3.0	-1.5	1.06	1.26	20.0	12.0
78	42.1	58.5	0.72	21.52	31.21	0.68	12.41	13.69	0.91	1.0	1.0	0.0	0.79	0.86	8.9	7.6
80	36.3	110.5	0.33	13.82	28.60	0.48	4.09	15.99	0.26	1.5	1.0	0.5	0.93	0.83	14.3	11.7
1071	137.9	184.7	0.75	22.43	26.98	0.83	4.52	5.06	0.89	2.0	2.0	0.0	1.23	1.30	19.0	13.8
AM	73.1	88.6	--	18.36	29.23	--	7.05	11.82	--	1.7	1.6	--	0.95[1]	0.98[1]	9.1[1]	10.8[1]
SD	45.7	47.0	--	2.97	8.79	--	3.12	6.85	--	1.3	0.7	--	0.21[1]	0.17[1]	3.9[1]	3.2[1]
Med	48.8	73.1	--	18.07	27.32	--	6.06	13.19	--	1.5	1.5	-0.1[2]	0.93	1.00	8.9	12.0
GM[3]	62.5	79.1	0.79	18.14	28.15	0.64	6.45	10.13	0.64	--	--	--	--	--	--	--

A: 600-mg efavirenz qd x 14 days with 400-mg MK-0518 on Day 12.

B: 400 mg single dose MK-0518.

AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean.

[1] Values reported for half-lives are harmonic mean and jackknife standard deviation.

[2] For T_{max}, represents Hodges-Lehman estimate of median treatment difference.

[3] Based on least squares mean from an ANOVA performed on the natural-log transformed values.

Figure 2. Individual MK-0518 C_{12hr} Ratios [MK-0518 Coadministered with Efavirenz (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Efavirenz Once-Daily to Young, Healthy, Male Subjects (n=9)

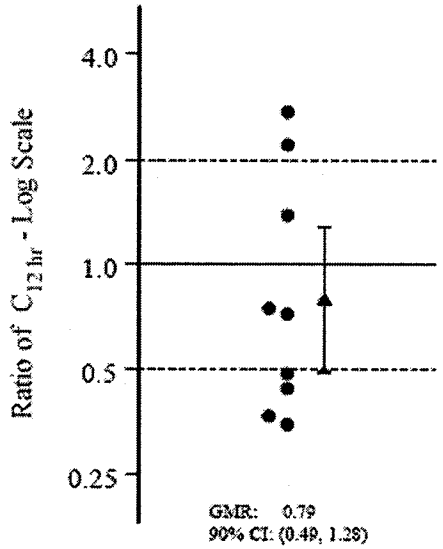


Figure 3. Individual MK-0518 $AUC_{0-\infty}$ Ratios [MK-0518 Coadministered with Efavirenz (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Efavirenz Once-Daily to Young, Healthy, Male Subjects (n=9)

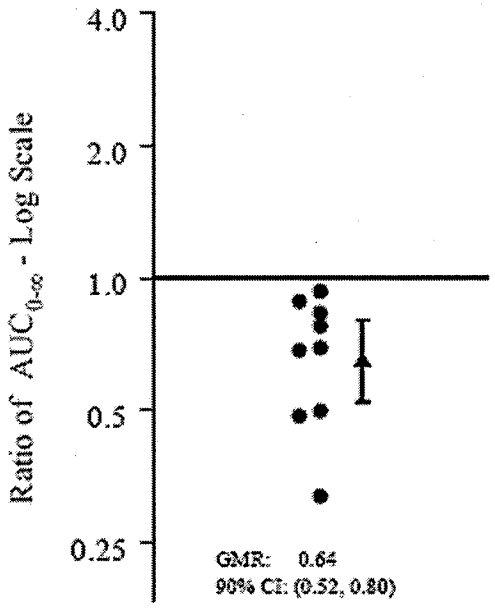
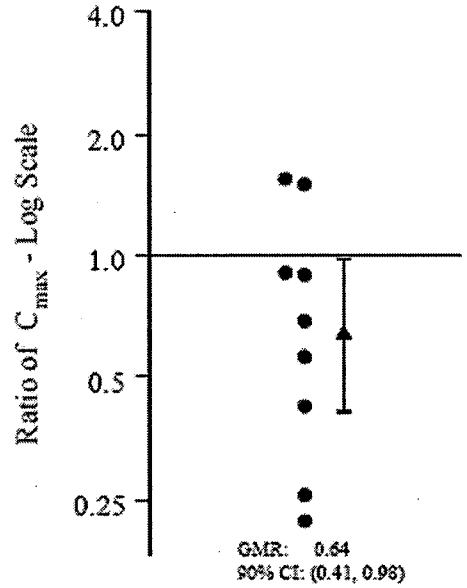


Figure 4. Individual MK-0518 C_{max} Ratios [MK-0518 Coadministered with Efavirenz (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Efavirenz Once-Daily to Young, Healthy, Male Subjects (n=9)



SAFETY RESULTS: MK-0518 was generally well tolerated in young, healthy, male subjects. No serious clinical or serious laboratory adverse experiences were reported. Two (2) of the 14 subjects discontinued the study due to a nonserious clinical adverse experience judged as unrelated to MK-0518 by the investigator. A total of 114 nonserious clinical adverse experiences were reported by 14 subjects enrolled in the study; 97 of which were judged drug related to either MK-0518 or efavirenz. Five of the 97 drug related clinical adverse experiences were judged as possibly drug related to MK-0518 by the investigator with the remaining 92 adverse experiences related to efavirenz, all of which were completely consistent with adverse experiences reported in the label for this drug. There were no adverse experiences reported as being possibly drug related to MK-0518 which occurred in subjects treated in combination with efavirenz or with placebo for MK-0518. There were no laboratory adverse experiences reported in this study.

DISCUSSION AND CONCLUSIONS: With co-administration of 600 mg efavirenz twice daily for 12 days, the C_{12hr} geometric mean ratio for (MK-0518 + efavirenz/MK-0518) was 0.79 with a corresponding 90% CI of (0.49, 1.28). The $AUC_{0-\infty}$ geometric mean ratio (MK-0518 + efavirenz/MK-0518) was 0.64 with a corresponding 90% confidence interval of (0.52, 0.80), while the C_{max} geometric mean ratio was 0.64 with a corresponding 90% confidence interval of (0.41, 0.98).

Efavirenz is known to activate the pregnane X receptor (PXR), which is involved in regulating activity of CYP3A, as well as of UGT1A1. Efavirenz has been shown to induce P-450 enzymes and thus has the potential to induce UGT1A1 by which MK-0518 is metabolized, thereby influencing the pharmacokinetic profile of MK-0518. The study results confirmed that multiple doses of efavirenz decreased plasma levels of MK-0518 ($AUC_{0-\infty}$, C_{max}, and $C_{12\,hr}$).

The lower bound of 90% CI of MK-0518 C_{12hr} ratios was 0.49 (>0.4) but a few individual MK-0518 C_{12hr} ratios were slightly below 0.4.

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.

Efavirenz may be used with the recommended dose of MK-0518.

Protocol 004 (Phase 2 study in treatment naïve patients)

TITLE: Multicenter, Double-Blind, Randomized, Dose-Ranging Study to Compare the Safety and Activity of MK-0518 Plus Tenofovir and Lamivudine (3TC) Versus Efavirenz Plus Tenofovir and Lamivudine (3TC) in ART-Naive, HIV-Infected Patients

OBJECTIVES:

Part I (monotherapy phase): To evaluate the efficacy, safety and tolerability of MK-0518 given b.i.d., at the studied doses, compared to placebo in monotherapy for 10 days. To evaluate the pharmacokinetics and pharmacokinetic-pharmacodynamic relationship of MK-0518 given b.i.d, at the studied doses.

Part II (combination therapy phase): To evaluate the antiretroviral activity, safety and tolerability of MK-0518 given b.i.d., at the studied doses, compared to efavirenz, each in combination with tenofovir and lamivudine for 24 weeks. To evaluate the pharmacokinetic-pharmacodynamic associations including data from the population PK of MK-0518 in combination with tenofovir and lamivudine, and to evaluate the pharmacokinetic profiles of MK-0518 and lamivudine in the combination therapy.

STUDY CENTERS: Twenty-nine centers participated in this study. Fourteen of these study centers were in the United States; 2 were in Canada; 6 were in South America (2 in Peru, 2 in Chile, and 2 in Colombia); 2 were in Thailand; and 5 were in Australia.

SUBJECTS AND STUDY DESIGN: This multicenter, double-blind (with in-house blinding), randomized, 2-part, dose-ranging, placebo- and active-controlled study enrolled ART-naïve HIV-infected patients.

Patients were stratified by their initial (screen) HIV RNA level (≤50,000 copies/mL; and >50,000 copies/mL). Part I consisted of a 10-day period of MK-0518 monotherapy (at doses of 100 mg b.i.d., 200 mg b.i.d., 400 mg b.i.d., or 600 mg b.i.d.) versus placebo. Preliminary data from Part I were reviewed in order to determine the doses that had acceptable tolerability and antiviral activity to be used in Part II of the study; these data indicated that all MK-0518 doses used in Part I appeared acceptable.

Part II consisted of a 48-week period of MK-0518 combination therapy at the same doses of MK-0518 as used in Part I versus efavirenz (control group) in combination with tenofovir (TFV) and lamivudine (3TC). Part II included patients who participated in Part I (Cohort I) as well as new patients randomized at the start of Part II (Cohort II). Cohort I patients participated in the Part II combination phase of the study at the same dose level of MK-0518 (e.g., the 200 mg b.i.d. MK-0518 monotherapy patients received 200 mg b.i.d. MK-0518 in the combination phase). Cohort I patients who were assigned to placebo were placed in the efavirenz combination therapy arm. In addition, new Cohort II patients were randomized to receive 1 of 4 doses of MK-0518 or efavirenz in combination with tenofovir and lamivudine.

Patients who reached Week 48 of the original protocol were given the option to continue in the double-blind extension.

Patients who received any dose of MK-0518 in the original protocol continued in the extension on MK-0518 at 400 mg b.i.d. Patients who received efavirenz in the original protocol continued on efavirenz in the extension. Both open-label drugs, tenofovir, 300 mg daily (q.d.) and lamivudine, 300 mg q.d. continued unchanged in the extension.

Study drug was taken with or without food.

Overall Disposition of Patients (Cohort I; Monotherapy Phase)

Description	MK-0518 100 mg b.i.d. n (%)	MK-0518 200 mg b.i.d. n (%)	MK-0518 400 mg b.i.d. n (%)	MK-0518 600 mg b.i.d. n (%)	Placebo n (%)	Total n (%)
Total Enrolled	7	7	6	8	7	35
Treated	7 (100)	7 (100)	6 (100)	8 (100)	7 (100)	35 (100)
Patients completed Part I and did not continue to Part II				2 (25.0)	3 (42.9)	5 (14.3)
Patients completed Part I and continued to Part II	7 (100)	7 (100)	6 (100)	6 (75.0)	4 (57.1)	30 (85.7)
n (%) = Number (percent) of patients in each category.						

Overall Disposition of Patients (Cohort II; Combination Therapy Phase)

Description	MK-0518 100 mg b.i.d. n (%)	MK-0518 200 mg b.i.d. n (%)	MK-0518 400 mg b.i.d. n (%)	MK-0518 600 mg b.i.d. n (%)	Efavirenz 600 mg q.d. n (%)	Total n (%)
Total Enrolled	34	33	35	34	35	171
Never Treated	1 (2.9)				1 (2.9)	2 (1.2)
Treated	33 (97.1)	33 (100)	35 (100)	34 (100)	34 (97.1)	169 (98.8)
Patients continuing	33 (97.1)	27 (81.8)	34 (97.1)	31 (91.2)	31 (88.6)	156 (91.2)
Patients discontinued		6 (18.2)	1 (2.9)	3 (8.8)	3 (8.6)	13 (7.8)
Lack of Efficacy		2 (6.1)				2 (1.2)
Laboratory adverse experience				1 (2.9)		1 (0.6)
Consent withdrawn		2 (6.1)		2 (5.9)	3 (8.6)	7 (4.1)
Loss to follow-up		1 (3.0)	1 (2.9)			2 (1.2)
Other		1 (3.0)				1 (0.6)
Note: MK-0518 and efavirenz (EFV) were administered with tenofovir (TFV) and lamivudine (3TC). n (%) = Number (percent) of patients in each category.						

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Baseline Patient Characteristics (Cohorts I and II Combined; Combination Therapy Phase)

	MK-0518				Rhivirent	
	100 mg b.i.d. (N = 39)	200 mg b.i.d. (N = 40)	400 mg b.i.d. (N = 41)	600 mg b.i.d. (N = 40)	600 mg q.d. (N = 38)	Total (N = 198)
Gender n (%)						
Male	33 (84.6)	29 (72.5)	37 (90.2)	29 (72.5)	29 (76.3)	157 (79.3)
Female	6 (15.4)	11 (27.5)	4 (9.8)	11 (27.5)	9 (23.7)	41 (20.7)
Race n (%)						
White	7 (17.9)	14 (35.0)	14 (34.1)	14 (35.0)	12 (31.6)	61 (30.8)
Black	2 (5.1)	2 (5.0)	1 (2.4)	0 (0.0)	0 (0.0)	5 (2.5)
Asian	3 (7.7)	6 (15.0)	8 (19.5)	7 (17.5)	9 (23.7)	33 (16.7)
Hispanic American	14 (35.9)	11 (27.5)	13 (31.7)	9 (22.5)	11 (28.9)	58 (29.3)
Others	13 (33.3)	7 (17.5)	5 (12.2)	10 (25.0)	6 (15.8)	41 (20.7)
Region n (%)						
North America	14 (35.9)	13 (32.5)	15 (36.6)	13 (32.5)	9 (23.7)	64 (32.3)
Central/South America	21 (53.8)	16 (40.0)	14 (34.1)	15 (37.5)	16 (42.1)	82 (41.4)
Asia Pacific	4 (10.3)	11 (27.5)	12 (29.3)	12 (30.0)	13 (34.2)	52 (26.3)
Age (years)						
16-64 n (%)	38 (97.4)	40 (100.0)	41 (100.0)	40 (100.0)	38 (100.0)	197 (99.5)
≥ 65 n (%)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Mean (SD)	37.8 (10.5)	34.4 (9.4)	35.6 (8.4)	36.7 (7.0)	35.5 (8.1)	35.8 (8.7)
Median	35.0	31.0	35.0	36.5	35.0	35.0
Range	19 to 65	21 to 57	19 to 55	20 to 49	22 to 54	19 to 65
CD4 Cell Count (cells/mm³)						
Mean (SD)	313.7 (178.5)	286.0 (148.7)	338.3 (190.7)	278.5 (155.7)	280.0 (153.9)	300.0 (165.0)
Median	272.0	277.0	293.0	243.5	225.0	265.5
Range	76 to 758	78 to 723	95 to 1,017	99 to 786	77 to 744	76 to 1,017
Plasma HIV RNA (log_{10} copies/mL)						
Mean (SD)	4.8 (0.5)	4.8 (0.5)	4.6 (0.6)	4.8 (0.6)	4.8 (0.5)	4.8 (0.5)
Median	4.8	4.8	4.6	4.8	4.9	4.8
Range	3.6 to 5.9	3.9 to 5.9	3.4 to 5.7	3.5 to 5.9	3.5 to 5.8	3.4 to 5.9
Plasma HIV RNA (copies/mL)						
Geometric Mean	58,205.6	64,715.4	43,083.4	57,918.8	67,554.4	57,437.2
Median	67,008.0	59,608.0	37,400.0	58,850.0	72,850.0	59,850.8
Range	4,200 to 750,000	7,490 to 750,000	2,440 to 499,000	3,450 to 750,000	3,348 to 675,000	2,440 to 750,000
Screening HIV RNA ≤50,000 copies/mL n (%)						
Yes	17 (43.6)	18 (45.0)	19 (46.3)	18 (45.0)	18 (47.4)	90 (45.5)
No	22 (56.4)	22 (55.0)	22 (53.7)	22 (55.0)	20 (52.6)	108 (54.5)

FORMULATION: MK-0518, final poloxamer formulation tablets 100 mg, 200 mg and 400 mg and matching placebo tablets; efavirenz 600 mg tablets and matching image placebo tablets, tenofovir disoproxil fumarate 300 mg tablets, and lamivudine 300 mg tablets.

SAMPLE COLLECTION: In Part I, extensive pharmacokinetic (PK) evaluation for MK-0518 was performed for all patients on Day 10 for determination of AUC0-12 hr, Cmax, and C12 hr. Samples were collected predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. The 12-hour blood sample was taken prior to the PM dose.

In Part II, extensive PK evaluation for MK-0518 and lamivudine were performed on only Cohort I at Week 2 for determination of AUC0-12 hr, Cmax, and C12 hr. Samples were collected predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose. The 12-hour blood sample was taken prior to

the PM dose. In addition, a 24-hour blood sample for lamivudine was taken the following day prior to the AM dose.

In Part II, population PK sampling was performed for all patients in Cohorts I and II. At Weeks 4, 8, 12, and 16, a plasma sample for MK-0518 was collected. 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.

ASSAYS: Plasma samples were analyzed at [redacted] for MK-0518 concentrations. A validated HPLC-MS/MS assay was used for plasma MK-0518

[redacted]

PHARMACOKINETIC DATA ANALYSIS:

Part I: Summary statistics for the following MK-0518 pharmacokinetic parameters were analyzed by treatment group: trough concentration ($C_{12\ hr}$), area under the plasma concentration curve ($AUC_{0\text{-}12\ hr}$), and C_{max}. Geometric means of PK parameters were calculated.

Part II: To evaluate the effect of lamivudine on MK-0518, intensive PK data from Cohort I patients at Week 2 of Part II were summarized and compared to that obtained on Day 10 of Part I when these patients were on MK-0518 monotherapy. The geometric mean ratio (GMR) and associated 90% CI were calculated for MK-0518 Cmax, C12 hr, and AUC0-12 hr. The effect of MK-0518 on lamivudine were evaluated by comparing lamivudine Cmax, C24 hr, and AUC0-24 hr across treatment groups. This was an inter-subject comparison, comparing subjects receiving lamivudine plus MK-0518 and tenofovir to those receiving lamivudine plus efavirenz and tenofovir.

Population PK analyses were summarized in a separate document.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP:

Part I: PK/PD association was graphically explored. Efficacy responses during the 10-day monotherapy (e.g., change from baseline in log10 HIV RNA on Day 10, or slope of HIV RNA decrease) were plotted against the PK parameters (e.g., AUC0-12 hr, Cmax and C12hr). Pearson (parametric) correlation coefficient and Spearman (nonparametric) rank correlation coefficient between a PK parameter and an efficacy response were calculated.

Part II: The associations between efficacy responses and PK parameters were explored using similar approaches to those utilized in Part I.

Population PK and PD analyses were summarized in a separate document.

EFFICACY RESULTS:

Table 1. Change From Baseline in HIV RNA (Log10 Copies/mL) on Day 10
(Cohort I; Monotherapy Phase)

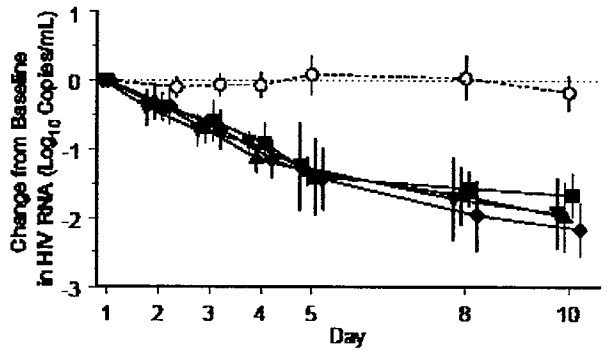
[redacted]

Table 2. Virologic Responses on Day 10
(Cohort I; Monotherapy Phase)

Treatment	N	Percent of Patients With HIV RNA<400 copies/mL		Percent of Patients With HIV RNA<50 copies/mL	
		n	% (95% CI)	n	% (95% CI)
MK-0518 100 mg b.i.d.	7	4	57.1 (18.4, 90.1)	1	14.3 (0.4, 57.9)
MK-0518 200 mg b.i.d.	7	4	57.1 (18.4, 90.1)	2	28.6 (3.7, 71.0)
MK-0518 400 mg b.i.d.	6	3	50.0 (11.8, 88.2)	2	33.3 (4.3, 77.7)
MK-0518 600 mg b.i.d.	8	4	50.0 (15.7, 84.3)	1	12.5 (0.3, 52.7)
Placebo	7	0	0.0 (0.0, 41.0)	0	0.0 (0.0, 41.0)

Note: The limit of reliable qualification (LoQ) = HIV RNA<400 copies/mL for the Standard assay, and HIV RNA<50 copies/mL for the UltraSensitive assay.
N = Number of patients in the treatment group.
n = Number of patients with HIV RNA value below LoQ.
CI = Confidence Interval, calculated by Clopper-Pearson method.

Figure 1. Mean (95% CI) Change From Baseline in HIV RNA (Log10 Copies/mL) Over Time
(Cohort I; Monotherapy Phase)



Number of Contributing Patients

MK-0518 100 mg b.i.d.	7	7	7	7	5	7	7
MK-0518 200 mg b.i.d.	7	7	7	7	6	7	7
MK-0518 400 mg b.i.d.	6	6	6	6	6	6	6
MK-0518 600 mg b.i.d.	8	8	8	8	7	8	8
Placebo	7	7	7	7	4	7	7

Table 3. Percent of Patients With HIV RNA <400 Copies/mL at Week 24 (Non-Completer=Failure Approach)
(Cohort II; Combination Therapy Phase)

Treatment	Percent of Patients With HIV RNA <400 Copies/mL at Week 24		MK-0518 Minus EFV
	n/N†	% (95% CI)	Difference† (98.75% CI)‡
MK-0518 100 mg b.i.d.	31/33	93.9 (79.8, 99.3)	-0.2 (-20.1, 19.4)
MK-0518 200 mg b.i.d.	27/33	81.8 (64.5, 93.0)	-12.3 (-34.9, 9.5)
MK-0518 400 mg b.i.d.	35/35	100.0 (90.0, 100.0)	5.9 (-9.9, 24.4)
MK-0518 600 mg b.i.d.	32/34	94.1 (80.3, 99.3)	0.0 (-19.5, 19.5)
Efavirenz 600 mg q.d.	32/34	94.1 (80.3, 99.3)	

† A positive value means MK-0518 is better than EFV.

‡ Bonferroni adjustment was employed for the two-sided Miettinen-Nurminen's confidence interval (CI) for the treatment difference.

Patients who discontinued assigned therapy regardless of reasons were considered as failures (NC=F).

Note: MK-0518 and efavirenz (EFV) were administered with tenofovir (TFV) and lamivudine (3TC).

For each treatment group, n/N = (number of responders) / (number of patients).

Figure 2. Percent (95% CI) of Patients With HIV RNA <400 Copies/mL Over Time
(Non-Completer=Failure Approach)
(Cohort II; Combination Therapy Phase)

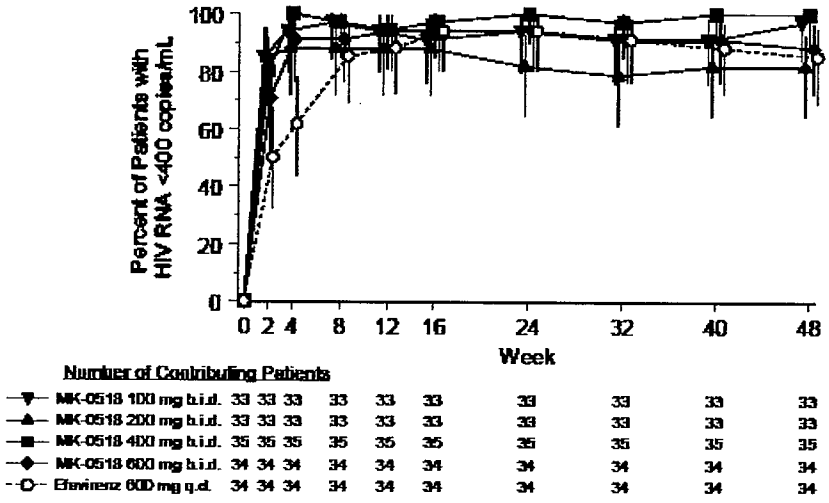
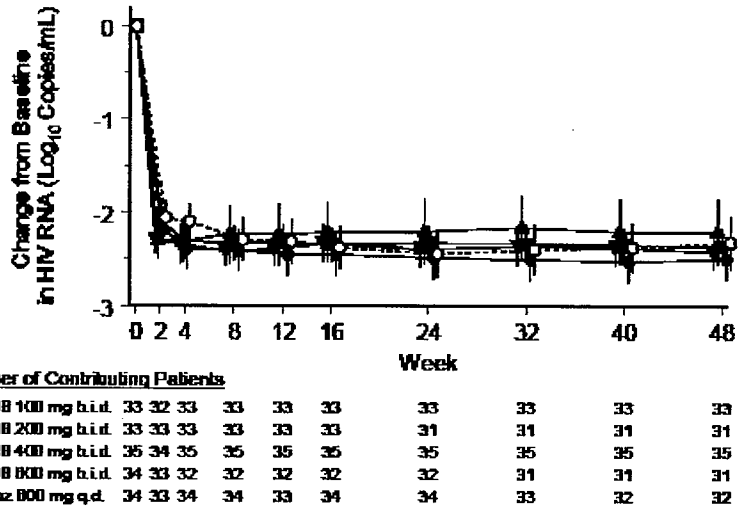


Figure 3. Mean (95% CI) Change From Baseline in HIV RNA (Log10 Copies/mL) Over Time
(Observed Failure Approach)
(Cohort II; Combination Therapy Phase)



SAFETY RESULTS: MK-0518 at the studied doses (100, 200, 400, and 600 mg b.i.d.) in treatment-naïve patients with HIV infection was generally well tolerated as monotherapy over 10 days and in combination with tenofovir and lamivudine over 48 weeks. See details in Medical Officer's review.

PHARMACOKINETIC RESULTS:

Part I, Monotherapy:

Table 4. Summary Statistics for MK-0518 Intensive PK Parameters on Day 10
(Cohort I; Monotherapy Phase)

Treatment	N	Arithmetic Mean (SD)	Geometric Mean (90% CI)	Median (Range)
AUC_{0-12h} (μM·hr)				
MK-0518 100 mg b.i.d.	7	6.0 (2.1)	5.8 (4.6, 7.3)	5.2 (4.3 to 10.2)
MK-0518 200 mg b.i.d.	7	10.3 (4.2)	9.4 (6.8, 13.1)	11.3 (4.8 to 15.9)
MK-0518 400 mg b.i.d.	6	17.3 (9.7)	14.3 (7.6, 26.7)	18.5 (3.8 to 28.8)
MK-0518 600 mg b.i.d.	8	19.3 (15.4)	14.6 (8.3, 25.8)	16.4 (2.9 to 53.9)
C_{max} (μM)				
MK-0518 100 mg b.i.d.	7	2.3 (1.1)	2.1 (1.4, 3.0)	2.3 (1.1 to 4.2)
MK-0518 200 mg b.i.d.	7	4.2 (2.0)	3.3 (1.9, 5.9)	3.9 (1.1 to 8.3)
MK-0518 400 mg b.i.d.	6	6.2 (4.1)	4.5 (2.0, 10.2)	6.6 (0.8 to 10.2)
MK-0518 600 mg b.i.d.	8	5.5 (5.7)	3.8 (2.0, 7.1)	4.0 (0.7 to 19.1)
C_{min} (nM)				
MK-0518 100 mg b.i.d.	7	55.2 (46.1)	42.6 (24.3, 75.0)	54.9 (14.3 to 151.9)
MK-0518 200 mg b.i.d.	7	133.3 (51.5)	112.4 (78.4, 161.1)	146.7 (58.2 to 179.1)
MK-0518 400 mg b.i.d.	6	161.6 (83.4)	141.7 (87.6, 229.1)	162.4 (65.7 to 265.5)
MK-0518 600 mg b.i.d.	8	290.3 (245.5)	204.9 (108.9, 385.7)	202.6 (43.1 to 771.8)

N = Number of patients in the treatment group.

Figure 4. Individual MK-0518 AUC0-12hr Values and Geometric Mean With 90% CIs (Cohort I; Monotherapy Phase)

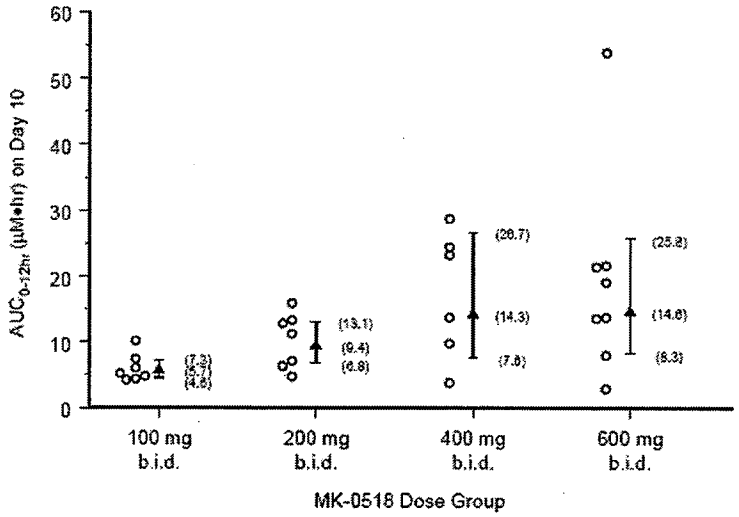


Figure 5. Individual MK-0518 Cmax Values and Geometric Mean With 90% CIs (Cohort I; Monotherapy Phase)

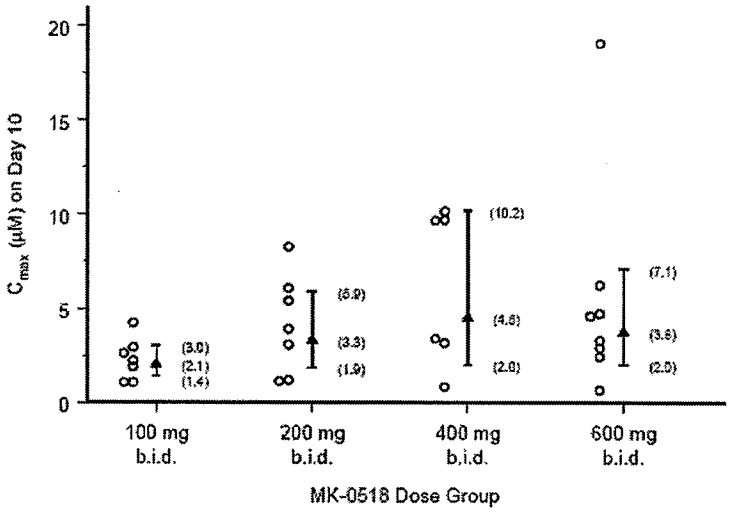
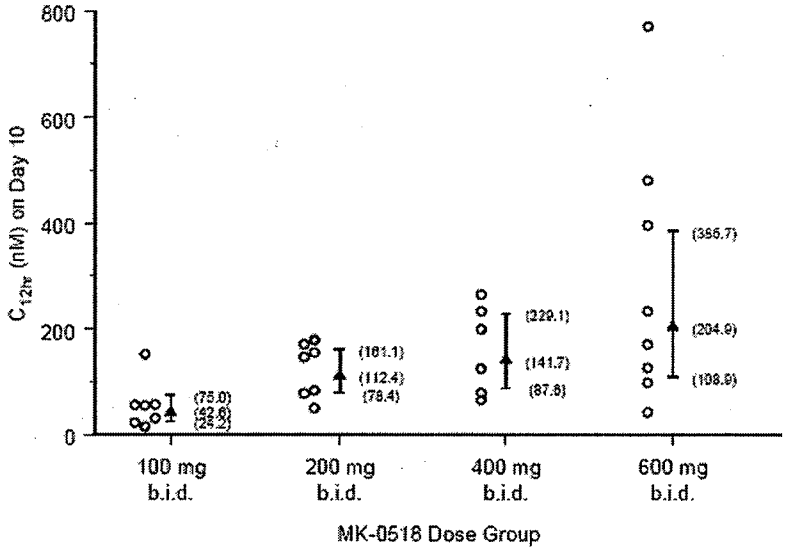


Figure 6. Individual MK-0518 C12hr Values and Geometric Mean With 90% CIs (Cohort I; Monotherapy Phase)



Part II, Combination Therapy:

Table 5. Summary Statistics for MK-0518 Intensive PK Parameters at Week 2 (Cohort I; Combination Therapy Phase)

Treatment	N	Arithmetic Mean (SD)	Geometric Mean (90% CI)	Median (Range)
$AUC_{0\text{-}12\ hr}$ (μM•hr)				
MK-0518 100 mg b.i.d.	6	6.5 (3.8)	5.4 (2.9, 9.9)	7.0 (1.7 to 12.0)
MK-0518 200 mg b.i.d.	7	15.4 (5.1)	14.9 (12.2, 18.2)	14.1 (11.5 to 26.6)
MK-0518 400 mg b.i.d.	6	25.9 (6.0)	25.3 (20.9, 30.8)	25.8 (19.9 to 32.4)
MK-0518 600 mg b.i.d.	6	21.1 (9.8)	18.3 (10.6, 31.6)	22.4 (5.2 to 34.9)
C_{max} (μM)				
MK-0518 100 mg b.i.d.	6	1.9 (1.6)	1.2 (0.5, 3.0)	1.7 (0.3 to 4.3)
MK-0518 200 mg b.i.d.	7	4.9 (1.6)	4.6 (3.6, 6.0)	5.3 (2.7 to 6.9)
MK-0518 400 mg b.i.d.	6	9.0 (2.8)	8.6 (6.5, 11.3)	9.6 (5.6 to 11.8)
MK-0518 600 mg b.i.d.	6	7.7 (3.7)	6.3 (3.2, 12.4)	8.0 (1.3 to 12.1)
C_{12hr} (nM)				
MK-0518 100 mg b.i.d.	6	213.7 (178.4)	155.1 (72.5, 331.5)	153.5 (37.8 to 522.1)
MK-0518 200 mg b.i.d.	7	235.8 (152.9)	182.6 (98.5, 338.6)	204.8 (55.1 to 441.0)
MK-0518 400 mg b.i.d.	6	270.6 (136.2)	239.2 (150.2, 381.0)	271.5 (105.5 to 447.8)
MK-0518 600 mg b.i.d.	6	125.8 (97.7)	67.7 (16.3, 280.6)	117.8 (2.3 to 290.3)

Note: MK-0518 was administered with tenofovir (TFV) and lamivudine (3TC).

N = Number of patients in the treatment group.

Table 6. Summary of Effects of Tenofovir and Lamivudine on MK-0518 by MK-0518 Intensive PK Parameters

Treatment	N	Geometric Mean (90% CI)		Geometric Mean Ratio (90% CI)†
		At Week 2 of Part II (A)	On Day 10 of Part I (B)	(A/B)
AUC_{0-24hr} (μM•hr) for MK-0518				
MK-0518 All Doses	25	13.9 (10.8, 18.0)	9.9 (7.7, 12.6)	1.41 (1.11, 1.79)
MK-0518 100 mg b.i.d.	6	5.4 (2.9, 9.9)	5.5 (4.2, 7.2)	0.98 (0.57, 1.67)
MK-0518 200 mg b.i.d.	7	14.9 (12.2, 18.2)	9.4 (6.8, 13.1)	1.58 (1.18, 2.15)
MK-0518 400 mg b.i.d.	6	25.3 (20.9, 30.8)	14.3 (7.6, 26.7)	1.78 (0.86, 3.68)
MK-0518 600 mg b.i.d.	6	18.3 (10.6, 31.8)	12.9 (5.8, 28.4)	1.42 (0.73, 2.78)
C_{max} (μM) for MK-0518				
MK-0518 All Doses	25	4.2 (3.0, 5.9)	3.2 (2.4, 4.3)	1.33 (0.98, 1.85)
MK-0518 100 mg b.i.d.	6	1.2 (0.5, 3.0)	2.0 (1.3, 3.1)	0.63 (0.28, 1.40)
MK-0518 200 mg b.i.d.	7	4.6 (3.6, 6.0)	3.3 (1.9, 5.9)	1.39 (0.89, 2.17)
MK-0518 400 mg b.i.d.	6	8.6 (6.5, 11.3)	4.5 (2.0, 10.2)	1.90 (0.78, 4.77)
MK-0518 600 mg b.i.d.	6	6.3 (3.2, 12.4)	3.3 (1.4, 8.1)	1.89 (0.94, 3.80)
C_{24hr} (nM) for MK-0518				
MK-0518 All Doses	25	147.7 (100.5, 217.0)	103.7 (77.6, 138.6)	1.42 (0.89, 2.28)
MK-0518 100 mg b.i.d.	6	155.1 (72.5, 331.5)	45.0 (22.8, 89.1)	3.44 (1.40, 8.46)
MK-0518 200 mg b.i.d.	7	182.6 (98.5, 338.6)	112.4 (78.4, 161.1)	1.62 (1.01, 2.61)
MK-0518 400 mg b.i.d.	6	239.2 (150.2, 381.0)	141.7 (87.6, 229.1)	1.69 (1.12, 2.54)
MK-0518 600 mg b.i.d.	6	87.7 (16.3, 280.6)	159.3 (71.8, 353.4)	0.43 (0.07, 2.41)

† Geometric mean ratio (GMR) is the ratio of geometric means of PK parameters from Cohort I subjects at Week 2 of the combination therapy phase (Part II) vs. those on Day 10 of the monotherapy phase (Part I); CI was calculated based on the paired *t* distribution.

Note: MK-0518 was administered with tenofovir (TFV) and lamivudine (3TC) in Part II; MK-0518 was administrated alone in Part I.

N = Number of patients who had intensive PK data at both Week 2 of Part II and Day 10 of Part I in the treatment group.

Table 7. Summary of Effects of MK-0518 Versus Efavirenz on Lamivudine PK Parameters

Treatment	N	Geometric Mean (90% CI)	GMR (90% CI)†
AUC_{0-24hr} (ng•hr/mL) for Lamivudine			
MK-0518 all doses	22	12714.1 (11224.1, 14401.9)	1.40 (0.95, 2.07)
MK-0518 100 mg b.i.d.	6	11828.7 (8063.2, 17352.7)	1.30 (0.77, 2.21)
MK-0518 200 mg b.i.d.	6	12857.3 (10601.6, 15592.9)	1.42 (0.94, 2.14)
MK-0518 400 mg b.i.d.	6	14162.1 (10816.0, 18543.4)	1.56 (0.99, 2.45)
MK-0518 600 mg b.i.d.	4	11850.9 (7687.8, 18268.3)	1.31 (0.78, 2.19)
Efavirenz 600 mg q.d.	4	9074.7 (5906.2, 13942.9)	
C_{max} (ng/mL) for Lamivudine			
MK-0518 all doses	22	2007.8 (1831.7, 2200.9)	1.20 (0.98, 1.47)
MK-0518 100 mg b.i.d.	6	2041.4 (1591.4, 2618.6)	1.22 (0.93, 1.60)
MK-0518 200 mg b.i.d.	6	1936.3 (1648.7, 2276.9)	1.16 (0.91, 1.48)
MK-0518 400 mg b.i.d.	6	2183.6 (1693.3, 2816.0)	1.30 (0.99, 1.72)
MK-0518 600 mg b.i.d.	4	1823.4 (1477.5, 2250.3)	1.09 (0.85, 1.39)
Efavirenz 600 mg q.d.	4	1676.3 (1369.1, 2052.3)	
C_{24hr} (ng/mL) for Lamivudine			
MK-0518 all doses	22	92.9 (71.2, 121.2)	1.11 (0.27, 4.61)
MK-0518 100 mg b.i.d.	6	70.3 (48.9, 100.9)	0.84 (0.20, 3.53)
MK-0518 200 mg b.i.d.	6	94.3 (77.1, 115.4)	1.13 (0.28, 4.59)
MK-0518 400 mg b.i.d.	6	132.0 (51.1, 340.9)	1.58 (0.30, 8.46)
MK-0518 600 mg b.i.d.	4	81.5 (32.5, 204.4)	0.98 (0.20, 4.80)
Efavirenz 600 mg q.d.	4	83.4 (16.3, 427.6)	

† Geometric mean ratio (GMR) is the ratio of geometric mean of lamivudine PK parameter of MK-0518 dose group vs. efavirenz group.

Note: MK-0518 and efavirenz (EFV) were administered with tenofovir (TFV) and lamivudine (3TC).

N = Number of patients in the treatment group.

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

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP ANALYSIS:

Part I, Monotherapy:

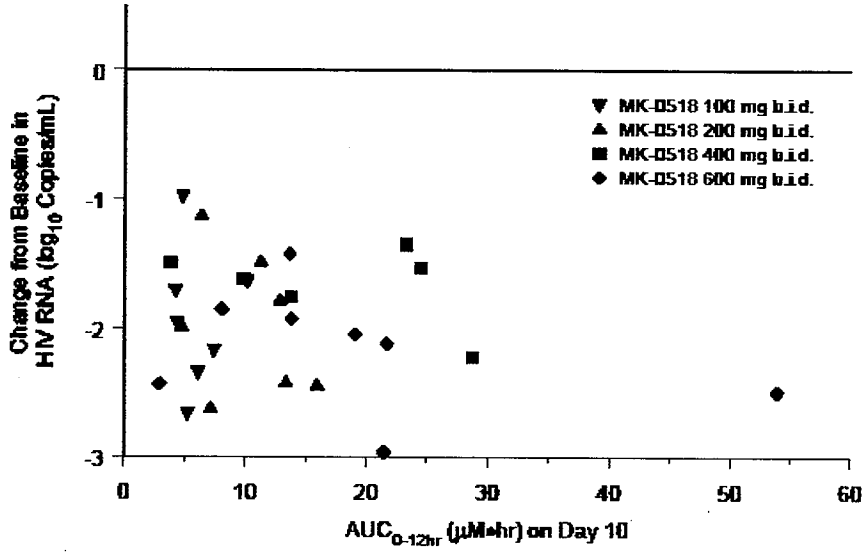
Table 8. Correlation Between MK-0518 Intensive PK Parameters and Antiretroviral Effects (Cohort I; Monotherapy Phase)

PK Parameter	Change From Baseline in Log_{10} HIV RNA On Day 10		Slope of Log_{10} HIV RNA Decrease (Day 2 to Day 8)	
	Correlation†	p-Value	Correlation†	p-Value
Pearson's Correlation				
$AUC_{0-12\,hr}$	-0.221	0.259	-0.219	0.262
C_{max}	-0.183	0.352	-0.055	0.782
C_{12hr}	-0.431	0.022	-0.529	0.004
Spearman's Rank Correlation				
$AUC_{0-12\,hr}$	-0.112	0.572	-0.038	0.855
C_{max}	-0.099	0.616	0.103	0.602
C_{12hr}	-0.408	0.031	-0.503	0.006

† Pearson's correlation coefficient and Spearman's rank correlation coefficient are between -1 and 1.

A negative correlation indicates that an increase in PK parameter leads to an increase in antiretroviral effect; a positive correlation indicates that an increase in PK parameter leads to a decrease in antiretroviral effect; zero correlation indicates no evidence of association.

Figure 7. Change From Baseline in Log10 HIV RNA on Day 10 Versus MK-0518 AUC0-12hr on Day 10 (Cohort I; Monotherapy Phase)



PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP ANALYSIS:

Part I, Monotherapy:

Table 8. Correlation Between MK-0518 Intensive PK Parameters and Antiretroviral Effects (Cohort I; Monotherapy Phase)

PK Parameter	Change From Baseline in Log_{10} HIV RNA On Day 10		Slope of Log_{10} HIV RNA Decrease (Day 2 to Day 8)	
	Correlation[1]	p-Value	Correlation[1]	p-Value
Pearson's Correlation				
AUC_{0-12hr}	-0.221	0.259	-0.219	0.262
C_{max}	-0.183	0.352	-0.055	0.782
C_{12hr}	-0.431	0.022	-0.529	0.004
Spearman's Rank Correlation				
AUC_{0-12hr}	-0.112	0.572	-0.036	0.855
C_{max}	-0.099	0.616	0.103	0.602
C_{12hr}	-0.408	0.031	-0.503	0.006

[1] Pearson's correlation coefficient and Spearman's rank correlation coefficient are between -1 and 1.

A negative correlation indicates that an increase in PK parameter leads to an increase in antiretroviral effect; a positive correlation indicates that an increase in PK parameter leads to a decrease in antiretroviral effect; zero correlation indicates no evidence of association.

Figure 7. Change From Baseline in Log10 HIV RNA on Day 10 Versus MK-0518 AUC0-12hr on Day 10 (Cohort I; Monotherapy Phase)

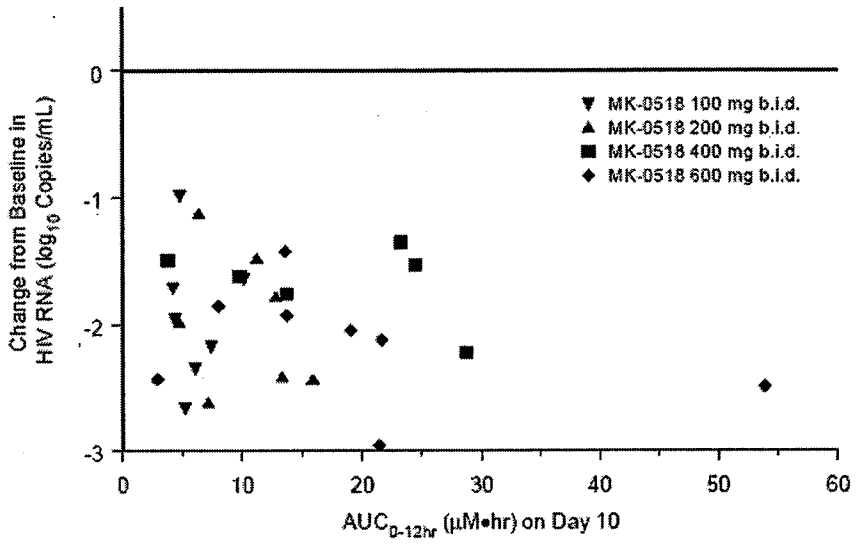


Figure 10. Slope of Log10 HIV RNA Decrease Between Day 2 and Day 8 Versus MK-0518 Cmax on Day 10 (Cohort I; Monotherapy Phase)

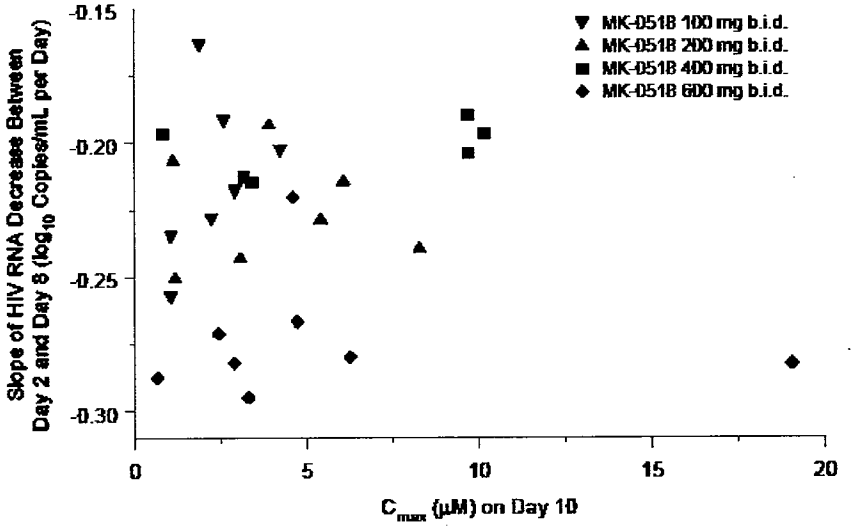


Figure 11. Change From Baseline in Log10 HIV RNA on Day 10 Versus MK-0518 C12hr on Day 10 (Cohort I; Monotherapy Phase)

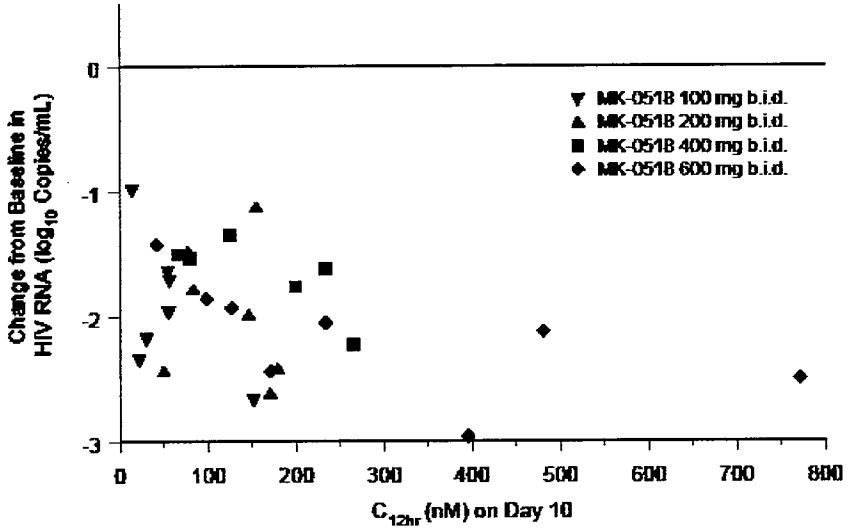
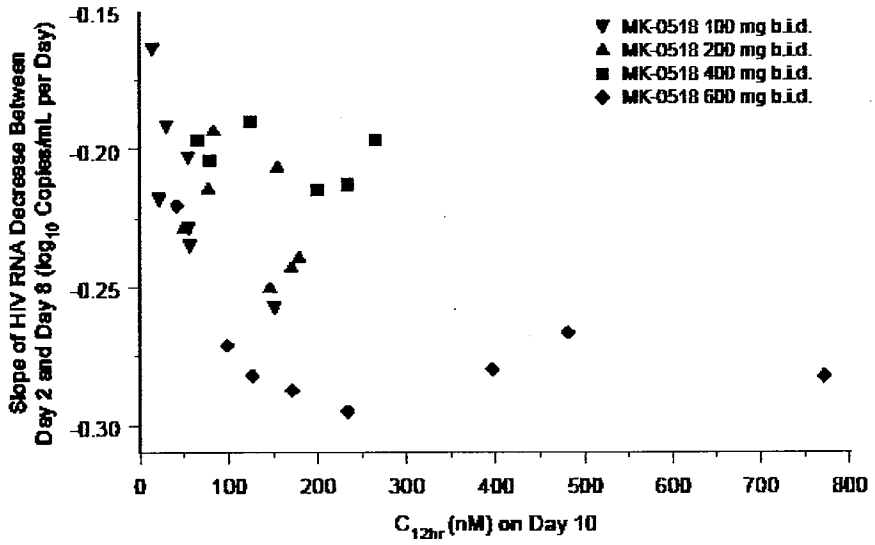


Figure 12. Slope of Log10 HIV RNA Decrease Between Day 2 and Day 8 Versus MK-0518 C12hr on Day 10 (Cohort I; Monotherapy Phase)



CONCLUSIONS AND DISCUSSION:

Efficacy

MK-0518 at all studied doses (100, 200, 400, and 600 mg b.i.d.) administered for 10 days monotherapy to treatment naïve patients with HIV infection has superior antiretroviral activity compared to placebo. It was not possible to distinguish among the MK-0518 doses studied based on efficacy data over 10 days of monotherapy.

MK-0518 at all studied doses (100, 200, 400, and 600 mg b.i.d.) doses in combination with TFV and 3TC in treatment naïve patients with HIV infection provides potent, rapid and durable antiretroviral efficacy in treatment naïve patients with HIV infection. MK-0518 at all studied doses in combination with TFV and 3TC had comparable antiretroviral efficacy compared with EFV in combination with TFV and 3TC at both Week 24 and Week 48. MK-0518 at all studied doses in combination with TFV and 3TC achieved viral suppression (HIV RNA <50 copies/mL) earlier than those receiving EFV in combination with TFV and 3TC. It was not possible to distinguish among the MK-0518 doses studied based on the 48-week efficacy data.

Pharmacokinetics

As observed in healthy subjects, the PK variability is quite large for MK-518 in HIV patients.
The plasma levels of MK-0518 are higher in combination with tenofovir and lamivudine than for MK-0518 alone, which is consistent with the findings in a Phase I drug interaction study with tenofovir in healthy volunteers, which demonstrated that MK-0518 exposure were higher when MK-0518 was coadministered tenofovir. 3TC is predominantly renally eliminated via active organic cationic secretion, and has not been reported to inhibit UDP glucuronosyltransferases (UGTs). Thus, the increase in MK-0518 exposure in Part II is likely a result of MK-0518 interactions with tenofovir and not 3TC. The pharmacokinetic properties for 3TC coadministered with MK-0518 and tenofovir are similar for 3TC coadministered with EFV and tenofovir.

PK/PD Relationships:

The analysis suggested a possible association between the short-term antiretroviral activity of MK-0518 and the corresponding C12hr value on Day 10 (nominal p-values <0.05 for Pearson's and Spearman correlations). However, all doses of MK-0518 were associated with potent antiretroviral effect and it is not possible to differentiate between the studied doses on the basis of antiretroviral activity. All patients receiving MK-0518 had substantial declines in HIV RNA by Day 10 including the 3 patients with trough concentrations of <33 nM; all of these 3 patients achieved either HIV RNA <400 copies/mL or a >2 log10 decline in HIV RNA by Day 10.

Protocol 005 (Phase 2 study in treatment experienced patients)

TITLE: Multicenter, Double-Blind, Randomized, Dose-Ranging, Placebo-Controlled Study to Evaluate the Safety, Pharmacokinetics, and Antiretroviral Activity of MK-0518 in Combination With an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV-Infected Patients With Documented Resistance to at Least 1 Drug in Each of the 3 Classes of Licensed Oral Antiretroviral Therapies

OBJECTIVES: The primary objective was to evaluate the antiretroviral activity, safety and tolerability of MK-0518 given b.i.d. at the studied doses compared to placebo, each in combination with OBT for 24 weeks. The secondary objectives included the evaluation of dose-response relationship for MK-0518 given b.i.d. in combination with OBT, as measured by safety and efficacy parameters.

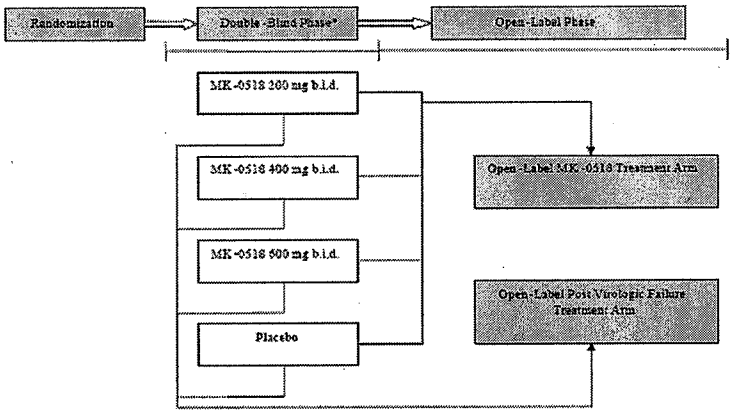
STUDY CENTERS: Thirty-one centers participated in this study. Fifteen of these study centers were in the United States; 13 were in Europe (Belgium, France, Germany, Great Britain, Italy, Spain, and Switzerland); 2 were in Americas (Brazil and Mexico); and 1 was in Asia (Malaysia).

SUBJECTS AND STUDY DESIGN: This multi-center, double-blind, randomized, dose-ranging, placebo-controlled study enrolled treatment-experienced HIV-infected patients who had failed therapy, to evaluate the safety, tolerability, pharmacokinetics, and efficacy of MK-0518 given b.i.d. at the studied doses (200, 400 and 600 mg b.i.d.) compared with placebo, each in combination with OBT. These patients had failed therapy, as documented by HIV RNA >5000 copies/mL and documented resistance to at least 1 drug in each of the 3 classes of licensed oral ARTs (NRTI, NNRTI, and PI) at screening. Because preliminary pharmacokinetic data suggested that co-administration of MK-0518 with atazanavir (ATV) increases overall drug exposure to MK-0518, there were 2 sub-studies depending on whether ATV was included in the OBT: patients who received non-ATV-containing OBT were enrolled in Sub-study A and patients who received ATV-containing OBT were enrolled in sub-study B. The study design allowed the evaluation of potential effects of different MK-0518 exposures on safety, tolerability, and efficacy of the treatment regimen.

When the MK-0518 dose of 400 mg b.i.d. was selected for Phase III, the protocol was amended (28-Feb-2006) to switch all patients who had completed at least 24 weeks of double-blind phase (DB) to receive open-label MK-0518 (open-label phase; OL). The study also had an open-label post virologic failure arm (OLPVF) for those patients who experienced virologic failure during DB or during OL. Under the original protocol, patients in this OLPVF arm received MK-0518 600 mg b.i.d. In the protocol amendment, all patients in the OLPVF arm received MK-0518 400 mg b.i.d.

Study drug was taken with or without food.

Study Design



* The Schema applies to both Substudy A and Substudy B.

Patient Baseline Characteristics (Studies A and B Combined)

Category	MK-0518 200 mg b.i.d. (N = 45)	MK-0518 400 mg b.i.d. (N = 45)	MK-0518 600 mg b.i.d. (N = 45)	Placebo (N = 45)	Total (N = 178)
Gender n (%)					
Male	36 (83.7)	40 (88.9)	41 (91.1)	40 (88.9)	157 (88.2)
Female	7 (16.3)	5 (11.1)	4 (8.9)	5 (11.1)	21 (11.8)
Race n (%)					
White	36 (83.7)	35 (77.8)	32 (71.1)	33 (73.3)	136 (76.4)
Black	3 (7.0)	5 (11.1)	7 (15.6)	5 (11.1)	20 (11.2)
Asian	0 (0.0)	0 (0.0)	2 (4.4)	1 (2.2)	3 (1.7)
Hispanic American	4 (9.3)	5 (11.1)	4 (8.9)	5 (11.1)	18 (10.1)
Others	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.6)
Region n (%)					
North America	13 (30.2)	13 (28.9)	18 (40.0)	12 (26.7)	56 (31.5)
Central/South America	10 (23.3)	8 (17.8)	9 (20.0)	9 (20.0)	36 (20.2)
Asia Pacific	0 (0.0)	0 (0.0)	1 (2.2)	1 (2.2)	2 (1.1)
Europe	20 (46.5)	24 (53.3)	17 (37.8)	23 (51.1)	84 (47.2)
Age (years)					
16-64 n (%)	43 (100.0)	43 (95.6)	45 (100.0)	45 (100.0)	176 (98.9)
≥ 65 n (%)	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.1)
Mean (SD)	44.0 (9.0)	45.1 (8.4)	43.8 (7.0)	43.3 (7.1)	44.1 (7.9)
Median	43.0	43.0	44.0	43.0	43.0
Range	18 to 57	32 to 69	25 to 63	29 to 59	18 to 69
CD4 Cell Count (cells/mm^3)					
Mean (SD)	244.9 (185.8)	220.6 (114.9)	220.4 (160.9)	274.0 (188.4)	239.9 (165.0)
Median	234.0	196.0	181.0	246.0	212.5
Range	30 to 1,153	68 to 673	30 to 663	37 to 880	30 to 1,153
Plasma HIV RNA (log_{10} copies/mL)					
Mean (SD)	4.6 (0.6)	4.8 (0.5)	4.7 (0.5)	4.7 (0.6)	4.7 (0.5)
Median	4.6	4.8	4.7	4.7	4.7
Range	3.5 to 5.9	3.7 to 5.9	3.8 to 5.8	3.6 to 5.8	3.5 to 5.9
Plasma HIV RNA (copies/mL)					
Geometric Mean	44,642.6	59,107.9	49,064.8	47,432.6	49,841.6
Median	43,200.0	64,300.0	44,800.0	53,000.0	45,750.0
Range	3,000 to 750,000	4,770 to 750,000	7,030 to 589,000	3,630 to 611,000	3,000 to 750,000
History of AIDS n (%)					
Yes	34 (79.1)	39 (86.7)	37 (82.2)	36 (80.0)	146 (82.0)
No	9 (20.9)	6 (13.3)	8 (17.8)	9 (20.0)	32 (18.0)

Prior Use of ARTs median (range)					
Number of ARTs	12.0 (3 to 18)	13.5 (8 to 17)	12.0 (3 to 21)	12.0 (5 to 18)	12.0 (3 to 31)
NRTI	6.0 (2 to 10)	6.0 (4 to 9)	6.0 (2 to 10)	6.0 (3 to 9)	6.0 (2 to 10)
NNRTI	1.0 (0 to 3)	1.0 (1 to 3)	2.0 (0 to 3)	2.0 (1 to 4)	1.5 (0 to 4)
PI	5.0 (3 to 7)	5.0 (1 to 7)	4.0 (1 to 8)	5.0 (1 to 8)	5.0 (1 to 8)
Year of ARTs Use	9.7 (0 to 16)	10.5 (3 to 14)	9.4 (3 to 16)	9.9 (3 to 17)	9.9 (0 to 17)
Stratum n (%)					
Enfuvirtide in OBT	14 (33.3)	18 (42.9)	15 (35.8)	16 (35.6)	64 (36.0)
Resistant >1 PI	43 (150.5)	45 (100.0)	43 (95.6)	44 (97.8)	175 (98.3)

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

n (%) = Number (Percent) of patients in each subcategory.

ART = Antiretroviral therapy; NRTI = Nucleoside reverse transcriptase inhibitor; NNRTI = Non-Nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

FORMULATION: MK-0518, final poloxamer formulation tablets 200 mg and 400 mg and matching placebo tablets.

SAMPLE COLLECTION: Population pharmacokinetic (PK) sampling was performed for all patients in the double blind treatment arms, the open-label treatment post virologic failure treatment arm, and the open-label MK-0518 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 MK-0518 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.

ASSAYS: Plasma samples were analyzed at [redacted] for MK-0518 concentrations. A validated HPLC-MS/MS assay was used for plasma MK-0518 [redacted]

PHARMACOKINETIC DATA ANALYSIS: A population pharmacokinetic analysis was performed on the MK-0518 concentration data collected during blinded treatment by [redacted] The results were reported separately.

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EFFICACY RESULTS:

Table 1. Change From Baseline in HIV RNA (Log10 Copies/mL) at Week 24 — (Observed Failure Approach for Data Summary / Treatment Related Discontinuation = Failure Approach for p-Values)
(Sub-study A; Double-Blind Phase)

Treatment	N	Baseline Mean	Change From Baseline† at Week 24 Mean (SD)	95% CI	Treatment Effect (MK-0518 vs. Placebo) Difference‡ (95% CI)	p-Value§
MK-0518 200 mg b.i.d.	30	4.71	-1.83 (0.19)	(-2.21, -1.45)	-1.57 (-2.03, -1.13)	<0.001
MK-0518 400 mg b.i.d.	31	4.81	-1.76 (0.19)	(-2.15, -1.37)	-1.51 (-1.97, -1.04)	<0.001
MK-0518 600 mg b.i.d.	31	4.73	-1.74 (0.16)	(-2.08, -1.41)	-1.49 (-1.90, -1.07)	<0.001
Placebo	33	4.73	-0.26 (0.13)	(-0.52, 0.01)		

† Amplicor Standard assay values reported as '<400 copies/mL HIV RNA Detected' were imputed by 400 copies/mL, and value reported as '<400 copies/mL HIV RNA Not Detected' were imputed as 200 copies/mL; Baseline HIV RNA level was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

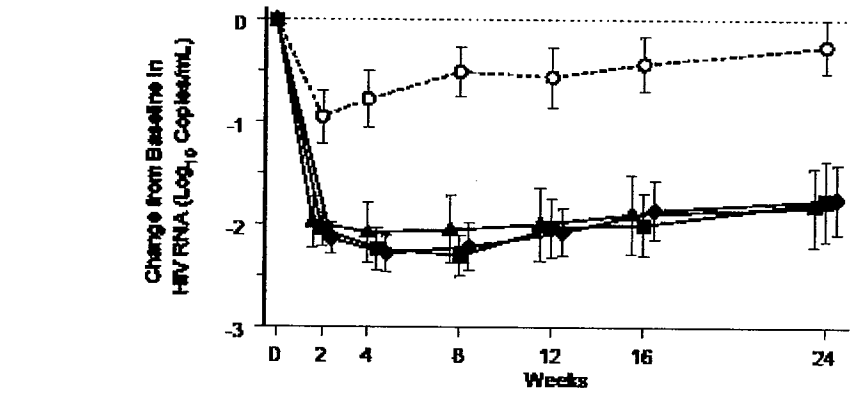
‡ A negative value means MK-0518 is better than Placebo.

§ Nominal p-values were calculated from Mann-Whitney-Wilcoxon nonparametric rank test. Patients who achieved HIV RNA <400 copies/mL were assigned best rank; Patients who discontinued assigned therapy due to adverse experiences or lack of efficacy were assigned worst rank.

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

Figure 1. Change From Baseline in Log10 HIV RNA (95% CI) Over Time – Observed Failure Approach (Sub-study A; Double-Blind Phase)



	D	2	4	8	12	16	24
▲ MK-0518 200 mg b.i.d.	30	30	29	29	29	29	29
■ MK-0518 400 mg b.i.d.	31	31	31	31	30	31	31
◆ MK-0518 600 mg b.i.d.	32	32	32	31	32	32	31
○ Placebo	33	33	33	33	32	33	33

Table 2. Change From Baseline in HIV RNA (Log10 Copies/mL) at Week 24 — (Observed Failure Approach for Data Summary / Treatment-Related Discontinuation = Failure Approach for p-Values)
(Sub-study B; Double-Blind Phase)

Treatment	N	Baseline Mean	Change From Baseline† at Week 24 Mean (SD)	95% CI	Treatment Effect (MK-0518 vs. Placebo) Difference‡ (95% CI)	p-Value§
MK-0518 200 mg b.i.d.	13	4.57	-1.73 (0.36)	(-2.09, -1.16)	-1.13 (-1.97, -0.28)	0.031
MK-0518 400 mg b.i.d.	14	4.69	-2.11 (0.18)	(-2.51, -1.72)	-1.51 (-2.37, -0.74)	0.001
MK-0518 600 mg b.i.d.	13	4.64	-2.07 (0.20)	(-2.51, -1.63)	-1.47 (-2.25, -0.68)	0.002
Placebo	12	4.56	-0.60 (0.31)	(-1.38, 0.09)		

† Amplicor Standard assay values reported as '<400 copies/mL HIV RNA Detected' were imputed by 400 copies/mL, and value reported as '<400 copies/mL HIV RNA Not Detected' were imputed as 200 copies/mL; Baseline HIV RNA level was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

‡ A negative value means MK-0518 is better than Placebo.

§ Nominal p-values were calculated from Mann-Whitney-Wilcoxon nonparametric rank test: Patients who achieved HIV RNA <400 copies/mL were assigned best rank; Patients who discontinued assigned therapy due to adverse experiences or lack of efficacy were assigned worst rank.

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

Figure 2. Change From Baseline in Log10 HIV RNA (95% CI) Over Time – Observed Failure Approach (Sub-study B; Double-Blind Phase)

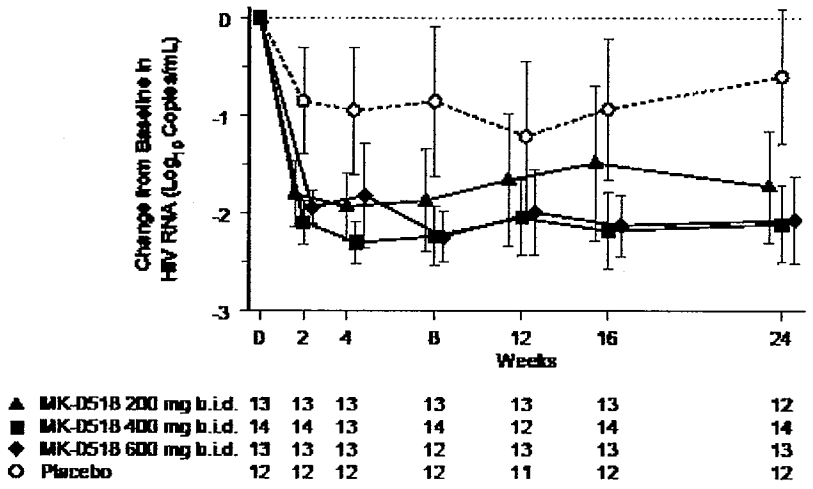
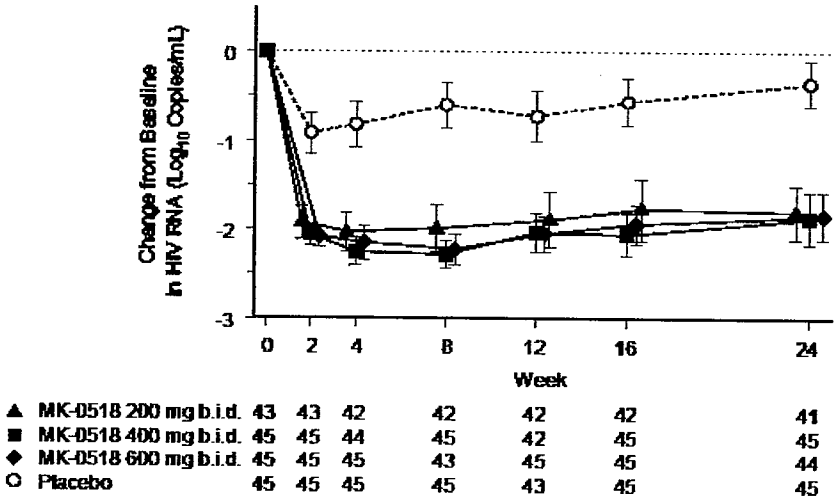


Table 3. Efficacy Response at Week 24 by Sub-study — Non-Completer=Failure Approach / Observed Failure Approach (Sub-studies A and B Combined; Double-Blind Phase)

Treatment	Substudy A (No ATV) N	Substudy A (No ATV) Mean (95% CI)	Substudy B (ATV) N	Substudy B (ATV) Mean (95% CI)	Total N	Total Mean (95% CI)
Percent of patients with HIV RNA<400 copies/mL at Week 24						
MK-0518 200 mg b.i.d.	30	70.00 (50.60, 85.27)	13	69.23 (38.57, 90.91)	43	69.77 (53.87, 82.82)
MK-0518 400 mg b.i.d.	31	64.52 (45.37, 80.77)	14	85.71 (57.19, 98.22)	45	71.11 (55.69, 83.63)
MK-0518 600 mg b.i.d.	32	62.50 (43.69, 78.90)	13	92.31 (63.97, 99.81)	45	71.11 (55.69, 83.63)
Placebo	33	12.12 (3.40, 28.20)	12	25.00 (5.49, 57.19)	45	15.56 (6.49, 29.46)
Percent of patients with HIV RNA <50 copies/mL at Week 24						
MK-0518 200 mg b.i.d.	30	63.33 (43.86, 80.07)	13	69.23 (38.57, 90.91)	43	65.12 (49.07, 78.99)
MK-0518 400 mg b.i.d.	31	48.39 (30.15, 66.94)	14	71.43 (41.90, 91.61)	45	55.56 (40.00, 70.38)
MK-0518 600 mg b.i.d.	32	56.25 (37.68, 73.64)	13	92.31 (63.97, 99.81)	45	68.89 (53.05, 80.00)
Placebo	33	12.12 (3.40, 28.20)	12	16.67 (2.89, 48.41)	45	13.33 (5.05, 26.79)
Percent of patients with >1 $\log_{10}$ Drop in HIV RNA or <400 copies/mL at Week 24						
MK-0518 200 mg b.i.d.	30	76.67 (57.72, 90.07)	13	76.92 (46.19, 94.96)	43	76.74 (61.37, 88.24)
MK-0518 400 mg b.i.d.	31	74.19 (55.39, 88.14)	14	92.86 (66.13, 99.82)	45	80.00 (65.40, 90.42)
MK-0518 600 mg b.i.d.	32	75.00 (56.60, 88.54)	13	92.31 (63.97, 99.81)	45	80.00 (65.40, 90.42)
Placebo	33	12.12 (3.40, 28.20)	12	33.33 (9.92, 65.11)	45	17.78 (8.00, 32.05)

Figure 3. Change From Baseline in Log10 HIV RNA (95% CI) Over Time -- Observed Failure Approach (Sub-studies A and B combined; Double-Blind Phase)



SAFETY RESULTS: MK-0518 at the studied doses (200, 400, and 600 mg b.i.d.) in treatment-experienced patients with HIV infection was generally well tolerated over 48 weeks. See details in Medical Officer's review.

PHARMACOKINETIC RESULTS:

The population pharmacokinetic (PPK) portion of the report will be reviewed in a separate PPK study report. See Pharmacometrics review.

CONCLUSIONS AND DISCUSSION:

Efficacy

The results from this Phase II dose-ranging study in HIV-infected, treatment-experienced patients failing antiretroviral therapies, with documented triple-class resistant virus, demonstrate that MK-0518, at all doses studied (200, 400, and 600 mg b.i.d.), in combination with OBT, had a favorable safety profile and provided superior antiretroviral efficacy, in comparison with placebo in combination with OBT at Week 24. There was no evidence of dose-related toxicity, and it was not possible to distinguish among the MK-0518 doses studied based on efficacy parameters. There is no evidence of a different treatment effect between sub-study A without atazanavir and sub-study B with atazanavir.

Protocol 006

TITLE: A Randomized, Double-Blind, Placebo-Controlled, 2-Period Study to Evaluate the Influence of Atazanavir on a Single Dose of MK-0518 in Healthy Male Subjects

OBJECTIVES: To evaluate the effect of coadministration of atazanavir and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\,hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of atazanavir coadministered with a single dose of MK-0518

SUBJECTS AND STUDY DESIGN: This was a randomized, double-blind, placebo-controlled, 2-period study in young, healthy, male subjects. In Period 1, 12 subjects received a single 100 mg oral dose of MK-0518 (N=10) or placebo (N=2). This was followed by at least a 4-day washout period prior to the start of Period 2. In Period 2, the same 12 subjects received 400 mg oral doses of atazanavir once daily for 9 days. On Day 7, subjects received their daily dose of atazanavir in combination with a 100 mg single oral dose of MK-0518 or placebo. Atazanavir was administered in an open-labeled fashion, while MK-0518 was administered in a double-blind fashion. The same 2 subjects in each period received placebo versus MK-0518.

All doses of study drug were administered following a moderate-fat meal. On days of pharmacokinetic samplings, the meal was administered ~30 minutes prior to dose and ingested within ~25 minutes. The dose was administered within ~5 minutes after completion of the meal.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518, Phase I lactose formulation tablets 100 mg, placebo MK-0518 (100 mg image) tablets, REYATAZ 200mg capsules

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. The

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

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PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following a Single Oral Dose of 100 mg MK-0518 With or Without Multiple Oral Doses of 400 mg Atazanavir Once-Daily to Young, Healthy, Male Subjects (Inset: semilog scale)

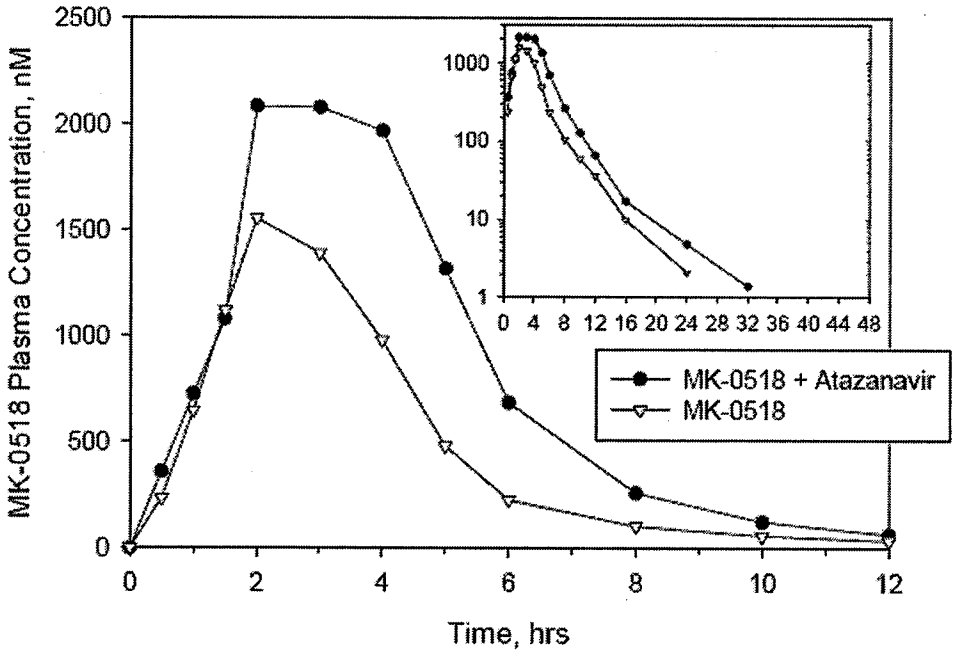


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics for Young, Healthy, Male Subjects Administered Single Oral Doses of 100-mg MK-0518 with or without Pre- and Coadministration of 400-mg Atazanavir Daily

Pharmacokinetic Parameter	MK-0518 + Atazanavir			MK-0518			(MK-0518 + Atazanavir/ 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) [‡]	10	57.7	(37.7, 88.3)	10	29.8	(19.3, 45.5)	10	1.95	(1.50, 2.92)	0.244
$AUC_{0-\infty}$ (μM•hr) [‡]	10	9.59	(8.11, 11.35)	10	5.57	(4.71, 6.59)	10	1.72	(1.47, 2.02)	0.038
C_{max} (μM) [‡]	10	3.56	(2.59, 4.35)	10	2.19	(1.69, 2.83)	10	1.53	(1.11, 2.12)	0.158
T_{max} (hr)	10	3.0 [§]		10	2.5 [§]		10	0.5 [‖]	(-0.5, 2.0) [‖]	
$t_{1/2}\alpha$ (hr)	6	1.02 [¶]		6	0.81 [¶]		5	0.26 [‖]	(-0.25, 0.43) [‖]	
$t_{1/2}\beta$ (hr)	10	3.6 [¶]		10	3.1 [¶]		10	0.9 [‖]	(-0.3, 2.0) [‖]	

[†] 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.
[¶] Harmonic mean reported for $t_{1/2}$.

Table 2. Individual MK-0518 Pharmacokinetics and Summary Statistics Following a Single Oral Dose of 100 mg MK-0518 With or Without Multiple Oral Doses of 400 mg Atazanavir Once-Daily to Young, Healthy, Male Subjects

	C_{12hr}, nM			$AUC_{0-\infty}$, μM•hr			C_{max}, μM			T_{max}, hr			$t_{½}$ α, hr		$t_{½}$ β, hr	
AN	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B	A	B	A	B
S1	27.5	16.2	1.51	7.89	5.08	1.55	4.42	2.00	2.21	1.0	3.0	-2.0	0.76	1.01	3.2	5.0
S2	92.3	76.7	1.20	7.33	7.53	0.97	2.99	3.15	0.95	4.0	2.0	2.0	0.82	0.65	3.6	2.6
S3	21.8	18.5	1.18	8.47	3.90	2.17	3.17	1.47	2.16	2.0	4.0	-2.0	ND	0.62	3.3[1]	4.0
S4	79.4	49.3	1.61	14.73	5.63	2.62	6.71	1.59	4.22	2.0	3.0	-1.0	ND	ND	5.2[1]	2.4[1]
S5	59.6	16.2	3.68	7.81	5.67	1.38	2.21	3.72	0.59	4.0	1.0	3.0	ND	ND	2.5[1]	2.0[1]
S6	38.0	22.7	1.67	7.93	3.78	2.10	1.96	1.31	1.50	4.0	3.0	1.0	ND	ND	1.9[1]	3.3[1]
S7	53.1	73.1	0.73	11.08	6.53	1.70	3.63	1.80	2.02	3.0	3.0	0.0	1.25	ND	6.2	2.5[1]
S8	115.0	15.3	7.52	11.15	7.32	1.52	2.86	3.32	0.86	4.0	2.0	2.0	1.42	0.99	6.8	4.6
S9	78.1	47.5	1.64	9.68	5.34	1.81	4.12	2.94	1.40	2.0	2.0	0.0	0.93	0.67	4.1	3.2
S2	85.5	20.9	4.09	12.36	6.29	1.97	3.47	1.98	1.75	3.0	2.0	1.0	1.29	0.87	4.8	3.4
AM	65.0	35.8	--	9.84	5.71	--	3.55	2.33	--	2.9	2.5	--	1.02[2]	0.81[2]	3.6[2]	3.1[2]
SD	30.2	24.0	--	2.43	1.27	--	1.35	0.87	--	1.1	0.8	--	0.27[3]	0.16[3]	1.6[2]	0.9[2]
Med	66.9	21.8	--	9.08	5.65	--	3.32	1.99	--	3.0	2.5	0.5[4]	1.09	0.85	4.5	3.7
GM[5]	57.7	29.6	1.95	9.59	5.57	1.72	3.36	2.19	1.53	--	--	--	--	--	--	--

A: 400-mg atazanavir qd x 9 days with 100-mg MK-0518 on Day 7
B: 100 mg single dose MK-0518
AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean
ND: Value not determined due to insufficient data
[1]Value determined from monoexponential, rather than biexponential equation; value may therefore represent a combination of the α and β phases
[2]Values reported for half-lives are harmonic mean and jackknife standard deviation
[3]For T_{max}, represents Hodges-Lehman estimate of median treatment difference
[4]Based on least squares mean from an ANOVA performed on the natural-log transformed values

Figure 2. Individual MK-0518 C_{12hr} Ratios [MK-0518 Coadministered with Atazanavir (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 100-mg MK-0518 With or Without Multiple Oral Doses of 400-mg Atazanavir Once-Daily to Young, Healthy, Male Subjects (n=10)

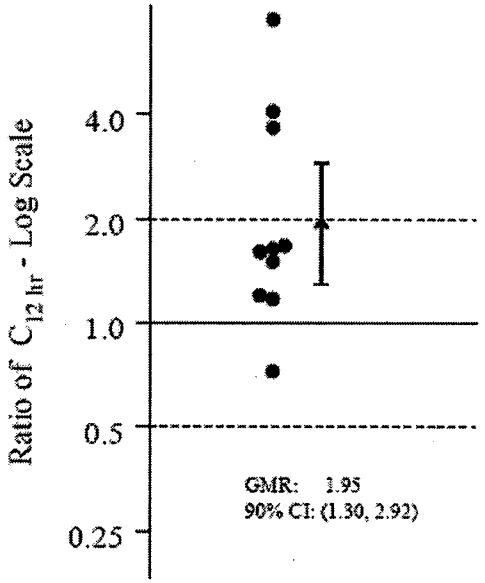


Figure 3. Individual MK-0518 AUC0-∞ Ratios [MK-0518 Coadministered with Atazanavir (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 100-mg MK-0518 With or Without Multiple Oral Doses of 400-mg Atazanavir Once-Daily to Young, Healthy, Male Subjects (n=10)

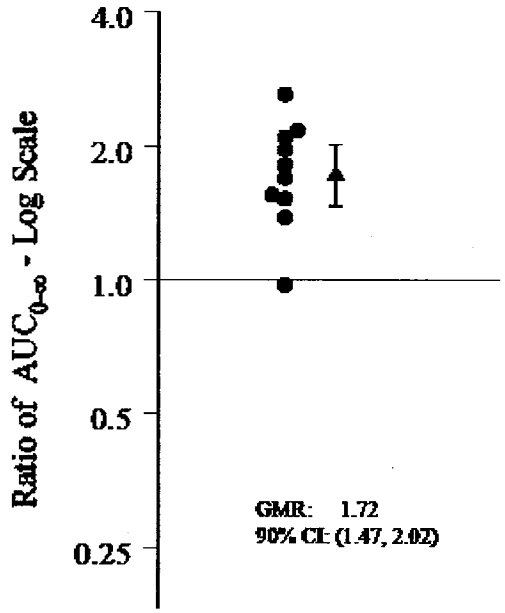
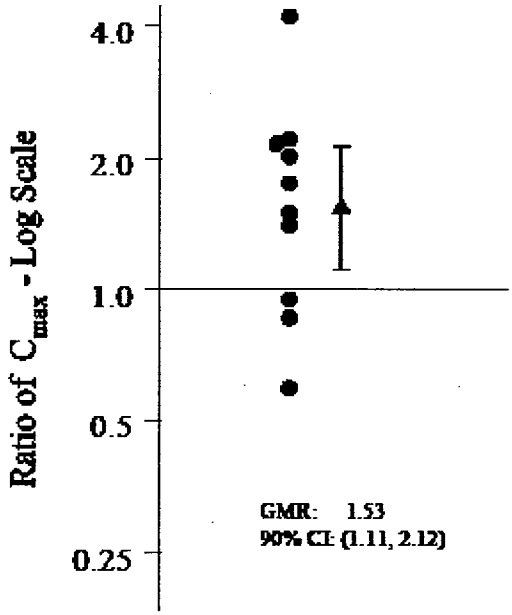


Figure 4. Individual MK-0518 Cmax Ratios [MK-0518 Coadministered with Atazanavir (A) / MK-0518 Administered Alone (B)] with Geometric Mean Ratio and 90% Confidence Interval Following a Single Oral Dose of 100-mg MK-0518 With or Without Multiple Oral Doses of 400-mg Atazanavir Once-Daily to Young, Healthy, Male Subjects (n=10)



SAFETY RESULTS: MK-0518 was generally well tolerated in young, healthy male subjects. No serious clinical adverse experiences were reported and no subject discontinued because of an adverse experience. Nine (9) subjects reported a total of 12 clinical adverse experiences, 8 of which were judged by the investigator to be related to study therapy. None of the adverse experiences reported occurred in subjects treated with MK-0518 alone. Elevations in total serum bilirubin were reported in some subjects after initiation of atazanavir administration and were judged by the investigator to be related to study therapy. Hyperbilirubinaemia is a known adverse experience of atazanavir, consistent with the label for this drug. All adverse experiences reported were transient and rated mild to moderate in intensity.

DISCUSSION AND CONCLUSIONS: With co-administration of 400 mg atazanavir once daily for 9 days, the C_{12hr} geometric mean ratio for (MK-0518 + atazanavir/MK-0518) was 1.95 with a corresponding 90% confidence interval of (1.30, 2.92). The $AUC_{0-\infty}$ geometric mean ratio (MK-0518 + atazanavir/MK-0518) was 1.72 with a corresponding 90% confidence interval of (1.47, 2.02), while the C_{max} geometric mean ratio was 1.53 with a corresponding 90% confidence interval of (1.11, 2.12).

Atazanavir inhibits CYP3A and UGT1A1at clinically relevant concentrations. Because MK-0518 is metabolized primarily by glucuronidation via UGT1A1, atazanavir may affect the pharmacokinetic profile of MK-0518. The study results confirmed that multiple doses of atazanavir increased plasma levels of MK-0518 ($AUC_{0-\infty}$, C_{max}, and $C_{12\ hr}$).

The upper bound of 90% CI of MK-0518 AUC ratios was 2.02 (~2.0) and a few individual MK-0518 AUC ratios were slightly above 2.0.

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.

In treatment experience HIV-1 patients, ritonavir boosted atazanavir regimen is recommended. Thus there is little clinical relevance of this study with regard to MK-0518 indicated patient population.

See Study 010 for drug interaction results from MK-0518 and atazanavir/ritonavir.

Protocol 007

TITLE: A Sequential, 3-Part Study: Part I - An Open-Label, 4-Period, Partially Randomized, Crossover Study to Investigate the Pharmacokinetics of Single Oral Doses of 3 New Formulations of MK-0518 in Healthy Male Volunteers; Part II – A Double-Blind, Randomized, Placebo-Controlled, Single Oral Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of MK-0518 in Healthy Female Volunteers; and Part III – An Open-Label, Randomized, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a Single Oral Dose of the MK-0518 Poloxamer Formulation

OBJECTIVES: Part I: To evaluate and compare, at the 400-mg dose level, the pharmacokinetic profiles of 3 new tablet formulations and the Phase I tablet in healthy male volunteers; Part II: To evaluate the safety, tolerability and pharmacokinetics of a single 400-mg oral dose of the MK-0518 Phase I tablet in healthy female volunteers; Part III: To evaluate the effects of a high-fat meal on plasma pharmacokinetics of a single 400-mg oral dose of the MK-0518 poloxamer tablet

SUBJECTS AND STUDY DESIGN: This was a sequential, 3-part study.

Part I was an open-label, single-dose, 4-period, crossover study in young, healthy, male subjects. Fifteen subjects each received 4 treatments (Treatments A, B, C, and D) in a partially randomized order. In the first period (Period 1), all 15 subjects received Treatment A, consisting of a 400-mg single oral dose of the MK-0518 poloxamer formulation tablet. In Periods 2, 3, and 4, all 15 subjects each received Treatments B, C, and D in a randomized, balanced, crossover manner. Treatment B consisted of a 400-mg single oral dose of the MK-0518 calcium phosphate formulation tablet. Treatment C consisted of a 400-mg single oral dose of the MK-0518 Phase II lactose formulation tablet. Treatment D consisted of a 400-mg single oral dose of the Phase I lactose formulation tablet. All doses were administered in the fasted state. There was at least a 4-day washout between each treatment period with the interval starting from dose administration of the previous period.

Part II was a double-blind, randomized, placebo-controlled, single-dose study in young, healthy, female subjects. Eight subjects were randomly assigned to receive a single oral dose of either 400-mg MK-0518 Phase I lactose formulation (N=6) or placebo (N=2). Doses were administered in the fasted state.

Part III was an open-label, single dose, partially randomized, 3-period, crossover study in young, healthy, male subjects. In Periods 1 and 2, 8 subjects received a 400-mg single oral dose of the MK-0518 poloxamer formulation in both the fed and fasted state in a randomized, balanced, crossover manner. In a fixed third period (Period 3), the same 8 subjects received an 800-mg single oral dose of the MK-0518 poloxamer formulation in the fasted state. There was at least a 4-day washout between each treatment period with the interval starting from dose administration of the previous period.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518 Phase I poloxamer tablets (400 mg), calcium phosphate tablets (400 mg), Phase II lactose tablets (400 mg), and Phase I lactose tablets (100 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 and urine MK-0518 concentrations. The lower limit of quantitation (LLOQ) for the plasma assay was

PHARMACOKINETIC DATA ANALYSIS:

The plasma pharmacokinetic profile (e.g., C12 hr, AUC0-∞, Cmax, Tmax, and apparent t½) of MK-0518 was calculated for each subject after a single-dose of MK-0518.

PHARMACOKINETIC RESULTS:

Part 1:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 400 mg of the Lactose, Calcium Phosphate, and Phase I Poloxamer Formulations of MK-0518 to Young, Healthy, Male Subjects (Fasted) (inset: semilog scale)

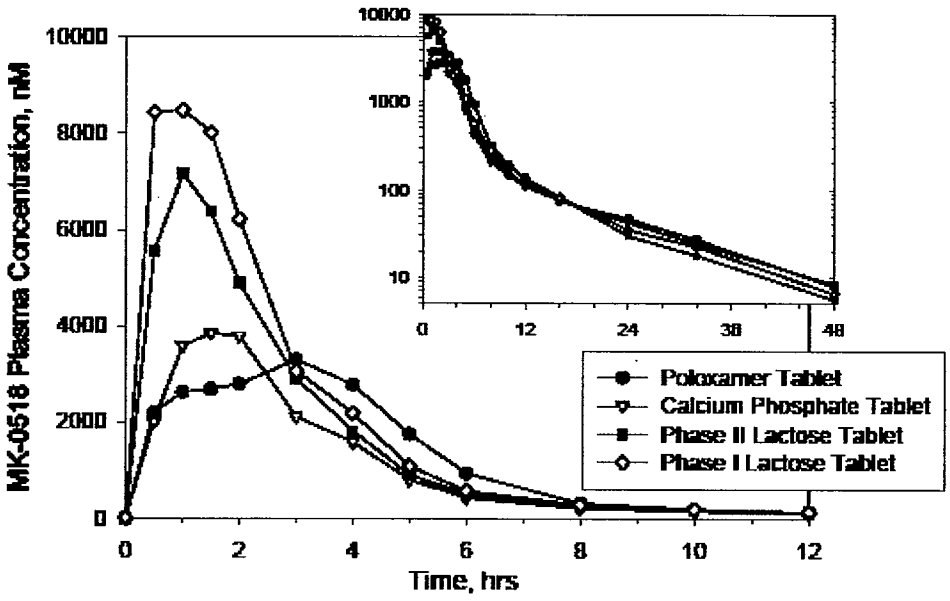


Table 1. Geometric Means and Corresponding Confidence Intervals for MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 400 mg of the Lactose, Calcium Phosphate, and Phase I Poloxamer Formulations of MK-0518 to Young, Healthy, Male Subjects (Fasted)

Pharmacokinetic Parameter	N[§]	Geometric Mean[†] for Treatment: Poloxamer (A)	Calcium Phosphate (B)	Phase II Lactose (C)	Phase I Lactose (D)	Geometric Mean (90% CI for GMR) for Treatment Ratio: (A/D)	(B/D)	(C/D)	(B/C)	MSE[‡]
$AUC_{0-\infty}$ (μM•hr)[¶]	15	16.07	14.12	20.18	25.69	0.63 (0.51, 0.77)	0.55 (0.45, 0.67)	0.79 (0.64, 0.96)	0.70 (0.57, 0.86)	0.11
$C_{12\,hr}$ (nM)[‡]	15	120.1	102.3	99.5	120.3	1.00 (0.78, 1.28)	0.85 (0.67, 1.09)	0.83 (0.65, 1.06)	1.03 (0.80, 1.32)	0.16
$C_{24\,hr}$ (nM)[‡]	15	40.5	33.2	25.8	30.8	1.31 (1.05, 1.65)	1.08 (0.86, 1.35)	0.84 (0.67, 1.05)	1.29 (1.03, 1.62)	0.14
C_{max} (μM)[†]	15	4.54	4.63	8.20	10.81	0.42 (0.30, 0.58)	0.43 (0.31, 0.60)	0.76 (0.55, 1.06)	0.56 (0.41, 0.78)	0.29
T_{max} (hr)	15	3.0[‖]	1.5[‖]	1.5[‖]	1.0[‖]	1.6 (1.0, 2.3)[‖]	0.5 (0.0, 1.0)[‖]	0.3 (-0.3, 1.0)[‖]	0.3 (-0.3, 0.8)[‖]	
$t_{½}\,\alpha$ (hr)	15[§]	0.94[¶]	0.89[¶]	0.89[¶]	0.91[¶]	-0.04 (-0.11, 0.05)[¶]	-0.01 (-0.13, 0.10)[¶]	0.00 (-0.16, 0.16)[¶]	-0.00 (-0.15, 0.12)[¶]	
$t_{½}\,\beta$ (hr)	15	9.2[#]	7.1[¶]	8.1[¶]	8.0[¶]	0.5 (-1.5, 2.3)[¶]	-1.0 (-2.4, 0.3)[¶]	0.5 (-0.6, 2.2)[¶]	-0.9 (-3.5, 0.6)[¶]	
C_{max} / C_{24hr}[‡]	15	37.8	45.2	82.4	89.8	0.42 (0.27, 0.65)	0.50 (0.33, 0.78)	0.92 (0.59, 1.42)	0.55 (0.36, 0.85)	0.50

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

[‡] MSE=Mean square error arising from ANOVA performed on the log-scale.

[§] N=14 for $t_{½}\,\alpha$ (hr) of Treatment C.

[‖] Median reported for T_{max} with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

[¶] Harmonic mean reported for $t_{½}$ with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Part II:

Figure 2. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 400 mg of the Phase I Lactose Formulation of MK-0518 to Young, Healthy, Male and Female Subjects (Fasted) (inset: semilog scale)

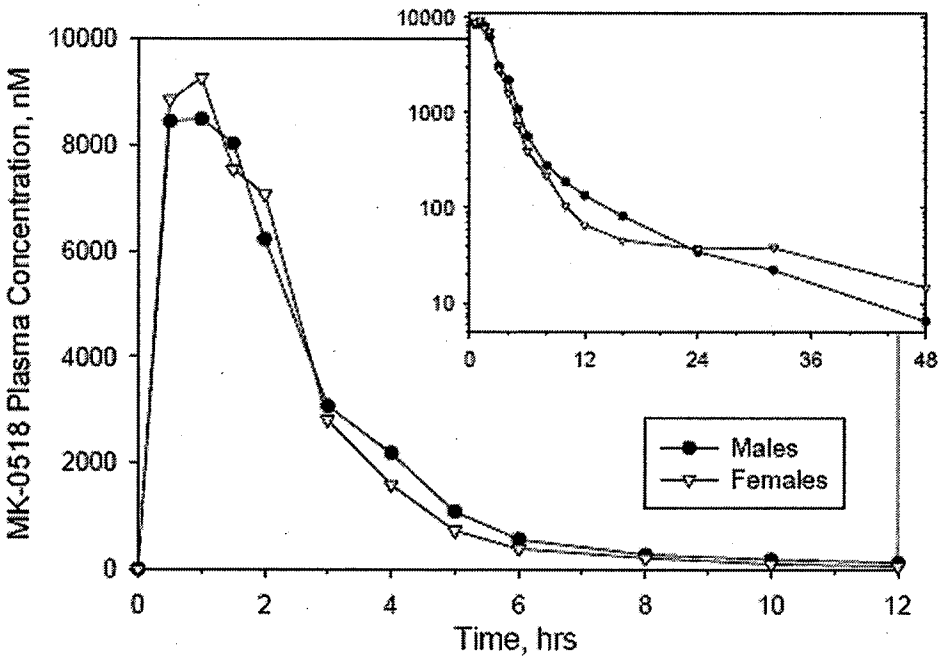


Table 2. Geometric Means, Geometric Mean Ratios, and Corresponding Confidence Intervals Following Single Dose Administration of 400 mg of the Phase I Lactose Formulation of MK-0518 to Young, Healthy, Male and Female Subjects (Fasted)

	Females (F)			Males (M)				
Pharmacokinetic Parameter	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	Geometric Mean Ratio (F/M)	90% Confidence Interval for Geometric Mean Ratio
$AUC_{0-\infty}$ (uM•hr)	6	24.90	(18.83, 32.91)	15	25.69	(22.64, 29.15)	0.97	(0.79, 1.18)
$C_{12\,hr}$ (nM)	6	51.1	(21.3, 122.2)	15	120.3	(92.4, 156.6)	0.42	(0.26, 0.70)
$C_{24\,hr}$ (nM)	6	26.4	(10.1, 68.8)	15	30.8	(23.3, 40.7)	0.86	(0.50, 1.46)
C_{max} (µM)	6	13.76	(12.20, 15.51)	15	10.81	(8.68, 13.46)	1.27	(0.95, 1.70)
T_{max} (hr)	6	1.0[†]		15	1.0[†]		0.0[†]	(-0.5, 0.5)[†]
$t_{1/2}$ α (hr)	6	0.87[‡]		15	0.91[‡]		-0.11[‡]	(-0.27, 0.12)[‡]
$t_{1/2}$ β (hr)	6	14.0[‡]		15	8.0[‡]		10.7[‡]	(1.0, 16.3)[‡]

[†] Median reported for T_{max}, with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.
[‡] Harmonic mean reported for Half-Life, with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

Part III:

Figure 3. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Single Dose Administration of 400 mg or 800 mg of the Phase I Poloxamer Formulation of MK-0518 to Young, Healthy, Male Subjects (Fasted or Fed) (inset: semilog scale)

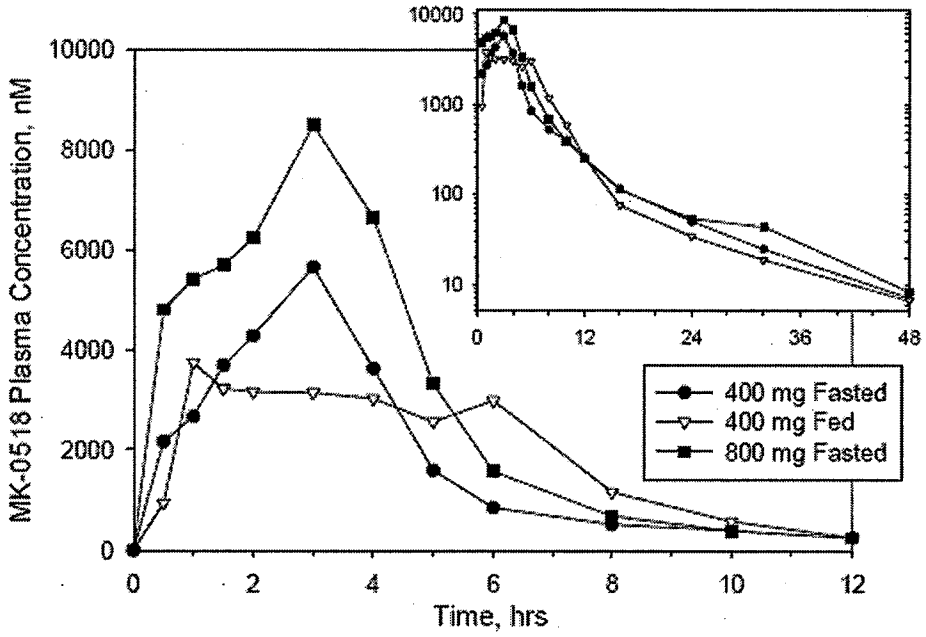


Table 3. Geometric Means, Geometric Mean Ratios, and Corresponding Confidence Intervals Following Single Dose Administration of 400 mg or 800 mg of the Phase I Poloxamer Formulation of MK-0518 to Young, Healthy, Male Subjects (Fasted or Fed)

		Geometric Mean (95% CI for Geometric Mean)			Geometric Mean (90% CI for GMR) for Treatment Ratio		
PK Parameter	N[‡]	400 mg[†] Fed	400 mg[†] Fasted	800 mg[†] Fasted	(400 mg Fed / 400 mg Fasted)[†]	(800 mg Fasted / 400 mg Fasted)[†]	MSE[§]
$AUC_{0-\infty}$ (nM·hr)	8	22.92 (16.94, 31.01)	22.00 (16.26, 29.77)	34.21 (25.74, 45.48)	1.04 (0.76, 1.42)	1.56 (1.18, 2.05)	0.10
$C_{12\,hr}$ (nM)	8	185.9 (78.2, 441.9)	151.7 (63.8, 360.5)	209.7 (107.6, 409.0)	1.23 (0.57, 2.63)	1.38 (0.81, 2.37)	0.62
$C_{24\,hr}$ (nM)	8	28.0 (15.2, 51.8)	39.0 (21.1, 72.2)	46.8 (28.4, 77.4)	0.72 (0.48, 1.07)	1.20 (0.85, 1.70)	0.17
C_{max} (nM)	8	6.80 (3.80, 9.46)	6.77 (4.29, 10.67)	10.07 (6.69, 15.16)	0.89 (0.49, 1.61)	1.49 (0.92, 2.40)	0.38
T_{max} (hr)	8	4.5[¶]	2.5[¶]	3.0[¶]	2.0 (0.0, 3.0)[¶]	0.1 (-1.0, 1.8)[¶]	
$t_{1/2}$ α (hr)	7[‖]	1.09[#]	0.88[#]	0.94[#]	0.29 (0.02, 0.56)[#]	0.08 (-0.05, 0.19)[#]	
$t_{1/2}$ β (hr)	8	8.4[#]	7.6[#]	8.5[#]	0.9 (-1.3, 3.3)[#]	0.9 (-0.8, 3.3)[#]	

† Computed from least squares estimate from a 2-period crossover ANOVA performed on the natural-log transformed values, 400 mg data only.
‡ Computed from least squares estimate from an ANOVA model with treatment as the lone fixed effect, performed on the natural-log transformed values, all treatments included.
§ MSE=Mean square error arising from a 2-period crossover ANOVA performed on the log-scale, 400 mg data only.
‖ N=5 for $t_{1/2}$ α (hr) of 400-mg Fed Group.
¶ Median reported for T_{max}, with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.
# Harmonic mean reported for $t_{1/2}$, with Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.

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

DISCUSSION AND CONCLUSIONS:

Part I of this study examined the plasma pharmacokinetics of MK-0518 in young, healthy, male subjects after the administration of a 400 mg single dose each of 3 candidate Phase II MK-0518 formulations, and compared the pharmacokinetics to that obtained after the administration of the Phase I Lactose formulation of MK-0518.

The phase I poloxamer formulation had Cmax value that was on average less than half that of the Phase I lactose formulation. Relative to the Phase I lactose formulation, Tmax was modestly longer for the poloxamer formulation. The phase I poloxamer formulation had the lowest peak-to-trough ratio thus was selected for further studies. But this is not the final clinical and to-be-marketed formulation.

In Part II of the study, plasma pharmacokinetic parameters were obtained in young, healthy, female subjects after administration of 400 mg single dose of MK-0518 Phase I lactose formulation and compared with the corresponding data obtained in young, healthy, male subjects from Part I. Overall exposure to MK-0518 (assessed through comparison of AUC0-∞ values) was similar in females compared to males. C12 hr values were 58% lower in females compared to males, although there was no clinically meaningful difference at 24 hours postdose. Cmax values were 27% higher in females compared to males.

In Part III of the study, the effect of a high-fat meal on plasma pharmacokinetics of a 400-mg single dose of the MK-0518 phase I poloxamer formulation administered to young, healthy, male subjects was assessed, and the plasma pharmacokinetics of an 800-mg single dose of MK-0518 phase I poloxamer formulation were characterized. There was no significant effect of food on the pharmacokinetics of MK-0518 phase I poloxamer formulation. AUC0-∞, C12 hr, and Cmax were similar for fasted versus fed. Tmax was slightly longer for a 400 mg dose of MK-0518 phase I poloxamer formulation in the presence of food compared to fasted dosing (median Tmax was 2.5 hours for fasted and 4.5 hours for fed). Mean plasma pharmacokinetic parameters for the 800 mg MK-0518 phase I poloxamer formulation (fasted) were increased by roughly 1.5-fold over a 400 mg fasted dose.

Protocol 008

TITLE: An Open-Label, 3-Period Study to Evaluate the 2-Way Interaction of MK-0518 and Tenofovir in Healthy Male Subjects

OBJECTIVES: To evaluate the effect of coadministration of tenofovir and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\ hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of tenofovir coadministered with multiple doses of MK-0518

SUBJECTS AND STUDY DESIGN: This was an open-label, 3-period study in young, healthy, male subjects. Ten subjects each received MK-0518 and tenofovir 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 except on Day 4 where only the morning dose of MK-0518 was given. In Period 2, the same 10 subjects were administered 300 mg tenofovir disoproxil fumarate once daily for 7 days. In Period 3, all 10 subjects received a combination of tenofovir disoproxil fumarate (300 mg once daily) and MK-0518 (400 mg twice daily) for 4 days. Period 3 began immediately after Period 2. All doses were administered in an open-label fashion.

All doses of tenofovir disoproxil fumarate were administered with food except for Day 4, in which case, subjects fasted for 8 hours prior to dosing. All morning doses of MK-0518 were administered with food except for the Day 4 morning dose, in which case subjects fasted for 8 hours prior to dosing. Evening doses of MK-0518 were administered without regard to food.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518, Phase I poloxamer formulation tablets 400 mg, placebo MK-0518 (400 mg image) tablets, Viread

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 serum concentrations of tenofovir at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours postdose.

ASSAYS: Validated HPLC-MS/MS assays were used for plasma MK-0518 concentrations. The lower limit of quantitation (LLOQ) for the plasma assay was

Serum samples were analyzed for tenofovir concentrations at the contract laboratory by an LC/MS/MS assay. The lower limit of quantitation (LLOQ) for the tenofovir assay was and the linear calibration range was

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

The serum pharmacokinetic parameters of tenofovir (e.g., C_{24hr}, AUC_{0-24hr}, C_{max}) in the presence and absence of MK-0518 were calculated for each subject. Geometric mean ratios (tenofovir + MK-0518/tenofovir) and associated 90% confidence intervals (CIs) of primary serum tenofovir PK parameters (C_{24h}, C_{max}, and $AUC_{(0-\infty)}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (Inset: semilog scale)

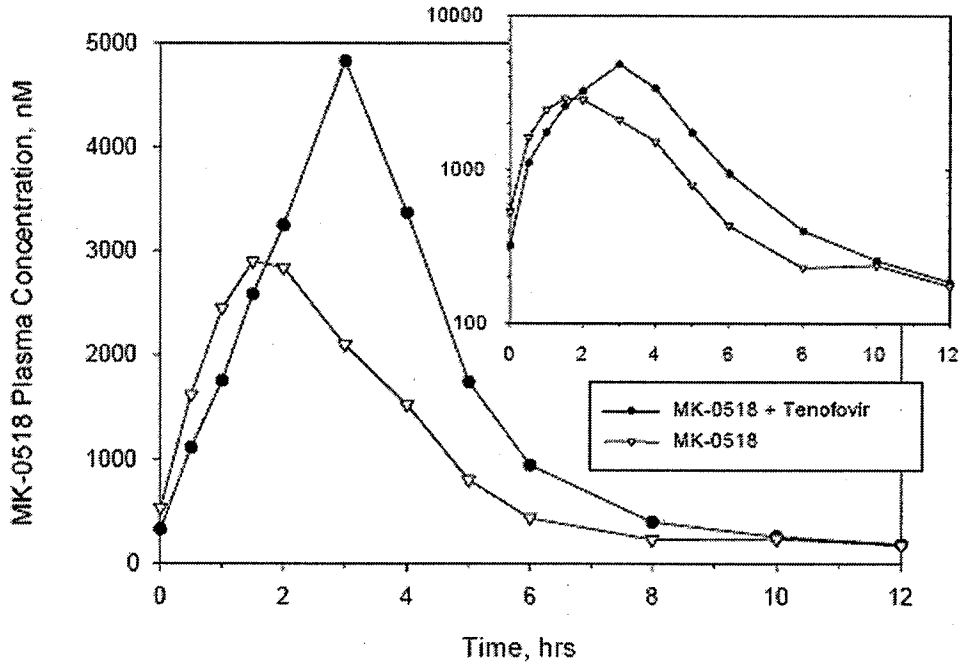


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics for Young, Healthy, Male Subjects Administered Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily

Pharmacokinetic Parameter	N	MK-0518 + Tenofovir		MK-0518		(MK-0518 + Tenofovir)/ MK-0518		MSE[†]
		GM	95% CI for GM	GM	95% CI for GM	GMR	90% CI for GMR	
$C_{12\,hr}$ (nM)[‡]	9	146.4	(88.5, 242.4)	142.3	(86.0, 235.5)	1.03	(0.73, 1.45)	0.153
$AUC_{0\text{-}12\,hr}$ (μM•hr)[‡]	9	15.35	(9.79, 24.07)	10.29	(6.56, 16.13)	1.49	(1.15, 1.94)	0.091
C_{max} (μM)[‡]	9	4.71	(2.87, 7.72)	2.87	(1.75, 4.71)	1.64	(1.16, 2.32)	0.157
T_{max} (hr)	9	3.0[§]		1.5[§]		1.0[‖]	(-0.3, 1.8)[‖]	

[†] 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.
GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio.

Table 2. Individual MK-0518 Plasma Pharmacokinetics and Summary Statistics Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects

	$C_{12\,hr}$, nM			$AUC_{0\text{-}12\,hr}$, 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
116	81.5	112.1	0.73	10.32	8.55	1.21	1.94	1.87	1.04	1.5	1.0	0.5
117	328.1	162.7	2.02	29.04	17.00	1.71	8.51	5.53	1.54	3.0	1.5	1.5
118	44.1	79.7	0.55	11.09	6.05	1.83	3.67	1.90	1.93	3.0	1.0	2.0
120	54.5	109.1	0.50	4.02	3.42	1.18	1.47	1.05	1.40	1.5	1.5	0.0
121	241.7	143.3	1.69	23.80	13.61	1.75	8.99	4.67	1.93	3.0	1.5	1.5
122	173.5	123.5	1.40	23.23	15.52	1.50	8.45	4.23	2.00	2.0	3.0	-1.0
123	124.7	118.4	1.05	27.48	7.74	3.55	9.40	1.70	5.53	2.0	4.0	-2.0
124	235.1	119.9	1.96	13.84	11.89	1.16	3.31	2.62	1.26	4.0	2.0	2.0
125	392.2	599.9	0.65	16.85	22.07	0.76	5.44	7.37	0.74	3.0	1.0	2.0
AM	186.2	174.3	–	17.74	11.76	–	5.69	3.44	–	2.6	1.8	–
SD	122.7	161.2	–	8.61	5.92	–	3.20	2.13	–	0.8	1.0	–
Med	173.5	119.9	–	16.85	11.89	–	5.44	2.62	–	3.0	1.5	1.0†
GM‡	146.4	142.3	1.03	15.35	10.29	1.49	4.71	2.87	1.64	–	–	–

A: 400-mg MK-0518 q12 hr + 300-mg tenofovir disoproxil fumarate qDay x 4 days.
B: 400-mg MK-0518 q12 hr x 4 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.
‡ Based on least squares mean from an ANOVA performed on the natural-log transformed values.

Figure 2. Individual MK-0518 C_{12hr} Ratios (MK-0518 Coadministered With Tenofovir/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 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)

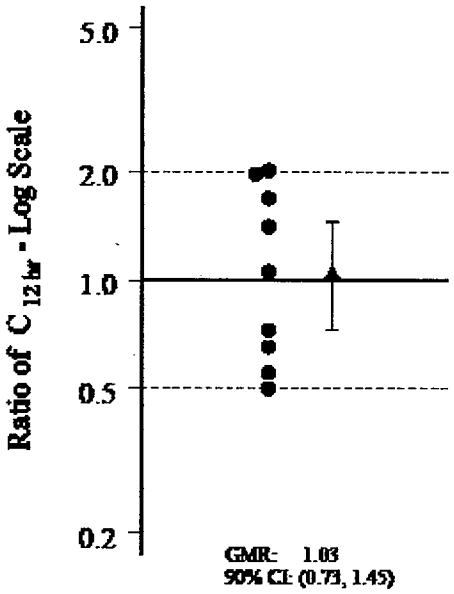


Figure 3. Individual MK-0518 $AUC_{0\text{-}12hr}$ Ratios (MK-0518 Coadministered With Tenofovir/MK-0518 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)

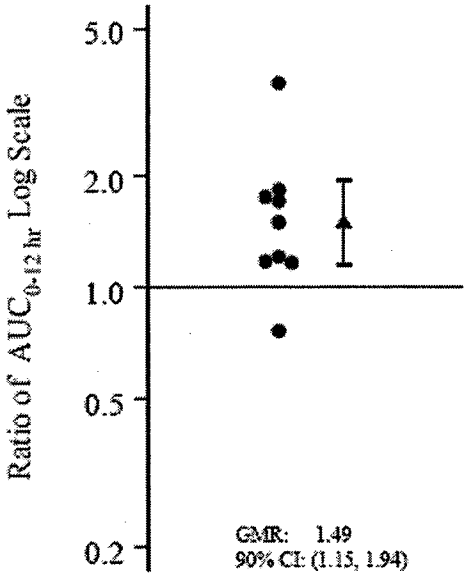


Figure 4. Individual MK-0518 Cmax Ratios (MK-0518 Coadministered With Tenofovir/MK-0518 Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)

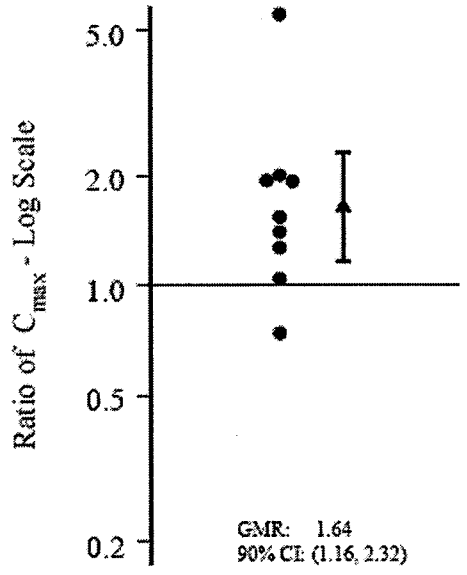


Table 3. Comparison of Tenofovir Serum Pharmacokinetics for Young, Healthy, Male Subjects Administered Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice Daily

Pharmacokinetic Parameter	N	Tenofovir + MK-0518		Tenofovir		(Tenofovir + MK-0518)/ Tenofovir		MSE[†]
		GM	95% CI for GM	GM	95% CI for GM	GMR	90% CI for GMR	
$C_{24\,hr}$ (ng/mL)[‡]	9	29.9	(24.3, 36.8)	34.4	(28.0, 42.3)	0.87	(0.74, 1.02)	0.033
$AUC_{0\text{-}24\,hr}$ (ng•hr/mL)[‡]	9	1563	(1336, 1828)	1737	(1485, 2032)	0.90	(0.82, 0.99)	0.011
C_{max} (ng/mL)[‡]	9	202	(171, 239)	263	(223, 311)	0.77	(0.69, 0.85)	0.013
T_{max} (hr)	9	1.0[§]		0.5[§]		0.3	(0.0, 0.8)[‖]	

[†] 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.
GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio.

Table 4. Individual Tenofovir Serum Pharmacokinetics and Summary Statistics Following Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Young, Healthy, Male Subjects

AN	C_{24hr}, ng/mL			$AUC_{0\text{-}24hr}$, ng•hr/mL			C_{max}, ng/mL			T_{max}, hr		
	518+tfv	tfv	(518+tfv/tfv)	518+tfv	tfv	(518+tfv/tfv)	518+tfv	tfv	(518+tfv/tfv)	518+tfv	tfv	(518+tfv)-tfv
116	29.2	40.3	0.72	1508	1857	0.81	140	224	0.63	2.0	0.5	1.5
117	42.9	56.7	0.76	1942	2401	0.81	242	354	0.68	2.0	1.0	1.0
118	30.2	33.5	0.90	1632	1717	0.95	227	304	0.75	0.5	0.5	0.0
120	30.5	26.4	1.16	1364	1277	1.07	176	284	0.62	0.5	0.5	0.0
121	19.9	26.6	0.75	1212	1420	0.85	204	257	0.79	1.0	1.0	0.0
122	35.8	35.2	1.02	1984	1934	1.03	219	238	0.92	1.0	1.0	0.0
123	40.3	44.8	0.90	1973	2318	0.85	291	360	0.81	1.0	0.5	0.5
124	32.9	25.7	1.28	1471	1333	1.10	172	170	1.01	1.0	1.0	0.0
125	17.4	30.9	0.56	1221	1735	0.70	186	237	0.78	0.5	0.5	0.0
AM	31.0	35.6	--	1590	1777	--	206	270	--	1.1	0.7	--
SD	8.4	10.3	--	312	402	--	45	62	--	0.6	0.3	--
Med	30.5	33.5	--	1508	1735	--	204	257	--	1.0	0.5	0.3[†]
GM[‡]	29.9	34.4	0.87	1563	1737	0.90	202	263	0.77	--	--	--

518+tfv: 300 mg tenofovir once daily + 400 mg MK-0518 every 12 hours x 4 days; Pharmacokinetic parameters on Day 4 of codosing = Day 11 of tenofovir disoproxil fumarate dosing.
tfv: 300 mg tenofovir once daily x 7 days; Pharmacokinetic parameters on Day 7.
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.
[‡] Based on least squares mean from an ANOVA performed on the natural-log transformed values.

Figure 5. Arithmetic Mean Tenofovir Serum Concentrations Following Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily With or Without Coadministration of Multiple Doses of 400 mg MK-0518 Twice-Daily to Young, Healthy, Male Subjects (Inset: semilog scale)

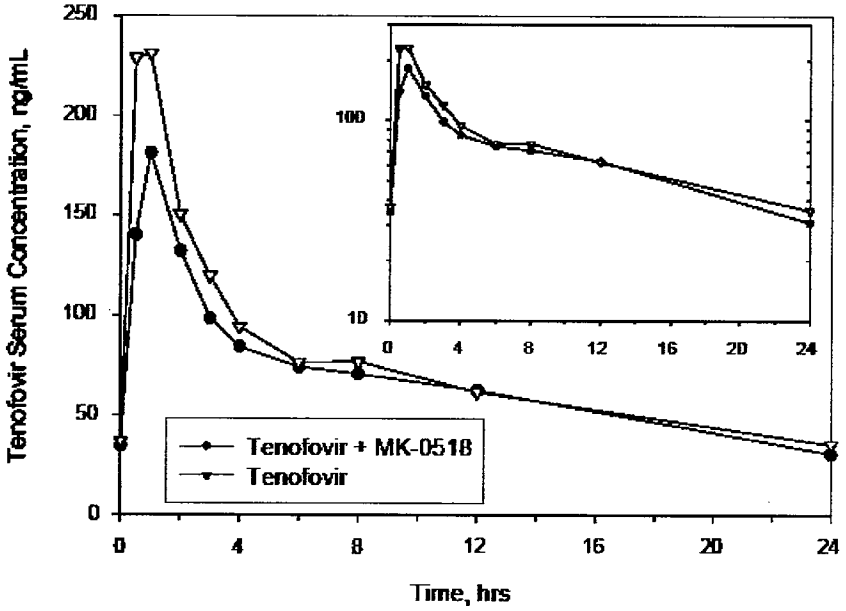


Figure 6. Individual Tenofovir C_{24hr} Ratios (Tenofovir Coadministered With MK-0518/Tenofovir Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)

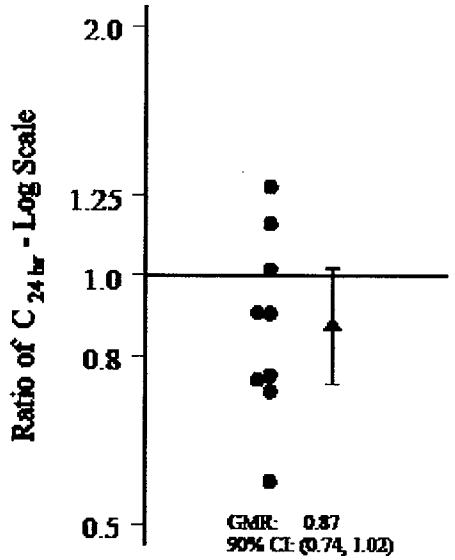


Figure 7. Individual Tenofovir AUC0-24 hr Ratios (Tenofovir Coadministered With MK-0518/Tenofovir Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)

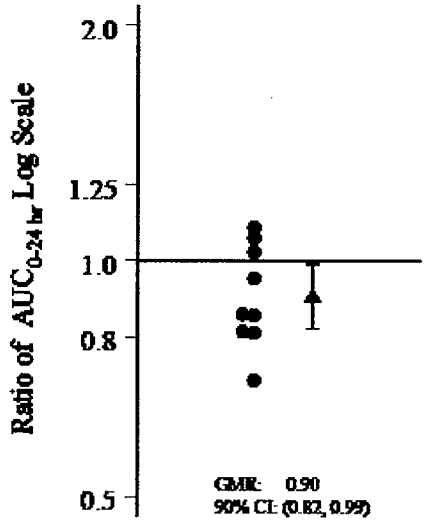
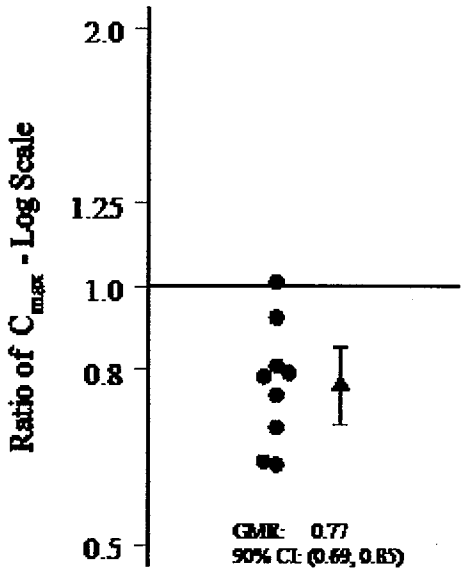


Figure 8. Individual Tenofovir Cmax Ratios (Tenofovir Coadministered With MK-0518/Tenofovir Administered Alone) With Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400 mg MK-0518 Twice-Daily With or Without Coadministration of Multiple Doses of 300 mg Tenofovir Disoproxil Fumarate Once-Daily to Young, Healthy, Male Subjects (n=9)



SAFETY RESULTS: Multiple dose administration of MK-0518 alone and in combination with tenofovir disoproxil fumarate was generally well tolerated. No serious clinical or laboratory adverse experiences were reported.

DISCUSSION AND CONCLUSIONS: With co-administration of 300 mg tenofovir twice daily for 11 days, the C_{12hr} geometric mean ratio for (MK-0518 + tenofovir/MK-0518) was 1.03 and the 90% confidence interval for the geometric mean ratio was (0.73, 1.45). The $AUC_{0-\infty}$ geometric mean ratio (MK-0518 + tenofovir/MK-0518) was 1.49 with a corresponding 90% confidence interval of (1.15, 1.94), while the C_{max} geometric mean ratio was 1.64 with a corresponding 90% confidence interval of (1.16, 2.32).

The upper bound of 90% CI of MK-0518 AUC ratios was 1.94 (~2.0) but a few individual MK-0518 AUC ratios were above 2.0.

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.

With co-administration of 400 mg MK-0518 twice daily for 4 days, the C_{24hr} geometric mean ratio for (tenofovir + MK-0518/tenofovir) was 0.87 with a corresponding 90% CI of (0.74, 1.02). The AUC_{0-24hr} geometric mean ratio (tenofovir + MK-0518/tenofovir) was 0.90 with a corresponding 90% CI of (0.82, 0.99), while the C_{max} geometric mean ratio was 0.77 with a corresponding 90% CI of (0.69, 0.85).

The mechanism of this drug interaction is not clear. Similar to atazanavir/ritonavir, tenofovir markedly increases plasma concentrations of MK-0518. However, concomitant use of MK-0518 and atazanavir/ritonavir was well tolerated in the Phase II and Phase III studies. Based on these data, tenofovir may be coadministered with MK-0518 without dose adjustment of MK-0518.

Protocol 009

TITLE: An Open-Label, 2-Period Study to Evaluate the Influence of Rifampin on a Single Dose of MK-0518 in Healthy Subjects

OBJECTIVES: To evaluate the effect of coadministration of rifampin and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\ hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of rifampin coadministered with a single dose of MK-0518

SUBJECTS AND STUDY DESIGN: This was an open-label, 2-period study in 10 young, healthy, male and female subjects. In Period 1, 10 subjects were given a single oral dose of 400 mg MK-0518 followed by at least a 4-day washout period prior to the start of Period 2. In Period 2, the same 10 subjects were given 600 mg rifampin once daily in an open-labeled fashion for 15 days. On Day 14, all 10 subjects were given the daily dose of rifampin in combination with a single oral dose of 400 mg MK-0518.

In Period 1, MK-0518 was administered in the fasted state. On Day 14 Period 2, MK-0518 and rifampin were administered in the fasted state. All other doses of rifampin in Period 2 were administered either 1 hour before or 2 hours after a meal.

Subject Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0141	Female	White	38	166.5	73.5
0142	Female	White	44	169.0	80.0
0143	Female	Hispanic	32	160.0	64.1
0144	Male	White	27	182.5	93.3
0145	Male	White	52	172.0	68.2
0146	Male	White	41	174.0†	73.0
0147	Male	Black	24	173.0	68.2
0148	Male	Hispanic	35	180.0	101.0
0149	Male	White	48	181.0	87.3
0150	Male	White	43	175.5	82.5
		Arithmetic Mean	38.4	173.3	79.1
		Range	24 to 52	160.0 to 182.5	64.1 to101.0

AN=Allocation Number.
† Data point was not included in the electronic study database and was subsequently obtained directly from the site.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518, Phase I poloxamer formulation tablets 400 mg, placebo MK-0518 (400 mg image) tablets, rifampin

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, 12, 16, 24, 32, and 48 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 $AUC_{0-\infty}$, C_{max}, $C_{12\,hr}$, T_{max}, and apparent $t_{½}$ for each subject in the presence or absence of multiple doses of rifampin. Geometric mean ratios (MK-0518 + rifampin/MK-0518) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{(0-\infty)}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Rifampin Once-Daily to Young, Healthy, Male and Female Subjects (Inset: semilog scale)

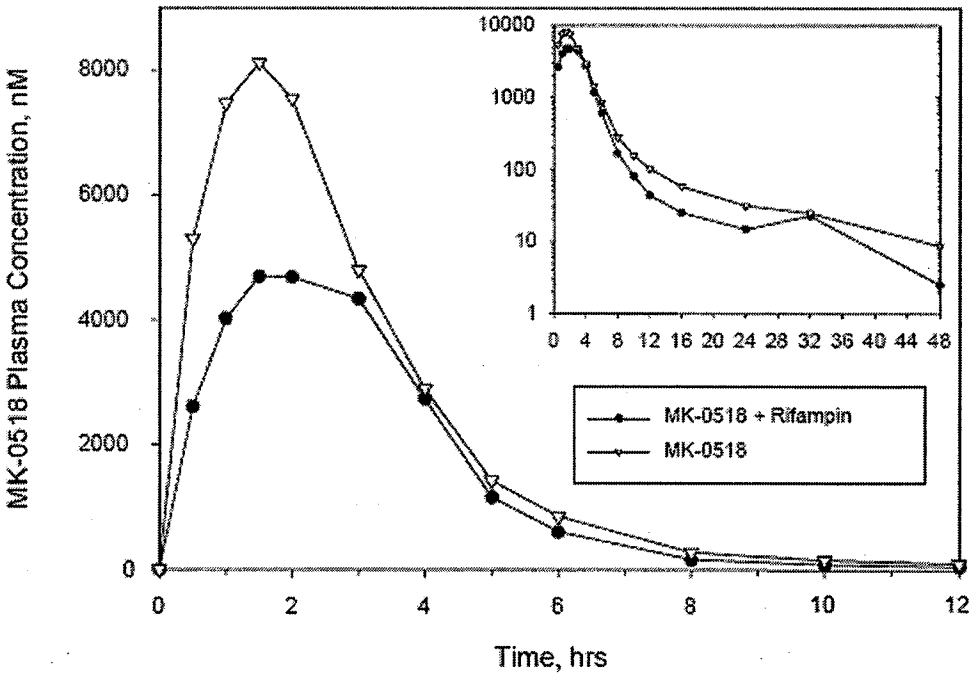


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics in Young, Healthy, Male and Female Subjects Administered Single Oral Doses of 400 mg MK-0518 With or Without Administration of 600 mg Rifampin Daily

Pharmacokinetic Parameter	N	MK-0518 + Rifampin		MK-0518		(MK-0518 + Rifampin/ MK-0518)		MSE[†]
		Geometric Mean	95% CI for Geometric Mean	Geometric Mean	95% CI for Geometric Mean	Geometric Mean Ratio	95% CI for Geometric Mean	
$C_{12\,hr}$ (nM)[‡]	9	36.3	(22.9, 57.6)	92.1	(58.1, 146.1)	0.39	(0.30, 0.51)	0.089
$AUC_{0-\infty}$ (μM•hr)[‡]	9	16.51	(11.67, 23.35)	27.57	(19.49, 39.00)	0.60	(0.39, 0.91)	0.226
C_{max} (μM)[‡]	9	5.34	(3.47, 8.23)	8.61	(5.59, 13.25)	0.62	(0.37, 1.04)	0.344
T_{max} (hr)	9	3.0[§]		1.5[§]		1.0[‖]	(-0.5, 1.5)[‖]	
$t_{½}\,\alpha$ (hr)	9	0.93[¶]		1.07[¶]		-0.15[‖]	(-0.23, -0.04)[‖]	
$t_{½}\,\beta$ (hr)	9	9.6[¶]		8.5[¶]		-0.1[‖]	(-4.5, 4.9)[‖]	

† 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}.
‖ Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.
¶ Harmonic mean reported for $t_{½}$.

Table 2. Individual MK-0518 Pharmacokinetics and Summary Statistics Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Rifampin Once Daily to Young, Healthy, Male and Female Subjects

AN	C_{12hr}, nM			$AUC_{0-\infty}$, μM·hr			C_{max}, μM			T_{max}, hr			$t_{1/2}$ α, hr		$t_{1/2}$ β, hr	
	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B	A	B	A	B
141	54.5	123.5	0.44	29.71	29.92	0.99	11.47	8.83	1.30	1.0	1.0	0.0	0.96	1.06	12.1	19.8
142	65.0	102.4	0.63	34.51	33.17	1.04	14.69	13.66	1.08	1.5	1.0	0.5	0.93	1.09	13.2	20.4
144	44.8	149.6	0.30	14.91	27.93	0.53	3.82	9.77	0.39	3.0	1.0	2.0	0.72	0.94	11.6	6.7
145	12.8	48.4	0.26	13.37	33.43	0.40	4.17	12.14	0.34	3.0	1.5	1.5	0.86	1.09	5.8	5.2
146	27.9	88.4	0.32	7.37	28.47	0.26	2.26	8.66	0.26	3.0	2.0	1.0	1.08	0.94	21.3	7.7
147	12.8	45.9	0.28	13.22	34.21	0.39	4.16	12.04	0.35	3.0	1.5	1.5	0.89	1.10	6.2	5.2
148	27.0	90.9	0.30	7.38	28.92	0.26	2.23	8.66	0.26	3.0	2.0	1.0	0.97	1.05	14.9	7.3
149	66.6	74.0	0.90	19.71	15.07	1.31	6.73	4.20	1.60	3.0	3.0	0.0	0.93	1.33	8.5	17.3
150	83.7	191.0	0.44	31.39	23.40	1.34	9.39	4.77	1.97	2.0	4.0	-2.0	1.21	1.16	7.8	9.6
AM	43.9	101.6	--	19.06	28.28	--	6.55	9.19	--	2.5	1.9	--	0.93†	1.07†	9.6†	8.5†
SD	25.3	47.1	--	10.38	5.99	--	4.39	3.21	--	0.8	1.0	--	0.14†	0.11†	4.1†	4.1†
Med	44.8	90.9	--	14.91	28.92	--	4.17	8.83	--	3.0	1.5	1.0‡	0.93	1.09	11.6	7.7
GM§	36.3	92.1	0.39	16.51	27.57	0.60	5.34	8.61	0.62	--	--	--	--	--	--	--

A: 600 mg rifampin qd x 15 days with 400 mg MK-0518 on Day 14.
B: 400 mg single dose MK-0518.
AM = Arithmetic Mean; SD = Standard Deviation; Med = Median; GM = Geometric Mean.
† Values reported for half-lives are harmonic mean and jackknife standard deviation.
‡ For T_{max}, represents Hodges-Lehman estimate of median treatment difference.
§ Based on least squares mean from an ANOVA performed on the natural-log transformed values.

Figure 2. Individual MK-0518 C_{12hr} Ratios [MK-0518 Coadministered With Rifampin (A)/MK-0518 Administered Alone (B)] With Geometric Mean Ratio and 90% CI Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Rifampin Once Daily to Young, Healthy, Male and Female Subjects (n=9)

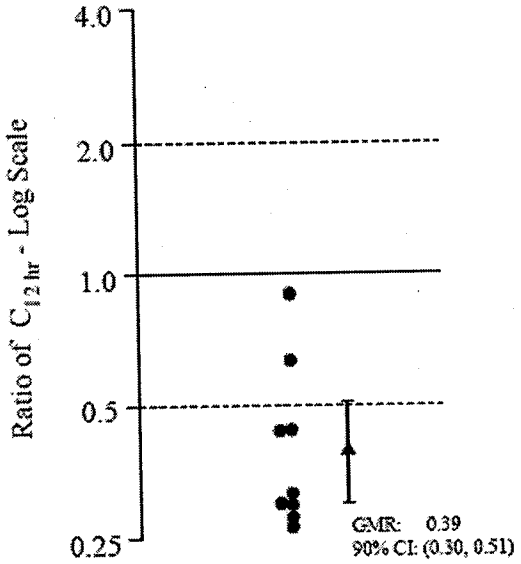


Figure 3. Individual MK-0518 $AUC_{0-\infty}$ Ratios [MK-0518 Coadministered With Rifampin (A)/MK-0518 Administered Alone (B)] With Geometric Mean Ratio and 90% CI Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Rifampin Once Daily to Young, Healthy, Male and Female Subjects (n=9)

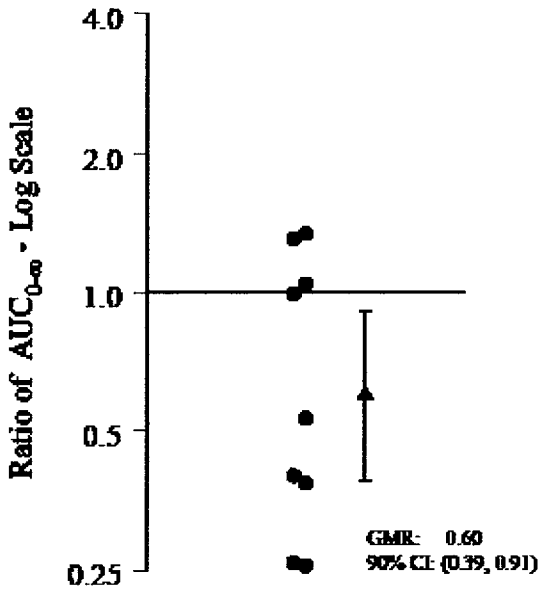
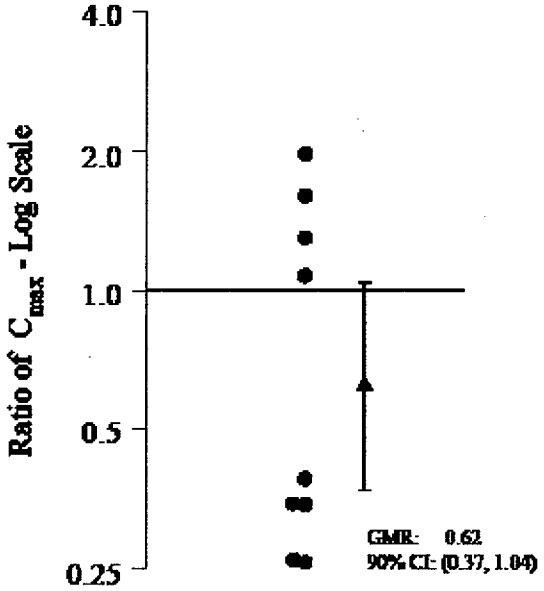


Figure 4. Individual MK-0518 C_{max} Ratios [MK-0518 Coadministered With Rifampin (A)/MK-0518 Administered Alone (B)] With Geometric Mean Ratio and 90% CI Following a Single Oral Dose of 400 mg MK-0518 With or Without Multiple Oral Doses of 600 mg Rifampin Once Daily to Young, Healthy, Male and Female Subjects (n=9)



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 and no subject discontinued due to an adverse experience. 10 subjects reported a total of 19 nonserious clinical adverse experiences,

15 of which were determined by the investigator as drug related. There were no laboratory adverse experiences reported.

DISCUSSION AND CONCLUSIONS: With co-administration of 600 mg rifampin twice daily for 14 days, the C_{12hr} geometric mean ratio for (MK-0518 + rifampin/MK-0518) was 0.39 with a corresponding 90% CI of (0.30, 0.51). The $AUC_{0-\infty}$ geometric mean ratio (MK-0518 + rifampin/MK-0518) was 0.60 with a corresponding 90% CI of (0.39, 0.91), while the C_{max} geometric mean ratio was 0.62 with a corresponding 90% CI of (0.37, 1.04).

The lower bound of 90% CI of MK-0518 C_{12hr} ratios was 0.30 (<0.4) and a few individual MK-0518 C_{12hr} ratios were between 0.25 and 0.3.

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.

Rifampin induces some cytochrome P450 enzymes and also induces Phase II enzymes such as UDP-glucuronosyl transferase including UGT1A1. MK-0518 is metabolized by UGT1A1 so the effect of rifampin on MK-0518 concentration is likely a result of UGT1A1 induction.

Caution should be used when co-administering MK-0518with rifampin.

Protocol 010

TITLE: An Open-Label, Sequential, 2-Period Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-0518 Coadministered With Atazanavir and Ritonavir in Healthy Subjects

OBJECTIVES: To evaluate the effect of coadministration of atazanavir, ritonavir and MK-0518 on the plasma pharmacokinetic profile of MK-0518 (e.g., $AUC_{0-\infty}$, $C_{12\,hr}$, C_{max}) and to evaluate the safety and tolerability of multiple doses of atazanavir and ritonavir coadministered with multiple doses of MK-0518

SUBJECTS AND STUDY DESIGN: This was an open-label, sequential, 2-period study in 10 young, healthy subjects. Period 1: oral doses of 400 mg MK-0518 twice daily with 240 mL of water for 4 days without regard to food with the exception on Day 4. On Day 4, the subjects fasted for 8 hours before and 4 hours after the morning dose of MK-0518 and the evening dose of MK-0518 was not given. Blood samples were obtained at specified times up to 12 hours postdose on Day 4 for MK-0518 assay. Period 2: the same subjects from Period 1 were coadministered 400 mg MK-0518 twice daily with 300 mg atazanavir once daily and 100 mg ritonavir once daily in the AM with 240 mL of water for 10 days. On Days 1 to 9, the morning doses of the combination were administered with food and the evening doses of MK- 0518 were administered without regard to food. On Day 10, the subjects fasted for 8 hours before and 4 hours after the morning dose of MK-0518 and the evening dose of MK-0518 was not given. Blood samples were obtained at specified times up to 12 hours postdose on Day 10 for MK-0518 assay. There was no washout interval in this study. Period 1 was conducted first and Period 2 immediately followed Period 1.

Subject Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0201	Female	multi	42	152.0	55.4
0202	Male	white	35	173.0	82.9
0203	Male	hispanic	43	172.5	76.0
0204	Male	white	43	177.5	82.5
0205	Male	white	47	188.5	94.5
0206	Male	white	50	186.0	97.7
0207	Male	white	32	189.5	91.7
0208	Male	white	46	182.0	76.3
0209	Male	black	24	183.5	84.2
0210	Male	white	25	187.0	105.7
		Arithmetic Mean	38.7	179.2	84.7
		Range	24 to 50	152.0 to 189.5	55.4 to 105.7
AN = allocation number					

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: MK-0518, Phase I lactose formulation tablets 100 mg, placebo MK-0518 (100 mg image) tablets, REYATAZ 200mg capsules, 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 atazanavir + ritonavir. Geometric mean ratios (MK-0518 + atazanavir + ritonavir/MK-0518) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{(0\text{-}\infty)}$) were calculated for treatment comparisons.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentrations Following Multiple Doses of 400-mg MK-0518 Twice Daily With or Without Multiple Doses of 300-mg Atazanavir + 100 mg Ritonavir Daily to Young, Healthy, Male and Female Subjects (Inset: semilog scale)

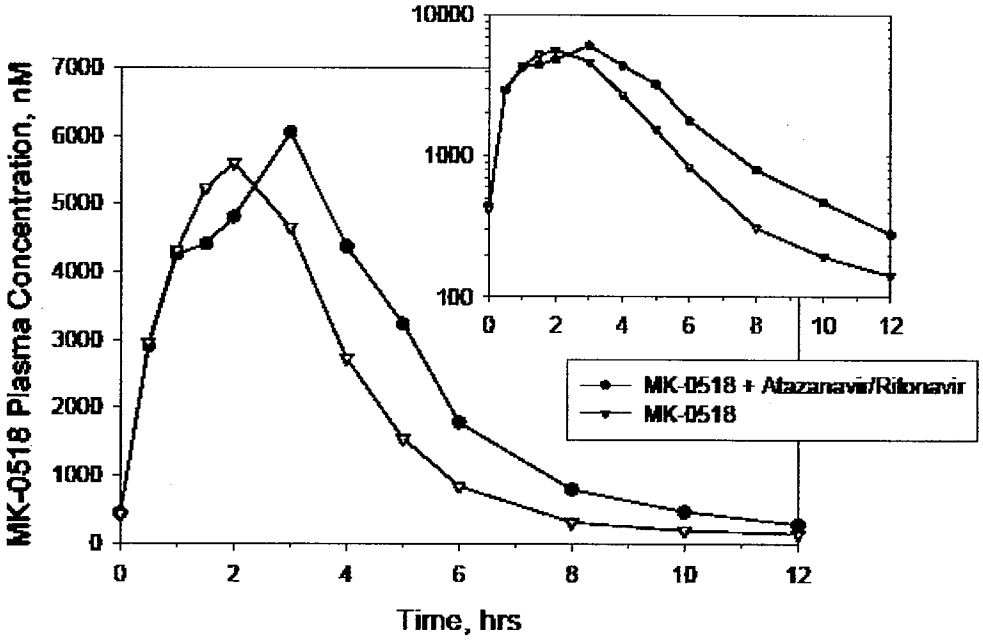


Table 1. Comparison of MK-0518 Plasma Pharmacokinetics in Young, Healthy, Male and Female Subjects Administered Multiple Doses of 400-mg MK-0518 Twice Daily with or without Multiple Doses of 300-mg Atazanavir and 100-mg Ritonavir Daily

	MK-0518 + Atazanavir + Ritonavir			MK-0518			(MK-0518 + Atazanavir + Ritonavir/ MK-0518)			
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†
$C_{12\,hr}$ (nM) ‡	10	220.2	(141.0, 343.9)	10	124.6	(79.8, 194.5)	10	1.77	(1.39, 2.25)	0.088
$AUC_{0\text{-}12\,hr}$ (μM•hr) ‡	10	27.14	(19.74, 37.31)	10	19.25	(14.00, 26.46)	10	1.41	(1.12, 1.78)	0.080
C_{max} (μM) ‡	10	7.38	(4.87, 11.20)	10	5.95	(3.93, 9.03)	10	1.24	(0.87, 1.77)	0.189
T_{max} (hr)	10	3.0 §		10	2.0 §		10	0.7 ‖	(0.0, 1.5) ‖	

† Mean square error 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-Lehmann 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 Multiple Doses of 400-mg MK-0518 Twice Daily With or Without Multiple Oral Doses of 300-mg Atazanavir + 100 mg Ritonavir Daily to Young, Healthy, Male and Female Subjects

AN	C_{12hr}, nM			$AUC_{0\text{-}12\,hr}$, μM•hr			C_{max}, μM			T_{max}, hr		
	A	B	A/B	A	B	A/B	A	B	A/B	A	B	A-B
201	144.9	149.4	0.97	33.77	28.26	1.19	11.22	9.45	1.19	3.0	3.0	0.0
202	149.9	64.4	2.33	22.81	20.78	1.10	5.96	6.56	0.91	4.0	3.0	1.0
203	202.7	108.5	1.87	31.72	27.61	1.15	11.03	11.44	0.96	1.0	1.5	-0.5
204	211.1	171.9	1.23	24.47	16.71	1.46	8.21	6.53	1.26	3.0	2.0	1.0
205	601.9	208.6	2.89	28.71	19.16	1.50	7.50	4.63	1.62	5.0	3.0	2.0
206	320.2	281.1	1.14	32.32	23.27	1.39	8.97	8.53	1.05	2.0	1.5	0.5
207	173.9	106.0	1.64	43.02	19.56	2.20	11.00	5.50	2.00	2.0	1.0	1.0
208	776.8	207.0	3.75	25.98	40.26	0.65	4.15	12.18	0.34	1.0	2.0	-1.0
209	113.6	63.9	1.78	13.95	5.05	2.76	3.64	0.98	3.71	4.0	4.0	0.0
210	97.4	61.0	1.60	25.05	14.54	1.72	7.08	4.67	1.52	3.0	1.5	1.5
AM	279.2	142.2	–	28.18	21.52	–	7.88	7.05	–	2.8	2.3	–
SD	228.6	74.6	–	7.75	9.37	–	2.76	3.41	–	1.3	1.0	–
Med	188.3	129.0	–	27.35	20.17	–	7.86	6.55	–	3.0	2.0	0.7[†]
GM[‡]	220.2	124.6	1.77	27.14	19.25	1.41	7.38	5.95	1.24	–	–	–

A: 400-mg MK-0518 q12 hr + 300-mg atazanavir qDay + 100-mg ritonavir qDay x 10 days; pharmacokinetic parameters after AM dose on Day 10
B: 400-mg MK-0518 q12 hr x 4 days; pharmacokinetic parameters after AM dose on Day 4
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
[‡]Based on least squares mean from an ANOVA performed on the natural-log transformed values

Figure 2. Individual MK-0518 C_{12hr} Ratios [MK-0518 Coadministered with Atazanavir and Ritonavir/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 Multiple Doses of 300-mg Atazanavir + 100-mg Ritonavir Daily to Young, Healthy, Male and Female Subjects (n=10)

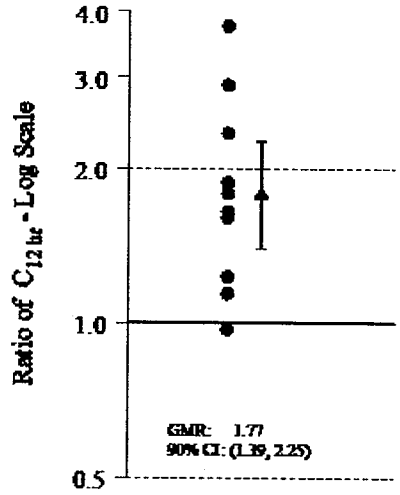


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Figure 3. Individual MK-0518 $AUC_{0\text{-}12hr}$ Ratios [MK-0518 Coadministered with Atazanavir and Ritonavir/MK-0518 Administered Alone] with Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400-mg MK-0518 Twice Daily With or Without Multiple Doses of 300-mg Atazanavir + 100-mg Ritonavir Daily to Young, Healthy, Male and Female Subjects (n=10)

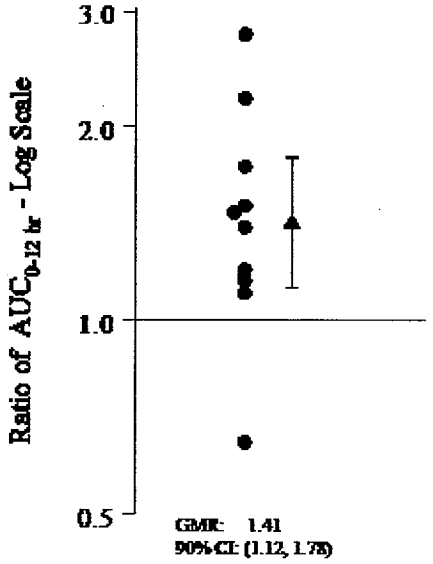
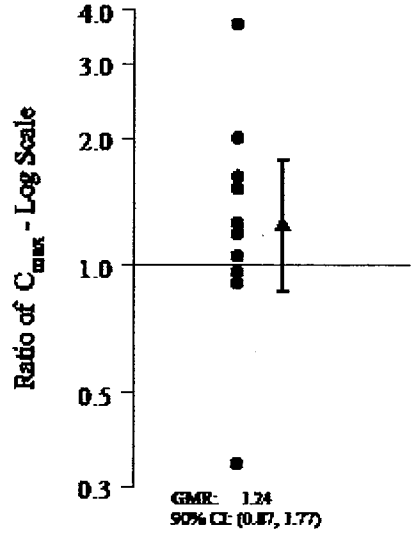


Figure 4. Individual MK-0518 C_{max} Ratios [MK-0518 Coadministered with Atazanavir and Ritonavir/MK-0518 Administered Alone] with Geometric Mean Ratio and 90% Confidence Interval Following Multiple Doses of 400-mg MK-0518 Twice Daily With or Without Multiple Doses of 300-mg Atazanavir + 100-mg Ritonavir Daily to Young, Healthy, Male and Female Subjects (n=10)



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 and no subject discontinued because of an adverse experience. Nine subjects reported a total of 32 nonserious clinical adverse experiences, 17 of which in 6 subjects were determined by the investigator as possibly drug related. Eight non-serious laboratory adverse experiences of blood bilirubin increased were reported in eight subjects in this study. All of the laboratory adverse experiences were reported on Period 2 Day 9 when MK-0518 400

mg twice daily was coadministered with atazanavir 300 mg daily and ritonavir 100 mg daily and were considered to be definitely drug related by the investigator. Hyperbilirubinemia is a known adverse experience of atazanavir, consistent with the label for this drug. All adverse experiences reported were transient and rated mild in intensity.

DISCUSSION AND CONCLUSIONS: With co-administration of 300 mg atazanavir + 100 mg ritonavir once daily for 10 days, the C_{12hr} geometric mean ratio for (MK-0518 + atazanavir + ritonavir/MK-0518) was 1.77 with a corresponding 90% confidence interval (CI) of (1.39, 2.25). The AUC_{0-12hr} geometric mean ratio (MK-0518 + atazanavir + ritonavir/MK-0518) was 1.41 with a corresponding 90% CI of (1.12, 1.78), while the C_{max} geometric mean ratio was 1.24 with a 90% CI of (0.87, 1.77).

The upper bound of 90% CI of MK-0518 AUC ratios was 1.78 (<2.0) but a few individual MK-0518 AUC ratios were slightly above 2.0.

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.

As anticipated, raltegravir plasma levels were increased with coadministration with atazanavir alone and in combination with ritonavir, which is consistent with inhibition of UGT1A1. However, concomitant use of raltegravir and atazanavir was well tolerated in the Phase II and Phase III studies. Based on these data, atazanavir may be coadministered with raltegravir without dose adjustment of raltegravir. The current intended treatment population for raltegravir, treatment experienced patients, should only receive atazanavir/ritonavir.

Protocol 011

TITLE: An Open-Label Study to Investigate the Absorption, Distribution, Metabolism, and Excretion of a Single Dose of [^{14}C]-MK-0518 in Healthy Male Subjects

OBJECTIVES: To investigate the route(s) of elimination and mass balance of MK-0518 after oral administration of a single 200-mg [185.92 microcurie (µCi)] dose of [^{14}C]-MK-0518 in healthy adult male subjects, to quantitate total radioactivity and MK-0518 concentrations in plasma after oral administration of a single 200-mg (185.92 µCi) dose of [^{14}C]-MK-0518 and to examine the metabolism of MK-0518 in humans and identify major metabolites in biological specimens.

SUBJECTS AND STUDY DESIGN: This was a single-dose, open-label study to investigate the absorption, distribution, metabolism, and excretion of [^{14}C]-MK-0518. Eight subjects received a single oral dose of 200-mg [^{14}C]-MK-0518 (185.92 µCi) in the fasted state. Drug administration was followed by collection of serial blood samples to obtain plasma, and all urine and stool samples were collected for 240 hours postdose.

INVESTIGATORS AND STUDY LOCATIONS:

FORMULATION: [^{14}C]-MK-0518 50 mg capsules

SAMPLE COLLECTION: Blood samples were collected at selected time points to determine total radioactivity and drug/metabolite concentrations. Urine and stool were continuously collected over pre-specified intervals through 240 hour postdose for total radioactivity and drug/metabolite assay.

Procedures	Pre-study	Pre-dose	Hours Postdose																						
			0	0.5	1	2	3	4	5	6	8	10	12	16	20	24	36	48	60	72	96	120	144	168	192	216	240
Blood collection for assays		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for assays[1]		X	X					X			X			X			X			X	X	X	X	X	X	X
Stool collection for assays[1]		X[2]	X																								X
Blood for polymorphism archive		X																									

ASSAYS: A validated HPLC-MS/MS assay was used for plasma MK-0518 concentrations.

Plasma, urine, and fecal samples, as well as toilet tissue, were analyzed for radioactive content by liquid scintillation counting (LSC).

Plasma, urine, and feces extracts were profiled by HPLC/MS radiochromatography.

PHARMACOKINETIC DATA ANALYSIS: The plasma pharmacokinetic parameters (e.g., $AUC_{0\text{-}240hr}$, C_{max}, and T_{max}) of MK-0518 and radioactivity were calculated for each subject after a single dose of [^{14}C]-MK-0518.

PHARMACOKINETIC RESULTS:

Table 1. Summary Statistics of MK-0518 Pharmacokinetics Compared to Radioactivity and Proportion of the Radioactive Dose Recovered Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518 to Young, Healthy, Male Subjects

MK-0518 Plasma Pharmacokinetics Compared to Radioactivity (N=8)			
	MK-0518	Radioactivity	MK-0518/Radioactivity
Parameter	Geometric Mean	Geometric Mean	GMR (95% CI)‡
$AUC_{0\text{-}240\ hr}$ (μM·hr or μM eq·hr)†	10.45	15.12	0.69 (0.43, 1.10)
C_{max} (μM or μM eq)†	4.60	5.80	0.79 (0.51, 1.24)
$C_{12\ hr}$ (nM or μM eq)†	43.0	76.8	0.56 (0.38, 0.83)
T_{max} (hr)	1.0§	1.0§	–
Proportion of the Radioactive Dose Recovered (N=7)‖			
	Urine	Feces	Total
Percent Recovery of Radioactivity (%)	31.8	51.1	83.0
95% Confidence Interval	(23.0, 40.5)	(41.5, 60.7)	(70.9, 95.0)

† Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
‡ GMR = Geometric least-squares mean ratio (MK-0518 / Radioactivity); CI = confidence interval.
§ Median reported for T_{max}.
‖ Data from AN 0211 excluded.

Figure 1. Mean Concentration-Time Profiles of MK-0518 and Total Radioactivity in Plasma Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518 to Young, Healthy, Male Subjects (N=8)

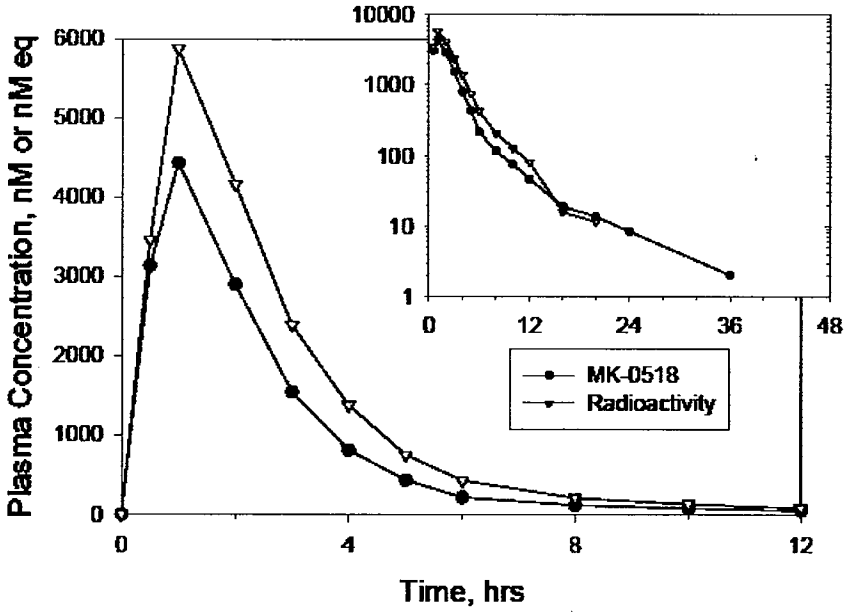


Figure 2. A Representative Radiochromatogram Obtained from Extracts of Pooled Plasma (0-6 hr) From a Subject (AN 1211) Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518

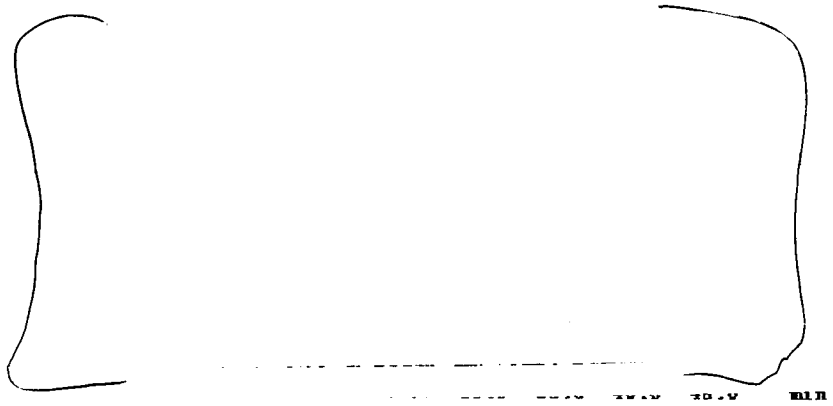


Table 2. Relative Contribution of M2 to Radioactivity in Human Plasma Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518 to Young, Healthy, Male Subjects

Figure 3. Mean Percent of the Radioactivity Dose Recovered with Time Following Administration of a Single Oral Dose of 200-mg [14 C]-MK-0518 to Young, Healthy, Male Subjects (N=7)

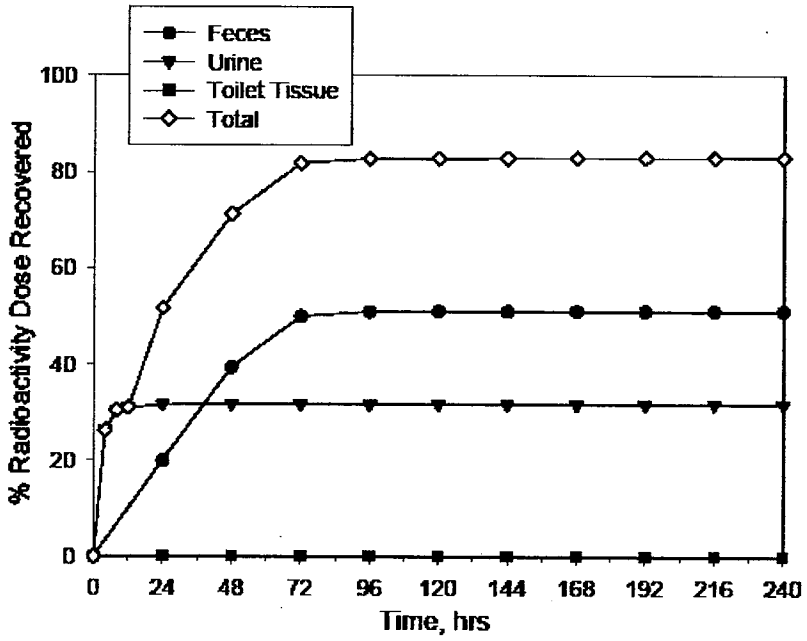


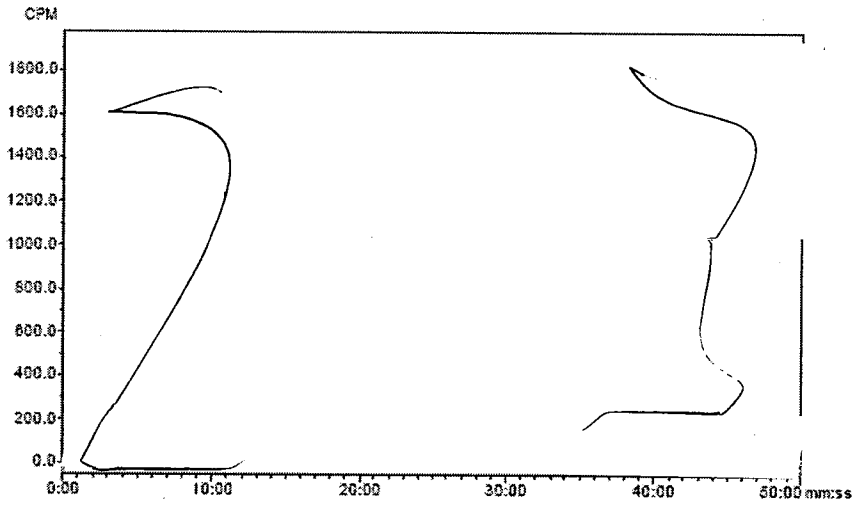
Figure 4. A Representative Radiochromatogram Obtained from Extracts of Pooled Urine (0-8 hr) From a Subject (AN 0215) Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518

Table 3. Percent of Dose Accounted for by M2 and MK-0518 in Urine Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518 to Young, Healthy, Male Subjects†

	Contribution (Percent of Radioactive Dose)	
AN	M2	MK-0518
0212 0213 0215 0216 0217 0218 1211		
AM	22.9	8.8
SD	6.1	4.7

AN = Allocation Number; AM = Arithmetic Mean; SD = Standard Deviation.
[1] AN0211 samples were not assayed for metabolites and data were excluded from summary statistics.

Figure 5. A Representative Radiochromatogram Obtained from Extracts of Pooled Feces (0-48 hr) From a Subject (AN 0215) Following Administration of a Single Oral Dose of 200-mg [^{14}C]-MK-0518



SAFETY RESULTS: [^{14}C]-MK-0518 was generally well tolerated in young, healthy, male subjects. No serious clinical or serious laboratory adverse experience was reported and no subject discontinued due to an adverse experience. Two subjects reported a total of 3 nonserious clinical adverse experiences, 2 of which were determined by the investigator as drug related. There were no laboratory adverse experiences reported.

DISCUSSION AND CONCLUSIONS: Following administration of a single dose of 200 mg [^{14}C]-MK-0518 to young healthy subjects, approximately 83.0% of the radioactivity dose was recovered, with 51.1% in feces and 31.8% in urine over a 10-day period postdose. MK-0518 accounted for approximately 69% of the radioactivity in plasma, as determined by the AUC ratio of MK-0518 to radioactivity. Parent compound and the glucuronide derivative M2 were the only radioactive species detected in plasma. M2 was the primary species detected in urine (23% of radioactive dose), with a smaller contribution from parent compound (9% of radioactive dose). In fecal extracts, the only detectable radioactive peak represented the parent compound (51% of the radioactive dose); however, fecal radioactivity may represent excreted glucuronide that was back-converted to parent after biliary excretion. The data collectively indicate that glucuronidation plays a major role in the clearance of MK-0518 in humans.

Protocol 014

TITLE: An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of MK-0518 in Patients With Moderate Hepatic Insufficiency

OBJECTIVES: To compare the plasma concentration-time profile and pharmacokinetics of MK-0518 after administration of a single 400 mg oral dose of MK-0518 to patients with moderate hepatic insufficiency to that of healthy subjects matched to each patient for race, age, gender, and body mass index (BMI) and to evaluate the safety and tolerability of MK-0518 after administration of a 400 mg single oral dose to patients with moderate hepatic insufficiency and to healthy subjects

SUBJECTS AND STUDY DESIGN: This was an open-label, single-dose study comparing the pharmacokinetics of a single 400 mg dose of MK-0518 in patients with moderate hepatic insufficiency (assessed by the criteria of Child-Pugh) with healthy matched control subjects (race, age, gender, and body mass index [BMI]). Eight (8) patients with moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh scale) and 8 healthy matched control subjects were enrolled in the study. Each patient/subject received a single 400 mg dose of MK-0518 under fasted conditions. Blood samples were obtained predose and at selected time points up to 96 hours postdose.

Individual Child-Pugh's Classification Scores and Laboratory Values for Moderate Hepatic Patients Enrolled in MK-0518 Protocol 014

AN	Encephalopathy CP Score	Ascites CP Score	Albumin Value (g/dL)	Albumin CP Score	PT Seconds†	PT CP Score	Bilimbin Value (mg/dL)	Bilimbin CP Score‡	Total CP Score
0275	2	2	5.1	1	0.8	1	1.1	1	7
0276	2	2	4.9	1	0.6	1	1.3	1	7
0277	2	2	4.0	1	0.7	1	1.0	1	7
0278	2	2	4.4	1	0.9	1	1.1	1	7
0279	2	2	3.2	2	0	1	0.8	1	8
0280	2	2	4.1	1	3.7	1	2.0	2	8
0281	2	2	4.0	1	2.0	1	0.8	1	7
0282	2	2	4.7	1	0.3	1	0.6	1	7

† Seconds over control.
‡ Not for primary biliary cirrhosis.
AN=Allocation number; CP =Child-Pugh; PT=Prothrombin time.

Demographics for Subjects/Patients in MK-0518 Protocol 014

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)	BMI	Site
0275	Male	White	56	175.3	94.1	30.6	014-0001
0276	Female	White	58	162.6	73.2	27.7	014-0001
0277	Male	Black	48	165.1	50.9	18.7	014-0001
0278	Male	White	54	177.8	92.7	29.3	014-0001
0279	Female	White	63	152.4	48.2	20.8	014-0001
0280	Male	White	54	182.9	88.6	26.5	014-0001
0281	Male	White	53	170.2	77.3	26.7	014-0001
0282	Male	White	64	162.6	79.1	29.9	014-0001
		Mean	56.3	168.6	75.5	26.3	NA
		Range	48 to 64	152.4 to 182.9	48.2 to 94.1	18.7 to 30.6	
0283	Male	White	57	175.3	90.0	29.3	014-0001
0284	Female	White	56	160.0	70.0	27.3	014-0001
0285	Male	White	52	170.2	86.4	29.8	014-0001
0286	Male	White	51	167.6	72.7	25.9	014-0001
1287	Male	White	65	155.0	66.4	27.6	014-0002
1288	Male	White	57	173.0	80.0	26.7	014-0002
0289	Female	White	59	158.0	55.0	32.8	014-0002
0290	Male	Black	49	175.6	55.9	18.1	014-0003
		Arithmetic Mean	55.8	166.8	72.1	27.2	NA
		Range	49 to 65	155.0 to 175.6	55.0 to 90.0	18.1 to 32.8	

AN = Allocation number; BMI = Body mass index; Mean = Arithmetic mean; NA = Not applicable

INVESTIGATORS AND STUDY LOCATIONS:

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

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, 5, 6, 8, 10, 12, 16, 24, 32, 48, 72 and 96 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 $AUC_{0-\infty}$, C_{max}, $C_{12\,hr}$, T_{max}, and apparent $t_{½}$ for each subject. Geometric mean ratios (moderate hepatic insufficiency/control) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{0-\infty}$) were calculated.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Administration of Single Oral Doses of 400 mg MK-0518 to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects (N=8/Panel; Inset = Semilog Scale)

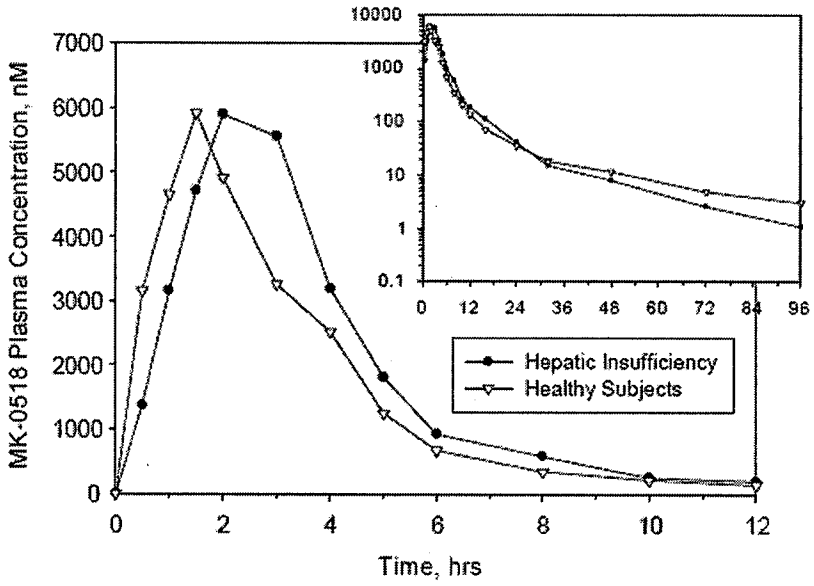


Table 1. Mean MK-0518 Plasma Pharmacokinetic Parameter Values Following Administration of Single Oral Doses of 400 mg MK-0518 to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects

Pharmacokinetic Parameter	Hepatic Insufficiency			Healthy Subjects			Hepatic Insufficiency/Healthy Subjects		
	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	MSE[†]
$AUC_{0-\infty}$ (µM•hr)[‡]	8	17.67	(8.93, 34.99)	8	20.66	(10.29, 41.47)	0.86	(0.41, 1.77)	0.649
C_{max} (µM)[‡]	8	4.41	(1.74, 11.20)	8	6.99	(2.70, 18.09)	0.63	(0.23, 1.70)	1.208
C_{12hr} (nM)[‡]	8	143.4	(77.3, 266.1)	8	113.8	(60.6, 213.8)	1.26	(0.65, 2.43)	0.532
T_{max} (hr)	8	2.5[§]		8	1.5[§]		0.4[¶]	(-1.0, 1.5)[¶]	
$t_{1/2}$ α (hr)	8	1.49[§]		8	1.12[§]		0.26[¶]	(-0.15, 0.74)[¶]	
$t_{1/2}$ β (hr)	8	7.0[§]		8	9.3[§]		-1.9[¶]	(-7.7, 6.8)[¶]	

[†] Mean square error on log-scale.
[‡] Geometric mean computed from least squares estimate from an ANCOVA performed on the natural-log transformed values, with fixed effect terms for hepatic status, age, gender, and Body Mass Index.
[§] Median reported for T_{max}. Harmonic mean reported for half-life.
[¶] Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference.

Figure 2. Individual MK-0518 AUC0-∞ Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects (N=8/Panel)

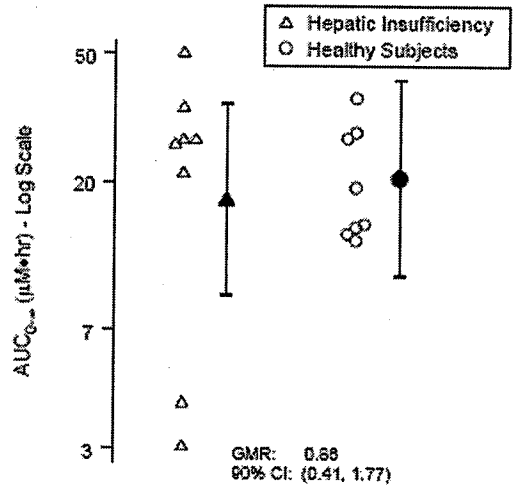


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Figure 3. Individual MK-0518 Cmax Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects (N=8/Panel)

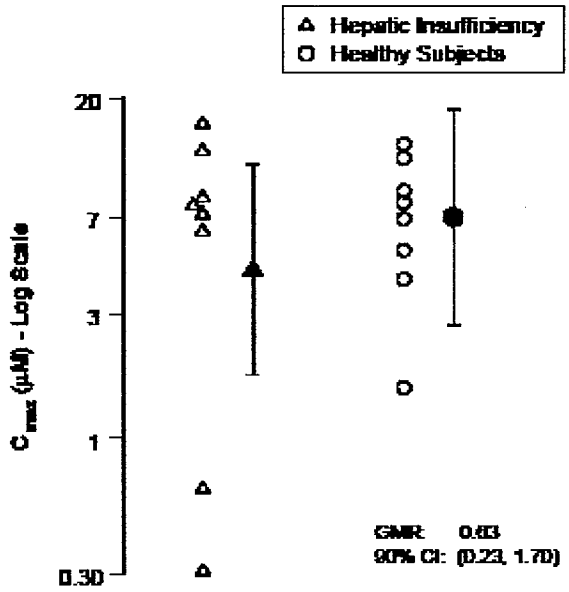
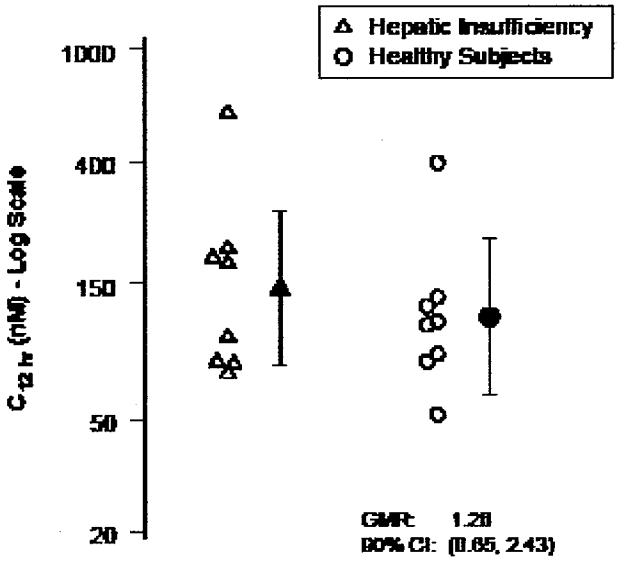


Figure 4. Individual MK-0518 C12 hr Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Moderate Hepatic Insufficiency and Matched Healthy Control Subjects (N=8/Panel)



SAFETY RESULTS: Administration of a single 400-mg MK-0518 dose to patients with moderate hepatic insufficiency and healthy matched control subjects was generally well tolerated. No clinical or laboratory adverse experiences were reported and no study participant was discontinued because of an adverse experience.

DISCUSSION AND CONCLUSIONS:

The geometric mean ratio (hepatic insufficiency/healthy controls) for MK-0518 $AUC_{0-\infty}$ was 0.86, with a corresponding 90% confidence interval of (0.41, 1.77). The geometric mean ratios and corresponding 90% confidence intervals for C_{max} and $C_{12\,hr}$ were 0.63 (0.23, 1.70) and 1.26 (0.65, 2.43), respectively.

Although the primary clearance mechanism of MK-0518 is metabolism, this metabolism is mediated by UGT1A1. Unlike CYP-based metabolism, glucuronidation is generally unaffected by hepatic disease, in part due to excess capacity within the major glucuronidation pathways in people with normal hepatic function. The findings for MK-0518 in patients with hepatic insufficiency are consistent with results from other compounds primarily cleared by glucuronidation.

Overall, there was no clinically important effect of moderate hepatic insufficiency on the MK-0518 pharmacokinetic profile.

Protocol 015

TITLE: An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of MK-0518 in Patients With Severe Renal Insufficiency

OBJECTIVES: To compare the plasma concentration-time profile and pharmacokinetics of MK-0518 after administration of a single 400 mg oral dose of MK-0518 to patients with severe renal insufficiency to that of healthy subjects matched to each patient for race, age, gender, and body mass index (BMI) and to evaluate the safety and tolerability of MK-0518 after administration of a 400 mg single oral dose to patients with severe renal insufficiency and to healthy subjects

SUBJECTS AND STUDY DESIGN: This was an open-label, single-dose study comparing the pharmacokinetics of a single 400 mg dose of MK-0518 in non-dialyzed patients with severe renal insufficiency (as defined below) with healthy matched control subjects (race, age, gender, and body mass index [BMI]). Ten patients with severe renal insufficiency and 10 healthy matched control subjects were enrolled in this study. Each patient/subject received a single 400 mg dose of MK-0518. Blood samples were obtained predose and at selected time points up to 72 hours postdose. Urine samples were also collected serially up to 24 hours postdose. Each patient/subject received a single 400-mg dose of MK-0518 in the fasted state.

Degree of Renal Insufficiency	24-Hour Creatinine Clearance
Normal	>80 mL/min/1.73 m^2
Severe	<30 mL/min/1.73 m^2

Subject/Patient Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)	BMI
			Site 015-0001[3]			
Severe Renal Patients						
0243	Male	White	68	163.0	72.5	27.29
0244	Male	White	59	174.0	72.0	23.78
0245	Male	White	46	188.0	108.5	30.13
0246	Male	White	43	172.0	70.0	23.66
0247	Female	White	51	163.0	78.0	29.36
0248	Female	White	56	156.0	73.0	30.00
0249	Male	White	70	160.5	74.0	28.73
Healthy Control Subjects						
0259	Male	White	69	169.0	86.0	30.11
0260	Female	White	36	169.0	84.5	29.59
0261	Female	White	58	158.4	68.0	27.10
0262	Male	White	43	173.0	75.0	25.06
0263	Male	White	52	171.0	83.0	28.38
			Site 015-0002[4]			
Severe Renal Patients						
0251	Female	White	62	157.5	78.3	31.56
0252	Male	White	24	174.0	66.1	21.83
0253	Male	White	71	166.4	81.7	29.51
Healthy Control Subjects						
0267	Male	White	21	179.1	67.9	21.17
0268	Male	White	54	175.3	81.2	26.42
0269	Female	White	60	167.6	85.6	30.47
0270	Male	White	66	171.5	80.0	27.20
0271	Male	White	70	188.6	96.5	27.13
		Overall N:	20	20	20	20
		Overall Range:	21 to 71	156.0 to 188.6	66.1 to 108.5	21.17 to 31.56
		Overall Arithmetic Mean:	53.0	169.8	79.0	27.4
		Severe Renal Patient N:	10	10	10	10
		Severe Renal Patient Range:	24 to 71	156.0 to 188.0	66.1 to 108.5	21.83 to 31.56
		Severe Renal Patient Arithmetic Mean:	53.0	167.4	77.2	27.59
		Healthy Subject Overall N:	10	10	10	10
		Healthy Subject Range:	21 to 70	158.4 to 188.6	67.9 to 96.5	21.17 to 30.47
		Healthy Subject Arithmetic Mean:	52.9	172.3	80.8	27.26

AN = allocation number.
BMI = body mass index.
N = number
[3] Site 015-0001: Richard Robson, M.D., Christchurch, New Zealand.
[4] Site 015-0002: Norman Martin Lunde, M.D., St. Paul, MN.

INVESTIGATORS AND STUDY LOCATIONS:

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

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, 5, 6, 8, 10, 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: Plasma concentrations of MK-0518 were used to calculate pharmacokinetic parameters including AUC $_{0-\infty}$, C_{max}, $C_{12\,hr}$, T_{max}, and apparent $t_{½}$ for each subject. Geometric mean ratios (severe renal insufficiency/control) and associated 90% confidence intervals (CIs) of primary plasma MK-0518 PK parameters (C_{12h}, C_{max}, and $AUC_{0-\infty}$) were calculated.

PHARMACOKINETIC RESULTS:

Figure 1. Arithmetic Mean MK-0518 Plasma Concentration Profiles Following Administration of Single Oral Doses of 400 mg MK-0518 to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects (N=10/Panel; Inset = Semilog Scale)

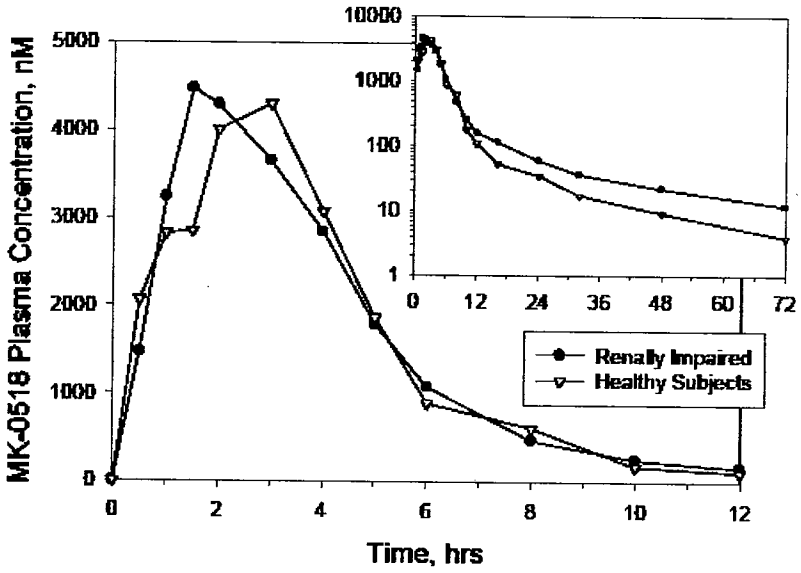


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Table 1. Mean MK-0518 Plasma Pharmacokinetic Parameter Values Following Administration of Single Oral Doses of 400 mg MK-0518 to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects

Pharmacokinetic Parameter	Renally Impaired			Healthy Subjects			Renally Impaired / Healthy Subjects		
	N	Geometric Mean	95% Confidence Interval for Geometric Mean	N	Geometric Mean	95% Confidence Interval for Geometric Mean	Geometric Mean Ratio	90% Confidence Interval for Geometric Mean Ratio	MSE†
$AUC_{0-\infty}$ (μM·hr)‡	10	16.80	(9.96, 28.36)	10	19.70	(11.84, 32.76)	0.85	(0.49, 1.49)	0.498
C_{max} (μM)‡	10	3.85	(3.06, 7.20)	10	5.68	(3.89, 10.43)	0.68	(0.35, 1.32)	0.713
C_{12hr} (nM)‡	10	135.0	(85.9, 211.9)	10	105.5	(68.8, 163.7)	1.28	(0.79, 2.06)	0.371
T_{max} (hr)	10	3.5§		10	3.8§		0.0‖	(-1.5, 1.0)‖	
$t_{1/2}$ α (hr)	10	1.38§		10	1.10§		0.26‖	(0.03, 0.46)‖	
$t_{1/2}$ β (hr)	10	17.2§		10	11.4§		5.8‖	(1.3, 10.6)‖	
f_e (%)	10	0.5§		10	4.1§				
Cl_R (mL/min)	10	2.7§		10	31.5§				

† Mean square error on log-scale.
‡ Geometric means computed from least squares estimate from an ANCOVA performed on the natural-log transformed values, with fixed effect terms for renal status, age, gender, and Body Mass Index.
§ Median reported for T_{max}. Harmonic mean reported for half-life. Arithmetic mean reported for percent dose in urine and renal clearance.
‖ Hodges-Lehmann estimate of median difference with corresponding 90% CI for true median difference.

The percent of the dose of MK-0518 excreted as unchanged drug in urine was lower for patients with renal insufficiency compared to matched healthy control subjects. As shown in Table 1, on average, 0.5 and 4.1 % of the dose were recovered in urine for patients with renal insufficiency and matched healthy control subjects, respectively. The renal clearance of MK-0518 was lower for patients with renal insufficiency compared to matched healthy control subjects. Mean renal clearance values were 2.7 and 31.5 mL/min for patients with renal insufficiency and matched healthy control subjects, respectively.

Figure 2. Individual MK-0518 AUC0-∞ Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects (N=10/Panel)

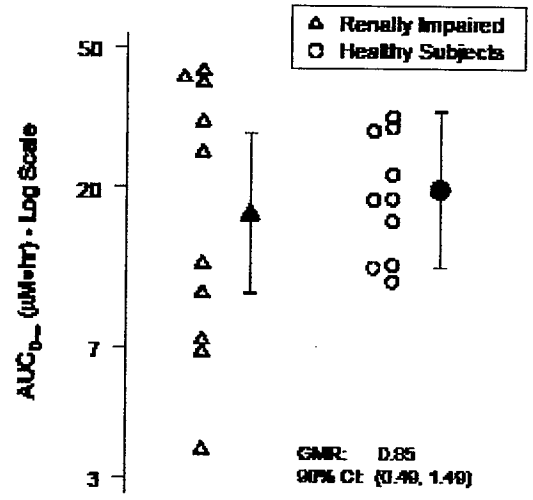

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Figure 3. Individual MK-0518 Cmax Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects (N=10/Panel)

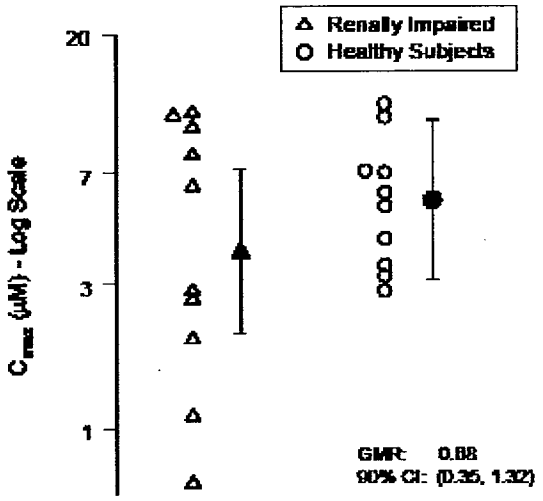
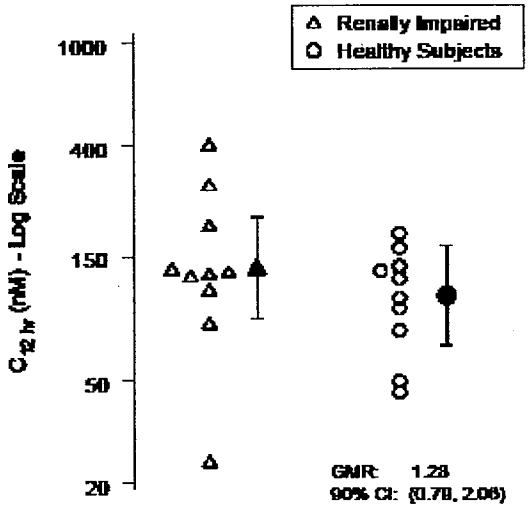


Figure 4. Individual MK-0518 C12 hr Values Following Single Oral Dose Administration of 400 mg MK-0518 to Patients With Severe Renal Insufficiency and Matched Healthy Control Subjects (N=10/Panel)



SAFETY RESULTS: MK-0518 was generally well tolerated in patients with severe renal impairment and matched healthy subjects. No serious clinical or serious laboratory adverse experiences were reported and no subject discontinued because of an adverse experience. Of the 33 non-serious clinical adverse experiences reported by 11 patients/subjects (5 in renal patients and 6 in healthy controls), 15 were considered by the investigator to be related to study drug. There were no laboratory adverse experiences reported.

DISCUSSION AND CONCLUSIONS:

The geometric mean ratio (renally impaired/healthy controls) for MK-0518 $AUC_{0-\infty}$ was 0.85, with a corresponding 90% confidence interval of (0.49, 1.49). The geometric mean ratios and corresponding 90% confidence intervals for C_{max} and $C_{12\ hr}$ were 0.68 (0.35, 1.32) and 1.28 (0.79, 2.06), respectively.

In contrast to the drug exposure parameters, clear evidence of alterations in the amount excreted in urine, the renal clearance, and the β-phase half-life were obtained in this study. The percent of the dose excreted in urine and the renal clearance were both considerably lower (~90%) for patients with renal insufficiency compared to healthy subjects. The slower rate of renal clearance appears to have prolonged the β phase of plasma elimination by ~50%. Because the overall elimination of MK-0518 via the renal pathway is minor in subjects with normal renal function, the differences in the percent of the dose excreted and in renal clearance did not result in large alterations in the exposure parameters (AUC, C_{max}, $C_{12\ hr}$). Because the β-phase has a minor contribution to AUC and C_{max}, the prolongation of the half-life in this phase did not result in meaningful elevations in AUC or C_{max}.

Overall, there was no clinically important effect of severe renal insufficiency on the MK-0518 pharmacokinetic profile.