アイセントレス錠600mg
に関する資料

MSD 株式会社

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Table of All Clinical Trials

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
0518-290 [Ref. 5.3.1.1: P290]	I	Canada	A Single Dose Food Effect Study of Raltegravir Formulations	Open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover, food-effect study.	Single dose, two tablets formulations, MK-0518 1200 mg Oral	Healthy male and female subjects Age: 20-55	MK-0518 1200 mg = 36

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
0518-291 [Ref. 5.3.1.1: P291]	I	Canada	A Multiple Dose Study of Raltegravir Formulations	Open-label, multiple-dose, randomized, three-period, three-treatment, six-sequence, crossover, comparative bioavailability study.	Treatment A: MK-0518 1200 mg (2 x 600 mg) once daily for 5 days Treatment B: MK-0518 1200 mg (3 x 400 mg) once daily for 5 days Treatment C: MK-0518 400 mg twice daily for 4 days and one AM dose on Day 5	Healthy male and female subjects Age: 25-55	Treatment A: N=23 Treament B: N=22 Treatment C: N=23

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
0518-812 [Ref. 5.3.2.2: P812]	I	USA	A Study to Evaluate the Influence of Efavirenz on a Single Dose of MK-0518 in Healthy Subjects	Open-label, randomized, 2-period, fixed-sequence study 9 weeks	Period 1: A single oral dose of 1200 mg MK-0518 on Day 1 Period 2: Multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 12	Males/Females Age: 21 - 52 Healthy subjects	MK-0518 1200 mg = 21 Efavirenz 600 mg = 21

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
0518-823 [Ref. 5.3.2.2: P823]	I	USA	A Study to Evaluate the Influence of Atazanavir on a Single Dose of MK-0518 in Healthy Subjects	Open-label, 2-period, fixed-sequence study under fed conditions 11.5 weeks	Period 1: A single oral dose of 1200 mg MK-0518 on Day 1 Period 2: Multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7	Males/Females Age: 21 - 55 Healthy subjects	MK-0518 exposure in healthy subjects = 14 Period 1: A single oral dose of 1200 mg MK-0518 on Day 1: 14 subjects Period 2: Multiple oral QD doses of 400 mg atazanavir for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7: 12 subjects

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regime	Trial population	Subject exposure
0518-824 [Ref. 5.3.2.2: P824]	I	USA	A Study to Evaluate the Influence of Metal Cation-Containing Antacids on MK-0518 Pharmacokinetics in HIV-Infected Subjects on a Stable Raltegravir-Containing Regimen	Open-label, non-randomized, 4-period, fixed-sequence study	Pre-treatment (5 days prior to Period 1): 1200 mg QD MK-0518 Between Periods: 1200 mg QD MK-0518 Period 1, Treatment A: 1200 mg QD MK-0518 alone Period 2, Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000, and 1200 mg QD MK-0518, taken concomitantly Period 3, Treatment C: 20 mL MAALOX® Maximum Strength (MS) (or generic equivalent*) given 12 hours after administration of 1200 mg QD MK-0518 (*Leader Antacid MS was used) Period 4, Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518	Males/Females Age: ≥ 18 HIV-infected subjects	Pre-treatment (5 days prior to Period 1): 1200 mg QD MK-0518: 20 subjects Period 1, Treatment A: 1200 mg QD MK-0518 alone: 20 subjects Period 2, Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000, and 1200 mg QD MK-0518, taken concomitantly: 19 subjects Period 3, Treatment C: 20 mL MAALOX® Maximum Strength (MS) (or generic equivalent*) given 12 hours after administration of 1200 mg QD MK-0518: 19 subjects Period 4, Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518: 19 subjects

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
0518-293 [Ref. 5.3.3.1: P293]	I	Netherlands	Placebo-controlled trial to evaluate the safety and tolerability, and to assess the pharmacokinetics of MK-0518 (raltegravir) in healthy subjects.	Single-site, multiple-dose, randomized, double- blind, placebo-controlled.	MK-0518 (raltegravir) tablets: 1800 mg (as 3x600 mg) o.d. for 28 days. Matching placebo for the same regimen and duration.	Males/females Age: 18-45 Healthy subjects	MK-0518 (raltegravir): 18 Placebo: 6

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
0518-292 [Ref. 5.3.5.1: P292V01]	3	Europe, North America, Asia/Pacific, Latin America, Africa	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Reformulated Raltegravir 1200 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Each in Combination With TRUVADA™, in Treatment-Naïve HIV-1 Infected Subjects	Randomized, double-blind, parallel, active-controlled, 96-week	Group 1: Raltegravir 1200 mg once daily (QD) + TRUVADA™ QD Group 2: Raltegravir 400 mg twice daily (BID) + TRUVADA™ QD	Males/Females Age: ≥18 Treatment-naïve, HIV-infected subjects	Raltegravir 1200 mg QD: 531 subjects Raltegravir 400 mg BID: 266 subjects

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

2.0 SYNOPSIS

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*
Title of Study: A Single Dose Food Effect Study of Raltegravir Formulations
Investigators: [redacted], MD, PhD, FRCP(C) [redacted], MD, FRCP(C), MSc [redacted], MD, MSc, CCFP [redacted], MD, FRCP (C), MSc
Study Centre(s): **Clinical Facility:** [redacted] Canada, [redacted] **Clinical Laboratory Facility:** [redacted] Canada, [redacted] **Bioanalytical Facility:** [redacted] The Netherlands **Pharmacokinetic and Statistical Facility:** [redacted] Canada, [redacted] **Report Issuing Facility:** [redacted] Canada, [redacted]
Phase of Development: Phase 1 - Food Effect
Study Periods: **Period 1:** [redacted] 20[redacted] **Period 2:** [redacted] 20[redacted] **Period 3:** [redacted] 20[redacted]
Objective: The objective of this study is to assess the effect of a low-fat and a high-fat breakfast on the pharmacokinetics (e.g., Cmax, AUCinf and C24) of raltegravir after administration of a 1200 mg dose of reformulated MK-0518 600 mg Tablets (2 x 600 mg) and Isentress® 400 mg Tablets (3 x 400 mg).

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Methodology:

- Cohort 1 and Cohort 2: This is an open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover, food-effect study.
- This study is designed to assess the effect of a low-fat and a high-fat breakfast on the pharmacokinetics (e.g., Cmax, AUCinf and C24) in healthy male and female subjects.
- Concentrations of raltegravir were measured from the samples collected over a 48-hour interval after dosing in each period.
- The pharmacokinetic (PK) parameters AUC0-last, AUC0-inf, Cmax, C24, Tmax, Kel and Thalf were estimated using a non-compartmental approach.

Number of subjects (planned and analyzed):

- Planned for inclusion: 36 subjects (18 in Cohort 1 and 18 in Cohort 2).
- Total number of subjects that completed all periods of the study: 32 subjects (16 in Cohort 1 and 16 in Cohort 2).
- Included in the safety dataset: 36 subjects.
- Included in the pharmacokinetic dataset: 36 subjects.
  - Subjects 290-1*, 290-2*, 290-3* and 290-4* did not complete all periods of the study but received at least one administration of a study treatment and were, therefore, included in the pharmacokinetic dataset.
- Included in the statistical dataset: 36 subjects (18 in Cohort 1 and 18 in Cohort 2).

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 55 years of age, with a BMI from 19.0 to 30.0 kg/m^2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements.

Drug Product 1 (Treatments A, B and C):
Reformulated MK-0518 600 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Re-Evaluation Date: [redacted] 20[redacted]
Potency: [redacted]
Manufacturing Date: [redacted] 20[redacted]
Dose: 1200 mg
Mode of Administration: Oral under fasting, low-fat fed and high-fat fed conditions

Drug Product 2 (Treatments D, E and F):
Isentress® 400 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: [redacted]
Expiry Date: [redacted] 20[redacted]
Dose: 1200 mg
Mode of Administration: Oral under fasting, low-fat fed and high-fat fed conditions

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*
Duration of treatment: Single-Dose treatment
Statistical Methods: ANOVA (PROC MIXED) was performed on log-transformed AUC0-last, AUC0-inf, C24 and Cmax. Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated for AUCt, AUCinf, C24 and Cmax for the following comparisons: <u>Cohort 1:</u> • Treatment B versus Treatment A • Treatment C versus Treatment A <u>Cohort 2:</u> • Treatment E versus Treatment D • Treatment F versus Treatment D In addition, pairwise 2x2 contingency tables for the C24 concentrations <=45 nM and >45 nM were provided. These statistics were used to evaluate the performance of both formulations under fed and fasted conditions.
Criteria for Evaluation: Hypothesis: The pharmacokinetic parameters of raltegravir after administration of a 1200 mg dose of reformulated MK-0518 600 mg Tablets and Isentress® 400 mg Tablets in the fasted, low-fat breakfast-fed and high-fat breakfast-fed conditions were estimated.

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Results:

Pharmacokinetic Results:

Based on Measured Plasma Raltegravir Concentrations (Cohort 1)

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC0-last	**A**	16	56484.1	41402.2 - 77060.0	**B vs A**	58.24	46.10 - 73.58	37.6
(hr·nM)	**B**	18	32895.8	28546.1 - 37908.3	**C vs A**	101.94	86.11 - 120.70	26.3
	C	17	57582.1	48242.0 - 68730.5		-	-	-
AUC0-inf	**A**	15	55474.9	40098.8 - 76747.2	**B vs A**	59.71	46.81 - 76.17	38.2
(hr·nM)	**B**	17	33126.3	28704.1 - 38229.7	**C vs A**	105.62	87.45 - 127.57	27.8
	C	16	58592.3	49041.7 - 70002.8		-	-	-
Cmax	**A**	16	22558.1	15926.2 - 31951.6	**B vs A**	47.78	36.55 - 62.48	43.4
(nM)	**B**	18	10778.9	9033.7 - 12861.2	**C vs A**	72.22	57.68 - 90.42	35.1
	C	17	16290.9	12799.4 - 20735.0		-	-	-
C24hr	**A**	16	57.7	38.3 - 86.9	**B vs A**	83.52	63.43 - 109.97	43.7
(nM)	**B**	18	48.2	36.6 - 63.5	**C vs A**	87.93	65.53 - 117.99	47.0
	C	17	50.7	35.4 - 72.7		-	-	-
			Median	***Range***				
Tmax	**A**	16	1.50	0.50- 8.00				
(h)	**B**	18	2.00	1.50- 6.00				
	C	17	3.00	1.50- 6.03				
			GM	***CV(%)*****				
t½	**A**	15	12.02	66.37				
(h)	**B**	17	11.62	47.81				
	C	16	8.51	57.60				

** Estimated based on the elements of the variance-covariance matrix as CV(%) = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*

*** CV(%) = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale*

Treatment A FASTING / Reformulated MK-0518 600 mg tablets (2 x 600 mg)
Lot No. [redacted] *(MSD Corp., USA)*

Treatment B LOW-FAT / Reformulated MK-0518 600 mg tablets (2 x 600 mg)
Lot No. [redacted] *(MSD Corp., USA)*

Treatment C HIGH-FAT / Reformulated MK-0518 600 mg tablets (2 x 600 mg)
Lot No. [redacted] *(MSD Corp., USA)*

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Based on Measured Plasma Raltegravir Concentrations (Cohort 2)

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC0-last	**D**	17	33804.4	20548.1 - 55612.6	**E vs D**	27.12	18.15 - 40.51	66.1
(hr·nM)	**E**	17	9166.9	6653.9 - 12629.0	**F vs D**	139.19	94.37 - 205.30	64.4
	F	17	47053.4	31912.7 - 69377.5		-	-	-
AUC0-inf	**D**	17	33959.3	20526.6 - 56182.4	**E vs D**	26.52	17.25 - 40.76	68.7
(hr·nM)	**E**	15	9005.8	6377.7 - 12716.9	**F vs D**	129.21	90.38 - 184.71	50.6
	F	11	43878.2	28021.9 - 68706.8		-	-	-
Cmax	**D**	17	9190.6	4747.9 - 17790.2	**E vs D**	24.86	14.69 - 42.06	87.0
(nM)	**E**	17	2284.4	1732.0 - 3013.0	**F vs D**	76.50	42.34 - 138.23	98.4
	F	17	7031.1	4382.8 - 11279.6		-	-	-
C24hr	**D**	17	46.7	36.6 - 59.7	**E vs D**	82.42	68.08 - 99.80	30.7
(nM)	**E**	17	38.5	29.3 - 50.7	**F vs D**	170.13	110.88 - 261.06	70.9
	F	17	79.5	42.0 - 150.7		-	-	-
			Median	***Range***				
Tmax	**D**	17	2.00	0.50- 8.00				
(h)	**E**	17	2.00	1.00- 4.00				
	F	17	6.00	2.00-24.00				
			GM	***CV(%)*****				
t½	**D**	17	8.58	51.85				
(h)	**E**	15	11.67	49.30				
	F	11	5.66	43.98				

** Estimated based on the elements of the variance-covariance matrix as CV(%) = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*
*** CV(%) = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale*
Treatment D FASTING / Isentress® 400 mg tablets (3 x 400 mg), Lot No. [redacted] (MSD Corp., USA)
Treatment E LOW-FAT / Isentress® 400 mg tablets (3 x 400 mg), Lot No. [redacted] (MSD Corp., USA)
Treatment F HIGH-FAT / Isentress® 400 mg tablets (3 x 400 mg), Lot No. [redacted] (MSD Corp., USA)

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Safety Results:

		PRE-DOSE	TRT A	TRT B	TRT C	TRT D	TRT E	TRT F	Total
Severity	MILD	2	2	5	8	3	2	3	25
	MODERATE	0	0	1	0	0	0	0	1
	SEVERE	0	0	0	0	0	0	0	0
Relation to the Drug	RELATED	0	0	3	3	2	1	2	11
	NOT RELATED	2	2	3	5	1	1	1	15
Action Taken	DOSE INCREASED	0	0	0	0	0	0	0	0
	DOSE NOT CHANGED	0	0	0	0	0	0	0	0
	DOSE REDUCED	0	0	0	0	0	0	0	0
	DRUG INTERRUPTED	0	0	0	0	0	0	0	0
	DRUG WITHDRAWN	0	0	0	0	0	0	0	0
	NOT APPLICABLE	2	2	6	8	3	2	3	26
	UNKNOWN	0	0	0	0	0	0	0	0

All study treatments were generally well tolerated and there were no discontinuations due to adverse events (AEs) during the treatment period.

No Serious Adverse Events (SAEs) were reported during the conduct of this study.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *Reformulated MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Conclusions:

Cohort 1 of this study evaluated the effect of a low-fat and high-fat breakfast on the pharmacokinetics of raltegravir following administration of a 1200 mg dose of Drug Product 1 (reformulated MK-0518 600 mg Tablets from Merck Sharp & Dohme Corp., USA). The administration of the reformulated MK-0518 600 mg Tablets with the low fat breakfast generated an approximately 40% decrease in AUC (42% for AUC0-last and 40% for AUC0-inf) and approximately 52% decrease in Cmax of raltegravir. The raltegravir concentration at 24 hours post-dose (C24hr) was less affected. The low-fat breakfast triggered only a 16% reduction as compared to the fasted state.

The concurrent administration of the reformulated MK-0518 600 mg Tablets with a high-fat breakfast had minimal effect on the AUC, the GMR values for the contrast to the fasting condition were 101.94% and 105.62% for AUC0-last and AUC0-infinity respectively. The Cmax decreased by approximately 28% in the presence of the high-fat meal while the raltegravir concentration 24 hours post-dose decreased by only 12%.

The magnitude of the food effect on the reformulated MK-0518 600 mg Tablets was greater for the low-fat breakfast compared to the high-fat breakfast. The difference in the food effect between the two types of meals was less significant on the C24hr.

Cohort 2 examined the effect of a low-fat and a high-fat breakfast on the pharmacokinetics of raltegravir following administration of a 1200 mg dose of Drug Product 2 (Isentress® 400 mg Tablets from Merck Sharp & Dohme Corp., USA). The results show that there was a food effect following both low-fat and high-fat breakfasts. Similarly to the results in Cohort 1the low-fat breakfast triggered a larger decrease in the peak and overall exposure of raltegravir. The AUC0-last and AUC0-inf were approximately 73% lower and Cmax was approximately 75% lower in the presence of the low-fat breakfast when compared to the fasted state. The C24hr was 18% lower in the presence of the low-fat breakfast.

The effect of a high-fat breakfast was a lower peak (23% lower) and higher overall systemic exposure of raltegravir 39% and 29% higher for AUC0-last and AUC0-inf, respectively. Also higher was the raltegravir concentration 24 hour post-dose; it showed an average increase of 70%.

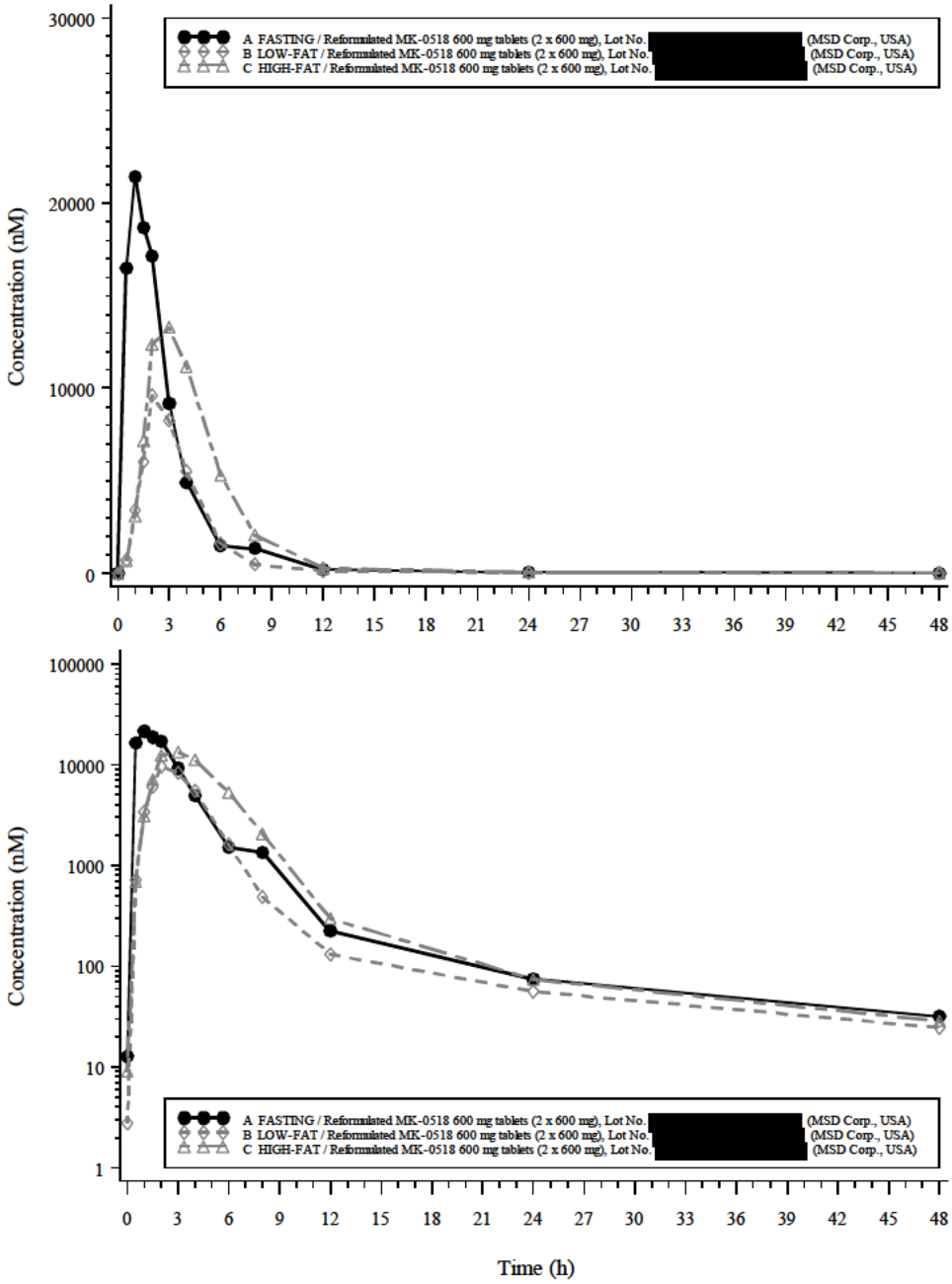
The food effect following the low-fat and high-fat breakfast was more pronounced for Drug Product 2 compared to Drug Product 1.

In conclusion, the results from this study show that there was a food effect following both a low-fat and high-fat breakfast on the pharmacokinetics of raltegravir for both formulations that were evaluated, when given as a single dose in healthy subjects. All study treatments were well tolerated.

Date of Report: Final Report: [redacted] 20[redacted]

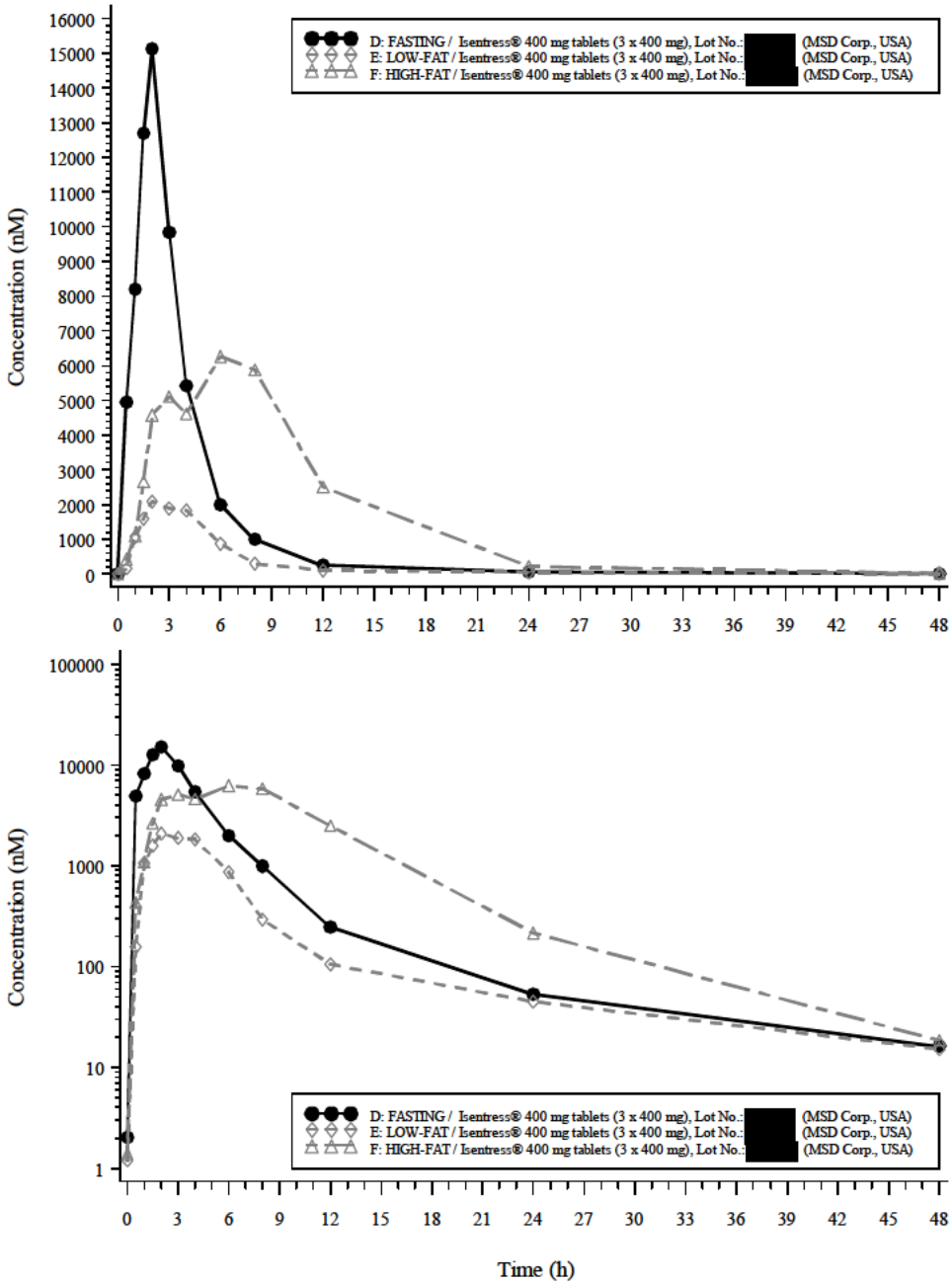
[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Mean Raltegravir Plasma Concentration-Time Profiles
A: n = 16 / B: n = 18 / C: n = 17
(top panel: linear scale / bottom panel: log-linear scale)



[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Food-Effect Study
[redacted] Study Number: 20[redacted]-3232
Protocol Number: 290-00

Mean Raltegravir Plasma Concentration-Time Profiles
D: n = 17 / E: n = 17 / F: n = 17
(top panel: linear scale / bottom panel: log-linear scale)



[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

2.0 SYNOPSIS

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*
Title of Study: A Multiple Dose Study of Raltegravir Formulations
Investigators: [redacted], MD, PhD, FRCP(C) [redacted], MD, FRCP(C), MSc [redacted], MD, MSc, CCFP [redacted], MD, FRCP (C), MSc
Study Centre(s): **Clinical Facility:** [redacted] Canada, [redacted] **Clinical Laboratory Facility:** [redacted] Canada, [redacted] **Bioanalytical Facility:** [redacted] The Netherlands **Pharmacokinetic and Statistical Facility:** [redacted] Canada, [redacted] **Report Issuing Facility:** [redacted] Canada, [redacted]
Phase of Development: Bioequivalence
Study Periods: **Period 1:** [redacted], 20[redacted] **Period 2:** [redacted], 20[redacted] **Period 3:** [redacted], 20[redacted]
Objective: The objective of this study is to assess the pharmacokinetics (e.g., AUC24, Cmax and Ctrough) of raltegravir after a multiple dose administration of reformulated MK-0518 600 mg Tablets (1200 mg QD) and Isentress® 400 mg Tablets (1200 mg QD and 400 mg q12).

[redacted] [redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Methodology:

- This is an open-label, multiple-dose, randomized, three-period, three-treatment, six-sequence, crossover, comparative bioavailability study.
- This study is designed to assess the pharmacokinetics (e.g., AUC24, Cmax and Ctrough) in healthy male and female subjects.
- Concentrations of raltegravir were measured from the samples collected over a 12 hour (Treatment C) or 24 hour (Treatments A and B) interval after dosing on Days 1 and 5.
- The pharmacokinetic (PK) parameters AUC24, Cmax, Ctrough (C24) and Tmax for Treatments A and B and AUC12, Cmax, Ctrough (C12), Tmax and AUC24 (AUC12 x 2) for Treatment C were estimated using a non-compartmental approach.

Number of subjects (planned and analyzed):

- Planned for inclusion: 24 subjects
- Total number of subjects that completed all periods of the study: 22 subjects
- Included in the safety dataset: 24 subjects
- Included in the pharmacokinetic dataset: 24 subjects
- Included in the statistical dataset: 24 subjects
  - Subjects 291-1* and 291-2* did not complete all periods of the study but received at least one administration of a study treatment and were, therefore, included in the pharmacokinetic dataset.

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 55 years of age, with a BMI from 19.0 to 30.0 kg/m^2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements.

Drug Product 1 (Treatment A):
MK-0518 600 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Re-Evaluation Date: [redacted] 20[redacted]
Potency: [redacted]
Manufacturing Date: [redacted] 20[redacted]
Dose: 1200 mg once daily for 5 days
Mode of Administration: Oral under fasting conditions

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*
Drug Product 2 (Treatments B and C): Isentress® 400 mg Tablets (Merck Sharp & Dohme Corp., USA) Lot No.: [redacted] Potency: [redacted] Expiry Date: [redacted] 20[redacted] Dose: 1200 mg once daily for 5 days (Treatment B) and 400 mg twice daily (q12) on Days 1 to 4 and once on Day 5 (Treatment C) Mode of Administration: Oral under fasting conditions
Duration of treatment: Multiple-Dose treatment

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Statistical Methods:
ANOVA (PROC MIXED) was performed on log-transformed AUC24, Ctrough and Cmax estimated on Day 5. AUC24 for Treatment C was calculated as 2 x AUC12.
A log transformation was applied to the AUC24, Cmax and Ctrough data. Back-transformed summary statistics and inferential results were reported for the pharmacokinetic parameters. Ninety percent (90%) confidence intervals (CIs), based on the t-distribution, were generated from the above mixed effect model for the geometric mean ratios for AUC24, Cmax and Ctrough of raltegravir for the following comparisons:

- Treatment A versus Treatment C
- Treatment B versus Treatment C
- Treatment A versus Treatment B

In addition, pairwise 2x2 contingency tables for the Ctrough concentrations <=45 nM and >45 nM were provided on Day 1 and 5.

Accumulation Ratio was estimated using two methods.

Primary Method: The individual AUC24 ratios (Day 5/Day 1) were used to estimate the effective rate of drug accumulation, ηi, for each subject. The values of ηi were used to estimate the fraction of steady state, fss, attained after each dosing interval N for each subject and treatment.

Where possible, the number of dosing intervals needed to reach 90% of steady state, T90, was calculated for each subject and treatment. These data were analyzed statistically to obtain the GM with the 95% confidence intervals for T90 for each treatment. The number of subjects who reached at least 90% of steady-state and their proportion of the total were summarized by treatments.

Secondary Method: Ctrough values were analyzed with a nonlinear mixed effects model that contained the dosing interval, T90, and the random effect of subject. The population mean values and their 95% confidence intervals were estimated for steady-state trough concentration, T90, and the corresponding variances. In addition, individual Ctrough values were plotted over time for each subject to further characterize the approach to steady state by treatment.

The pre-dose concentrations (Ctrough) were analyzed to estimate the inter-occasion variability for each treatment.

Criteria for Evaluation:
Hypothesis: The pharmacokinetic parameters of raltegravir after a multiple-dose administration of MK-0518 600 mg Tablets (at the 1200 mg QD dose) and Isentress® 400 mg Tablets (1200 mg QD and 400 mg q12 doses) of raltegravir were estimated.

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Results:
Pharmacokinetic Results:

Based on Measured Plasma Raltegravir Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC24	**A**	23	59535.4	51375.7 - 68991.0	**A vs C**	234.31	177.17 - 309.87	54.8
(hr·nM)	**B**	22	49013.6	36620.3 - 65601.2	**B vs C**	192.90	141.69 - 262.61	60.1
	C	23	25409.2	17456.7 - 36984.3	**A vs B**	121.47	93.94 - 157.06	49.0
Cmax	**A**	23	20563.5	17002.9 - 24869.9	**A vs C**	602.55	410.25 - 884.97	75.5
(nM)	**B**	22	14110.1	9823.7 - 20266.8	**B vs C**	413.45	280.41 - 609.62	75.4
	C	23	3412.8	2116.7 - 5502.3	**A vs B**	145.74	108.70 - 195.39	55.8
Ctrough	**A**	23	81.1	61.6 - 106.7	**A vs C**	61.96	50.21 - 76.45	40.3
(nM)	**B**	22	83.5	67.7 - 103.0	**B vs C**	63.83	52.39 - 77.78	37.9
	C	23	130.9	103.4 - 165.6	**A vs B**	97.06	79.12 - 119.07	39.4
			Median	***Range***				
Tmax	**A**	23	2.00	0.50- 3.00				
(h)	**B**	22	2.00	0.50- 6.00				
	C	23	1.50	0.50- 4.00				

For Treatment C: AUC24 = AUC12 x 2
** Estimated based on the elements of the variance-covariance matrix as: CV(%) = 100*sqrt[(σ_1^2 + σ_2^2 - 2*σ_{12})/2]*

Treatment A: MK-0518 600 mg tablets (2 x 600 mg q24), Lot No.: [redacted] *(MSD Corp., USA)*
Treatment B: Isentress® 400 mg tablets (3 x 400 mg q24), Lot No.: [redacted] *(MSD Corp., USA)*
Treatment C: Isentress® 400 mg tablets (1 x 400 mg q12), Lot No.: [redacted] *(MSD Corp., USA)*

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Inter-occasion Variability of The Pre-Dose Levels

Treatment	*Interoccasion Variance*	*CV(%)*
A	0.0483307	22.3
B	0.060309	24.9
C	0.4093694	71.1

Summary Statistics for Steady-State Parameters by Treatment / Based on AUC24 Ratios

	T90 (days)*		*Subjects (%) at 90% of Steady State*				
Trt	*GM*	*95% CI*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*
A	1.329	-0.024 , 2.683	3 (25.0)	7 (58.3)	12 (100)	12 (100)	12 (100)
B	3.948	1.518 , 6.377	0 (0.0)	2 (22.2)	4 (44.4)	4 (44.4)	6 (66.7)
C	3.461	-2.766 , 9.687	4 (30.8)	8 (61.5)	10 (76.9)	11 (84.6)	11 (84.6)

T90 = The time in days required to attain 90% of theoretical steady-state

Summary Statistics for Steady-State Parameters / Based on Ctrough Analysis

Trt	Parameter	GM	95% CI	CV(%)
A	Ctrough	86.2	68.2 - 108.9	52.9
	T90	2.0	1.5 - 2.8	23.5
	Intra-Sbj CV	25.5	19.4 - 30.5	
B	Ctrough	82.2	66.1- 102.1	42.7
	T90	2.2	1.5 - 3.1	25.5
	Intra-Sbj CV	30.4	23.0 - 36.6	

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Summary Descriptive Statistics for the Plasma Raltegravir Accumulation Ratio*

PK Parameter	Trt	GM	CV(%)**
AUC24	A	0.99	39.6
	B	1.16	121.0
	C	1.04	104.0
Cmax	A	0.91	53.8
	B	1.16	143.2
	C	0.85	126.1
Ctrough	A	1.48	63.6
	B	1.65	43.1
	C	1.58	48.9

** Calculated as the ratio of PK parameter of Day 5 versus Day 1*

*** CV(%) = 100*sqrt(exp(s²)-1), where s² is the observed between-subjects variance on the natural log-scale*

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

Name of Finished Product: *MK-0518 600 mg Tablets*

Name of Active Ingredient: *Raltegravir*

Safety Results:

		PRE-DOSE	TRT A	TRT B	TRT C	Total
Severity	Mild	4	12	9	10	35
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Relation to the Drug	Related	0	10	4	8	22
	Not Related	4	2	5	2	13
Action Taken	Dose Increased	0	0	0	0	0
	Dose Not Changed	0	0	0	0	0
	Dose Reduced	0	0	0	0	0
	Drug Interrupted	0	0	0	0	0
	Drug Withdrawn	0	0	0	0	0
	Not Applicable	4	12	9	10	35
	Unknown	0	0	0	0	0

No Serious Adverse Events (SAEs) were reported during the conduct of this study. One subject was discontinued by the investigator due to fever prior to the second treatment period; this event was not considered drug related.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

The study medications were well tolerated by the healthy volunteers that participated in this study.

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Conclusions:

The MK-0518 600 mg tablets exhibited higher bioavailability then Isentress®400 mg tablets when administered as 1200 mg dose once a day. The Ctrough concentrations were similar between the MK-0518 600 mg tablets and Isentress® 400 mg tablets administered as a 1200 mg dose q24.

The population mean values for the Ctrough were very similar between MK-0518 and Isentress® when administered as 1200 mg once a day: 86.2 nM and 82.2 nM respectively. Likewise, the number of days required to reach at least 90% of steady-state was also very similar between MK-0518 and Isentress®: 2.0 and 2.2, respectively.

MK-0518 600 mg tablets (A) and Isentress®400 mg tablets (B) administered as 1200 mg q24 showed higher bioavailability when compared to treatment Isentress® 400 mg tablets dosed as 400 mg q12 (C). The AUC24 GM was 2.3 and 1.9 times larger, respectively. This was larger than expected based on the ratio of the administered doses 1200/800 = 1.5.

Similarly, the GM for the Cmax parameter was 6.0 and 4.1 times larger for Treatments A and B when compared to Treatment C.

The raltegravir concentrations at the end of the dosing interval (Ctrough) was approximately 40% lower for both Treatments A and B as compared to Treatment C.

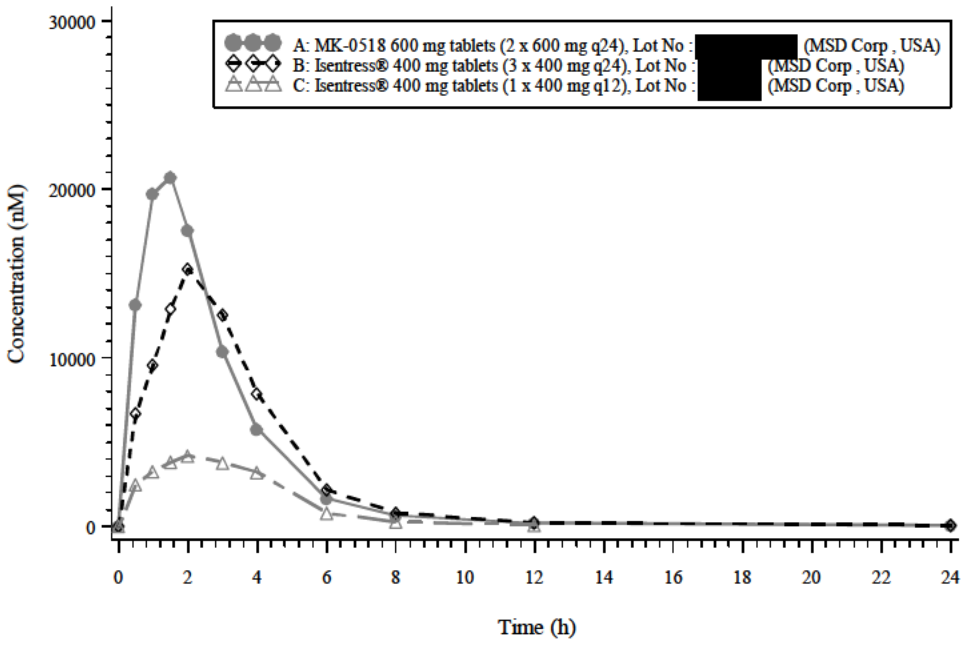
The within-treatment between-day variability estimated for the pre-dose levels in Days 3, 4 and 5 were very similar for MK-0518 600 mg tablets (2x600 mg q24) and Isentress® 400 mg tablets (3x400 mg q24): 22.3% and 24.9%, respectively. This inter-occasion variability of Ctrough was much higher (CV% of 71.1%) for the Isentress® 400 mg tablets administered as 400 mg every 12 hours.

The majority of the Ctrough concentrations measured in Day 5 are higher than 45 nM. Out of total Ctrough measured in Day 5 83% for Treatment A, 91% for Treatment B and 91% for Treatment C were higher than 45 nM. There were no statistically significant ($\alpha = 0.05$) differences in the distribution of the Day 5 Ctrough values between treatments in the tested contrasts. All study treatments were well tolerated.

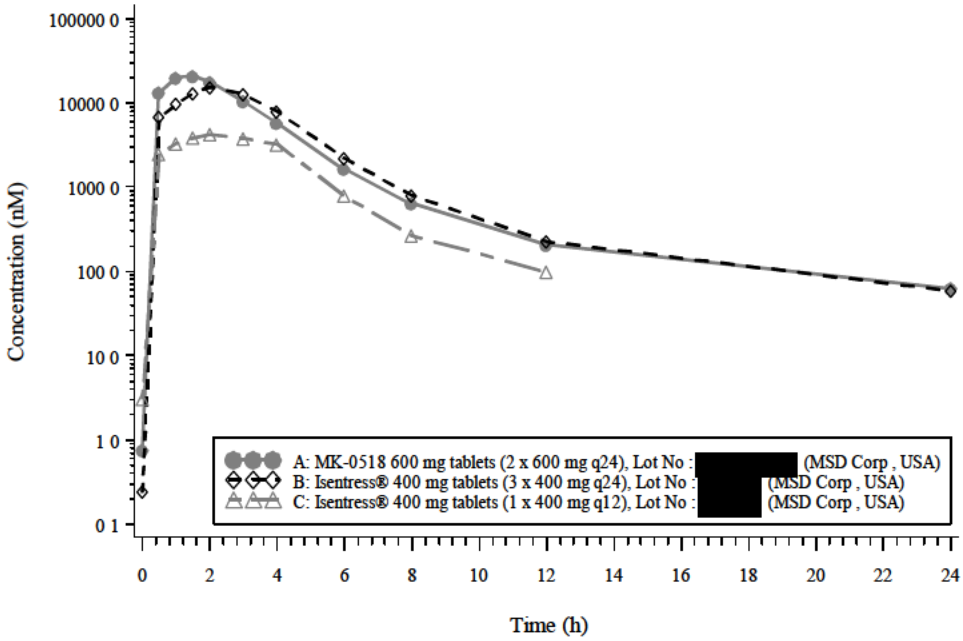
Date of Report: Final Report: [redacted] 20[redacted]

[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Mean Raltegravir Plasma Concentration-Time Profiles [Day 1]/ (Linear Scale)
A: n = 23 / B: n = 22 / C: n = 23

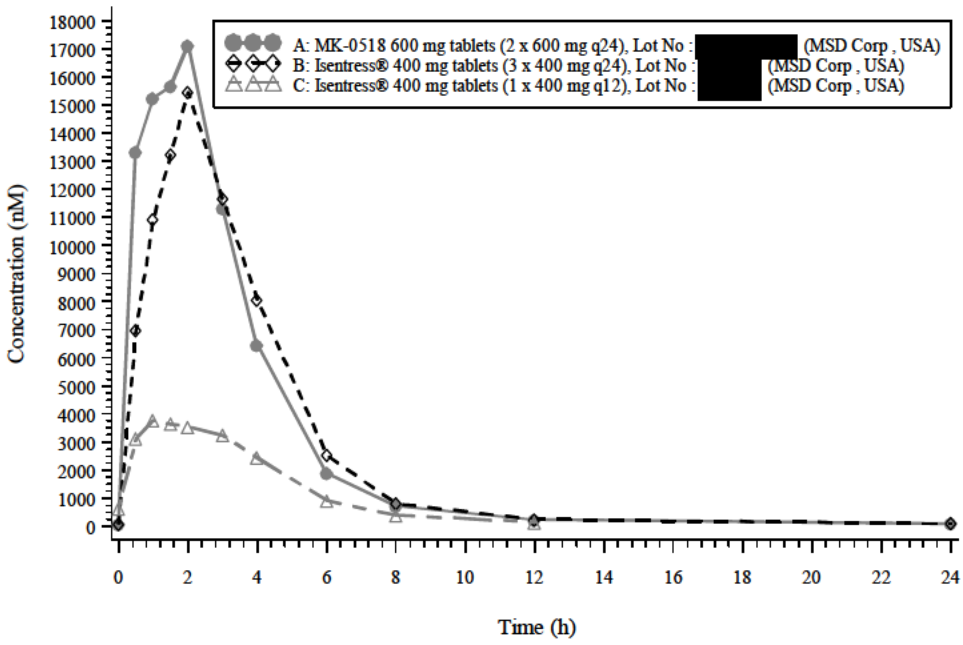


Mean Raltegravir Plasma Concentration-Time Profiles [Day 1]/ (Log-linear Scale)
A: n = 23 / B: n = 22 / C: n = 23

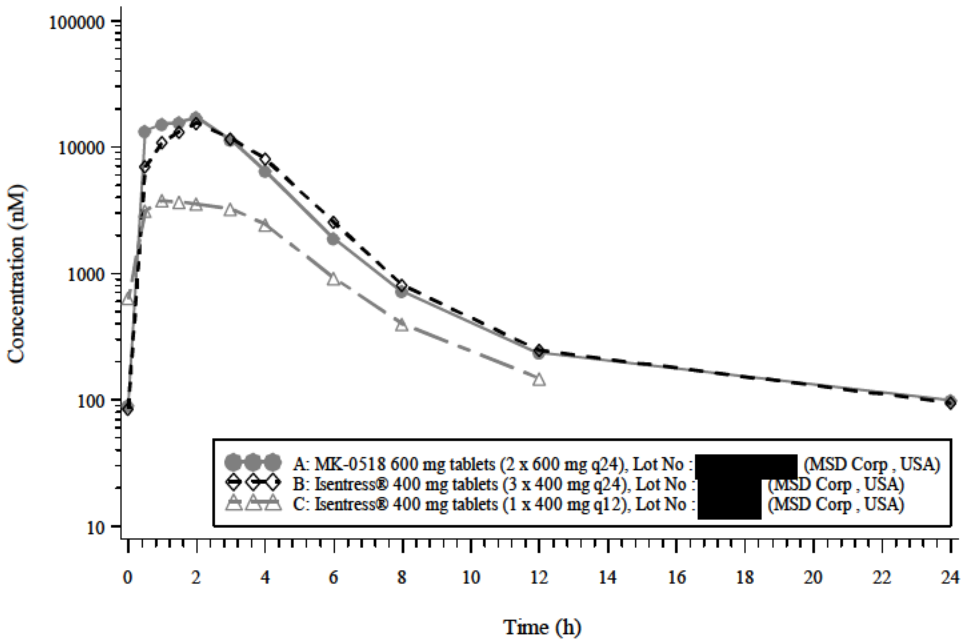


[redacted] – Study Report
Raltegravir 400 mg and 600 mg Tablets, Multiple Dose Study
[redacted] Study Number: 20[redacted]-3247
Protocol Number: 291-00

Mean Raltegravir Plasma Concentration-Time Profiles [Day 5]/ (Linear Scale)
A: n = 23 / B: n = 22 / C: n = 23



Mean Raltegravir Plasma Concentration-Time Profiles [Day 5]/ (Log-linear Scale)
A: n = 23 / B: n = 22 / C: n = 23



SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-0518, raltegravir	
INDICATION:	Treatment of human immunodeficiency virus (HIV-1) infection	
PROTOCOL TITLE:	A Study to Evaluate the Influence of Efavirenz on a Single Dose of MK-0518 in Healthy Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	812
	Clinical Phase:	1
	EudraCT Number:	Not Applicable
TRIAL CENTER:	[redacted], MD [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, randomized, 2-period, fixed-sequence study to evaluate the effect of co-administration of efavirenz and MK-0518 on the plasma pharmacokinetic (PK) profile of MK-0518. Twenty-one (21) healthy, adult, male and female (non-childbearing potential) subjects were enrolled. In Period 1, subjects received a single oral dose of 1200 mg (2 x 600 mg) MK-0518 on Day 1. There was a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2. In Period 2, subjects received multiple oral doses of 600 mg efavirenz once-daily (QD) for 14 consecutive days. Subjects received a single oral dose of 1200 mg (2 x 600 mg) MK-0518 co-administered with efavirenz on Day 12 of Period 2. **DIAGNOSIS/INCLUSION CRITERIA:** Adult healthy male or female subjects (non-childbearing potential) $\geq$ 19 and $\leq$ 55 years of age, with a body mass index (BMI) $\geq$ 18.5 and $\leq$ 32.0 kg/m^2 at the prestudy (screening) visit were eligible to enter the study.	
	Planned duration of main phase:	7 weeks from screening to Day 15 of Period 2 9 weeks from screening to follow-up
OBJECTIVE:	To evaluate the effect of co-administration of efavirenz and MK-0518 on the plasma PK profile of MK-0518 (e.g., $AUC_{0-\infty}$, C_{max}, C_{24}, T_{max}, and apparent terminal $t_{½}$).	
ESTIMATION:	The effect of multiple-dose administration of efavirenz on the single dose MK-0518 $AUC_{0-\infty}$, C_{max}, and C_{24} were estimated.	

TREATMENT GROUPS:	MK-0518 Alone	A single oral dose of 1200 mg (2 x 600 mg) MK-0518 on Day 1 of Period 1 21 Subjects enrolled
	MK-0518 + Efavirenz	Multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg (2 x 600 mg) MK-0518 on Day 12 of Period 2 21 subjects enrolled/[†]19 subjects completed [†]Two (2) subjects discontinued the study. One (1) subject discontinued for personal reasons and 1 subject was discontinued by the Investigator due to AEs.

Bulk product description and manufacturing lot numbers are provided in the table below.

Clinical Supplies Dispensed to Subjects

Bulk Product Description	**Manufacturing Lot Number**
FCT MK-0518 (003E) 600 mg Efavirenz ( ) 600 mg Tablet[†]	[redacted] Not Applicable
[†]Efavirenz ( ) 600 mg (lot number [redacted]; expiration date [redacted] 20[redacted]; [redacted]) was supplied by the Investigator.	

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Blood samples for the determination of plasma MK-0518 concentrations were collected from each subject at predose and selected time points over 72 hours postdose following a single oral dose of 1200 mg MK-0518 on Day 1 of Period 1 and following multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 12 of Period 2. Plasma MK-0518 PK was summarized using the following PK parameters: $AUC_{0-\infty}$, C_{max}, C_{24}, T_{max}, and apparent terminal $t_{½}$. Of these, the primary PK endpoints included MK-0518 $AUC_{0-\infty}$, C_{max}, and C_{24}.

ENDPOINTS AND DEFINITIONS (Continued):	**Primary Endpoints**	**Safety** The primary safety endpoints included adverse events (AEs), physical examinations, vital signs (heart rate and blood pressure), 12-lead electrocardiograms (ECGs), Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire, and clinical laboratory tests (hematology, serum chemistry, and urinalysis) obtained at pre-specified time points.	
DATABASE LOCK:	[redacted] 20[redacted]	**TRIAL STATUS:**	[redacted] 20[redacted] to [redacted] 20[redacted]

RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol.

Disposition of Subjects

	MK-0518 Alone n (%)	MK-0518 + Efavirenz n (%)	Overall n (%)
Subjects in study	21	21	21
Trial Disposition			
Completed	21 (100.0)	19 (90.5)	19 (90.5)
Discontinued	0 (0.0)	2 (9.5)	2 (9.5)
Adverse Event	0 (0.0)	1 (4.8)	0 (0.0)
Withdrawal by Subject	0 (0.0)	1 (4.8)	0 (0.0)

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1.
MK-0518 + Efavirenz: Multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 12 of Period 2.

ANALYSIS DESCRIPTION:	**Primary Analysis – Pharmacokinetics** $AUC_{0-\infty}$ was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations ('linear up, log down') calculation method option in Phoenix® WinNonlin® (Version 6.3). C_{max} and C_{24} were obtained directly from the bioanalytical data. T_{max} was obtained directly from merged clinical and bioanalytical data, with time presented as actual elapsed time relative to dose. Individual $AUC_{0-\infty}$, C_{max}, and C_{24} values for MK-0518 were natural log (ln)-transformed prior to analysis and evaluated separately using a linear mixed-effects model with a fixed-effects term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the 2 treatment measurements within each subject via the REPEATED statement in SAS® PROC MIXED. The Kenward-Roger adjustment was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR).

ANALYSIS DESCRIPTION (Continued):	**Primary Analysis – Pharmacokinetics (Continued)** The estimation was addressed by comparing $AUC_{0-\infty}$, C_{max}, and C_{24} values for MK-0518 from administration of MK-0518 with efavirenz to those obtained from administration of MK-0518 alone. A two-sided 90% confidence interval (CI) for the true mean difference [MK-0518 with efavirenz - MK-0518 alone] for each parameter on the ln-scale was computed from the above linear-mixed effects model. The 90% CI was exponentiated to obtain the 90% CI for the true GMR (MK-0518 + efavirenz/MK-0518 alone) for each parameter on the original scale.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	The Per Protocol Population consisted of the subset of subjects who complied with the protocol sufficiently to ensure that the data would likely exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. This population was used for the PK analyses. Twenty-one (21) healthy male and female subjects were enrolled in the study and 19 subjects completed the study per protocol. One (1) subject was discontinued on Day 2 of Period 2, due to an AE of feeling drunk and dizziness. One (1) subject withdrew from the study on Day 11 of Period 2, due to a personal reason of family emergency. These subjects had completed all PK assessments on Day 1 of Period 1. Therefore, data from all 21 subjects were included in the PK analyses on Day 1 of Period 1 (MK-0518 alone) and 19 subjects were included in the PK analyses on Day 12 of Period 2 (MK-0518 + efavirenz).
SUMMARY:	**Pharmacokinetics:** Results of the analyses of the plasma PK parameters ($AUC_{0-\infty}$, C_{max}, C_{24}, T_{max}, and apparent terminal $t_{½}$) for MK-0518 following the administration of a single oral dose of 1200 mg MK-0518 with and without the co-administration of multiple oral QD doses of 600 mg efavirenz are summarized in the table below. MK-0518 was rapidly absorbed with an observed median T_{max} of 1.5 hours following both treatments. The geometric mean apparent terminal $t_{½}$ values were similar following MK-0518 alone and MK-0518 + efavirenz (8.95 hours and 8.87 hours, respectively). Co-administration with efavirenz yielded GMRs (MK-0518 + efavirenz/MK-0518 alone) (90% CIs) for MK-0518 $AUC_{0-\infty}$, C_{max}, and C_{24} of 0.86 (0.73, 1.01), 0.91 (0.70, 1.17), and 0.94 (0.76, 1.17), respectively.

Statistical Comparison and Summary Statistics of MK-0518 Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 1200 mg MK-0518 With (Co-administered on Day 12) and Without Multiple Oral QD Doses of 600 mg Efavirenz Administered for 14 Days in Healthy Adult Subjects

MK-0518 Pharmacokinetic Parameters	MK-0518 Alone			MK-0518 + Efavirenz			MK-0518 + Efavirenz/ MK-0518 Alone		Pseudo Within Subject %CV‡
	N	GM	95% CI	N†	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$§ (µM•hr)	21	50.1	(42.4, 59.2)	19	43.1	(36.6, 50.9)	0.86	(0.73, 1.01)	29.3
C_{max}§ (µM)	21	15.7	(13.4, 18.5)	19	14.3	(11.4, 17.8)	0.91	(0.70, 1.17)	46.2
C_{24}§ (nM)	21	41.6	(31.8, 54.4)	19	39.2	(29.3, 52.2)	0.94	(0.76, 1.17)	38.9
T_{max}‖ (hr)	21	1.50	(0.50, 4.00)	19	1.50	(0.50, 6.01)			
Apparent terminal $t_{½}$¶ (hr)	21	8.95	95.64	19	8.87	95.23			

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1.
MK-0518 + Efavirenz: Multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 12 of Period 2.
†Two (2) subjects were discontinued and had no available data for MK-0518 + Efavirenz.
‡Pseudo Within-Subject %CV = $100*\text{sqrt}((\sigma_A^2 + \sigma_B^2 - 2\,\sigma_{AB})/2)$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
§Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
‖Median (Minimum, Maximum) reported for T_{max}.
¶Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{½}$
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

ANALYSIS DESCRIPTION:	**Secondary Analysis - Safety** Incidence of the number of subjects with AEs were descriptively summarized and listed by treatment. Incidence of the number of subjects with drug related AEs was descriptively summarized by treatment. Since no meaningful changes in individual values for laboratory safety tests, ECGs, and vital signs were observed, summary statistics were not provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	All Subjects as Treated Population - All subjects who received at least 1 dose of the investigational drugs were included in the analysis population. This population was used for assessments of safety and tolerability. All 21 subjects were included in the evaluation of safety.
SUMMARY:	Administration of single 1200 mg oral doses of MK-0518 alone and co-administered with multiple oral doses of efavirenz was generally well tolerated in healthy male and female subjects. There were no serious AEs (SAEs), events of clinical interest (ECIs), pregnancies, or deaths reported during the study.

SUMMARY (Continued):	Twenty subjects reported treatment-emergent AEs (TEAEs), including 5 subjects following MK-0518 alone, 20 subjects following efavirenz alone, and 5 subjects following MK-0518 + efavirenz. The most commonly reported AEs in the study were dizziness, headache, and abnormal dreams. With the exception of 4 AEs of which the outcome is unknown, all AEs resolved without interruption of study treatments. Twenty subjects reported drug-related AEs, including 3 subjects following MK-0518 alone, 20 subjects following efavirenz alone, and 2 subjects following MK-0518 + efavirenz. The most common drug-related AEs following efavirenz alone were dizziness and headache. One (1) subject discontinued from the study following the final dose of efavirenz alone due to the personal reason of family emergency and 1 subject by the Investigator prior to the second dose of efavirenz alone due to the AEs of dizziness and feeling drunk. The majority of AEs were of mild intensity, transient, and resolved without interruption of treatment. Two (2) AEs were of moderate intensity. The majority of AEs were resolved by the end of the study with the following exceptions: mild blepharospasm and mild rash for 1 subject; and mild dysuria and mild scrotal pain for 1 subject. These 4 AEs were considered not related to study drug by the Investigator. There were no clinically meaningful treatment-related changes in laboratory, vital signs, C-SSRS, or ECG safety parameter values.
CONCLUSION:	Based on assessment of clinical and laboratory adverse experiences, single doses of 1200 mg MK-0518 given alone or in combination with 600 mg efavirenz are generally well tolerated. While the co-administration of efavirenz and MK-0518 modestly reduces plasma levels of MK-0518, these changes are not considered to be clinically meaningful.
PUBLICATION:	None
REPORT DATE:	Final: [redacted] 20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-0518, raltegravir, tablet	
INDICATION:	Treatment of human immunodeficiency virus (HIV-1) infection	
PROTOCOL TITLE:	A Study to Evaluate the Influence of Atazanavir on a Single Dose of MK-0518 in Healthy Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	MK-0518-823-01
	Clinical Phase:	1
	EudraCT Number:	Not Applicable
	US IND Number:	69,928
INVESTIGATOR AND TRIAL CENTER:	[redacted] MD [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, 2-period, fixed-sequence study under fed conditions to evaluate the effect of co-administration of atazanavir and MK-0518 on the plasma pharmacokinetic (PK) profile of MK-0518. Fourteen (14) healthy, adult, male and female subjects were enrolled. In Period 1, subjects received a single oral dose of 1200 mg (2 x 600 mg) MK-0518 on Day 1. There was a washout period of at least 7 days between the dosing in Period 1 and the first dosing in Period 2. In Period 2, subjects received multiple oral doses of 400 mg atazanavir once-daily (QD) for 9 consecutive days with a single oral dose of 1200 mg MK-0518 co-administered on Day 7. **DIAGNOSIS/INCLUSION CRITERIA:** Adult healthy male or female subjects $\geq$ 19 and $\leq$ 55 years of age, with a body mass index (BMI) $\geq$ 18.5 and $\leq$ 32.0 kg/m^2 at the prestudy (screening) visit were eligible to enter the study.	
	Planned duration of main phase:	6.5 weeks from screening to Day 10 of Period 2 11.5 weeks from screening to follow-up
OBJECTIVE:	To evaluate the effect of co-administration of atazanavir and MK-0518 on the plasma PK profile of MK-0518 (e.g., $AUC_{0-\infty}$, C_{max}, C_{24}, T_{max}, and apparent terminal $t_{½}$).	

HYPOTHESIS:	Multiple-dose administration of atazanavir prior to and co-administered with a single oral dose of MK-0518 does not substantially affect $AUC_{0-\infty}$ and C_{max} of MK-0518, i.e., the true GMR of $AUC_{0-\infty}$ and C_{max} (MK-0518 + atazanavir/MK-0518) is < 1.25.	
TREATMENT GROUPS:	MK-0518 Alone	A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1 n = 14 Subjects enrolled/14 Subjects completed
	MK-0518 + Atazanavir	Multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7 of Period 2 n = 14 Subjects enrolled/12 Subjects completed (2 discontinued)

Bulk product description and manufacturing lot numbers are provided in the table below.

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
FCT MK-0518 (003E) 600 mg tablet	[redacted]
Atazanavir ([redacted]) 200 mg capsule†	Not Applicable
†Atazanavir ([redacted]) 200 mg (lot number [redacted]; expiration date [redacted]-20[redacted]; [redacted] Company) was supplied by the Investigator.	

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Blood samples for the determination of plasma MK-0518 concentrations were collected from each subject at predose and selected time points over 72 hours postdose following a single oral dose of 1200 mg MK-0518 on Day 1 of Period 1 and following multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7 of Period 2. MK-0518 PK values were summarized using the following PK parameters: $AUC_{0-\infty}$, C_{max}, C_{24}, T_{max}, and apparent terminal $t_{½}$. Of these, the primary PK endpoints were MK-0518 $AUC_{0-\infty}$ and C_{max}.

ENDPOINTS AND DEFINITIONS (CONTINUED):	**Other Endpoints**	**Safety** The safety endpoints included all types of adverse events (AEs), physical examinations, vital signs (heart rate and blood pressure), 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry, and urinalysis).	
DATABASE LOCK:	[redacted]20[redacted]	**TRIAL STATUS:**	[redacted]20[redacted] to [redacted]20[redacted]

RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol.

Disposition of Subjects

	MK-0518 Alone N (%)	MK-0518 + Atazanavir N (%)	Overall N (%)
Subjects in study	14	14	14
Trial Disposition			
Completed	14 (100.0)	12 (85.7)	12 (85.7)
Discontinued	0 (0.0)	2 (14.3)	2 (14.3)
AE	0 (0.0)	1 (7.1)	1 (7.1)
Withdrawal by Subject	0 (0.0)	1 (7.1)	1 (7.1)

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 Period 1.
MK-0518 + Atazanavir: Multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7 of Period 2.
Each subject is counted only once on each row within each treatment column based on the latest corresponding disposition record.
AE = Adverse event.
One subject was discontinued by the Investigator after not presenting at check-in for Period 2, and one subject was discontinued by the Investigator due to the laboratory AEs of increased blood bilirubin and increased blood bilirubin unconjugated.

ANALYSIS DESCRIPTION:	**Primary Analysis – Pharmacokinetics** Individual $AUC_{0-\infty}$, C_{max}, and C_{24} values for MK-0518 were natural log (ln)-transformed prior to analysis and evaluated separately using a linear mixed-effects model with a fixed-effects term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the 2 treatment measurements within each subject via the REPEATED statement in SAS® PROC MIXED. The Kenward-Roger adjustment was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). The hypothesis was addressed by comparing $AUC_{0-\infty}$ and C_{max} values for MK-0518 from co-administration of MK-0518 with atazanavir to those obtained from administration of MK-0518 alone. A two-sided 90% confidence interval (CI) for the true mean difference [MK-0518 with atazanavir - MK-0518 alone] for each parameter on the ln-scale was computed from the above linear mixed-effects model. The 90% CI was exponentiated to obtain the

ANALYSIS DESCRIPTION (CONTINUED):	**Primary Analysis – Pharmacokinetics (Continued)** 90% CI for the true geometric mean ratio (GMR) (MK-0518 + atazanavir/MK-0518 alone) for each parameter on the original scale.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	The Per-Protocol population consisted of the subset of subjects who complied with the protocol sufficiently to ensure that the data would likely exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. This population was used for the PK analyses. Fourteen (14) healthy male and female subjects were enrolled in the study and 12 subjects completed the study per protocol. One (1) subject was discontinued by the Investigator on Day 6 of Period 2 since this subject was not present at check-in. One (1) subject was discontinued by the Investigator on Day 5 of Period 2 due to mild laboratory AEs. This subject had increased blood bilirubin (maximum value of 4.6 mg/dL; 2.9 X upper limit of normal [ULN]; reference range: 0.2 – 1.6 mg/dL) and increased unconjugated blood bilirubin (maximum value of 3.9 mg/dL; 3.3 X ULN; reference range: 0 – 1.2 mg/dL), both entered as AEs and considered atazanavir-related. These subjects had completed all PK assessments on Day 1 of Period 1. Therefore, data from 14 subjects were included in the PK analyses on Day 1 of Period 1 (MK-0518 alone) and 12 subjects were included in the PK analyses on Day 7 of Period 2 (MK-0518 + atazanavir).
SUMMARY:	**Pharmacokinetics:** The results of the analyses of the plasma PK parameters ($AUC_{0-\infty}$ and C_{max}) for MK-0518 following the administration of a single oral dose of 1200 mg MK-0518 with and without the co-administration of multiple oral QD doses of 400 mg atazanavir administered for 9 days in healthy adult subjects are summarized in the table below. Co-administration with atazanavir yielded GMRs (90% CIs) for MK-0518 $AUC_{0-\infty}$, C_{max}, and C_{24} of 1.67 (1.34, 2.10), 1.16 (1.01, 1.33), and 1.26 (1.08, 1.46), respectively. Since the upper bounds of the 90% CIs for the true GMRs were more than 1.25, the primary hypothesis that the plasma $AUC_{0-\infty}$ and C_{max} for MK-0518 after a multiple-dose regimen of atazanavir were not substantially altered compared with administration of MK-0518 alone was not supported.

Statistical Comparison and Summary Statistics of MK-0518 Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 1200 mg MK-0518 With (Co-administered on Day 7) and Without Multiple Oral QD Doses of 400 mg Atazanavir Administered for 9 Days in Healthy Adult Subjects

MK-0518 Pharmacokinetic Parameters	MK-0518 Alone			MK-0518 + Atazanavir			MK-0518 + Atazanavir/ MK-0518 Alone		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N[¶]	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$[‡] (μM•hr)	12	49.6	(40.7, 60.5)	12	83.0	(67.3, 102)	1.67	(1.34, 2.10)	29.7
C_{max}[‡] (μM)	14	18.7	(15.6, 22.4)	12	21.6	(18.0, 26.0)	1.16	(1.01, 1.33)	18.8
C_{24}[‡] (nM)	14	89.6	(67.7, 118)	12	112	(84.4, 150)	1.26	(1.08, 1.46)	20.7
T_{max}[§] (hr)	14	2.00	(0.50, 6.01)	12	3.00	(1.00, 6.06)			
Apparent terminal $t_{½}$[‖] (hr)	12	18.28	46.7	12	12.49	64.2			

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1.
MK-0518 + Atazanavir: Multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7 of Period 2.
[†]Pseudo within-subject %CV = 100 x sqrt(($\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}$)/2), where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median and (Minimum, Maximum) reported for T_{max}.
[‖]Geometric mean and percent geometric coefficient of variation reported for apparent terminal $t_{½}$.
[¶]Two (2) subjects were discontinued and had no available data for MK-0518 + Atazanavir.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio
Note: $AUC_{0-\infty}$ and apparent terminal $t_{½}$ were set to missing for 2 subjects receiving MK-0518 alone.

ANALYSIS DESCRIPTION:	**Other Analysis – Safety** Incidence of the number of subjects with AEs were descriptively summarized and listed by treatment. A summary of the incidence of the number of subjects with drug related AEs was descriptively summarized by treatment and overall. Liver function tests (LFT) (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase [LDH], creatinine kinase [CK], and gamma-glutamyl transferase [GGT]) were summarized and presented graphically for the percent change from baseline by treatment group (MK-0518 alone, atazanavir alone (Day 3) and MK-0518 + atazanavir). In addition, for ALT and AST, fold change from baseline and fold change from the ULN were calculated for each postdose time point. Counts and percentages of subjects exceeding 1X, 2X, 3X, and 5X fold change from baseline and 1X, 2X, 3X, and 5X fold change from ULN were calculated. For the ECG parameter QTcF, counts and percentages of values falling in the following ranges: ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500 and > 500 msec were calculated. Counts and percentages by

ANALYSIS DESCRIPTION (CONTINUED):	**Other Analysis – Safety (Continued)** treatment and time point for QTcF change from baseline values falling in the following ranges: < 30, ≥ 30 to < 60 and ≥ 60 msec were also calculated.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	All Subjects as Treated Population - All subjects who received at least 1 dose of the investigational drugs were included in the analysis population. This population was used for assessments of safety and tolerability. All 14 subjects were included in the evaluation of safety.
SUMMARY:	Multiple oral doses of atazanavir and single oral doses of MK-0518 were generally well tolerated when co-administered in healthy adult subjects in this study. No deaths, serious adverse events (SAEs), events of clinical interest (ECIs), or pregnancies were reported during the study. The Investigator discontinued 1 subject on Day 5 of Period 2 due to the mild laboratory AEs of increased blood bilirubin (maximum value of 4.6 mg/dL; 2.9 X ULN; reference range: 0.2 - 1.6 mg/dL) and increased unconjugated blood bilirubin (maximum value of 3.9 mg/dL; 3.3 X ULN; reference range: 0 - 1.2 mg/dL) that were considered related to atazanavir alone. Concurrent to these laboratory AEs, the subject experienced the AE of ocular icterus (verbatim term: slight yellow discoloration of the eyes), also considered related to atazanavir alone by the Investigator. Ten (10, 71%) subjects reported AEs in this study, including 9 (65%) subjects who experienced AEs that were considered by the Investigator to be drug- related (1 subject each following MK-0518 alone and MK-0518 + atazanavir and 7 subjects following atazanavir alone). All AEs were of mild intensity and resolved by the end of the study. The most common drug-related AE reported in the study was nausea, which was reported by 3 (21%) subjects. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameter values.
CONCLUSIONS:	All treatments were generally well tolerated in this study. Multiple oral QD doses of 400 mg atazanavir co-administered with a single oral dose of 1200 mg MK-0518 resulted in 1.67 and 1.16-fold increases in MK-0518 $AUC_{0-\infty}$ and C_{max}, respectively, compared to the administration of a single oral dose of MK-0518 alone. These changes in MK-0518 AUC and C_{max} failed to meet the pre-specified upper bound of 1.25. Results from the ongoing clinical studies will be used to determine the clinical significance of these findings.
PUBLICATIONS:	None
REPORT DATE:	Final: [redacted]20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-0518, also known as raltegravir, or ISENTRESS®	
INDICATION:	HIV treatment	
PROTOCOL TITLE:	A Study to Evaluate the Influence of Metal Cation-Containing Antacids on MK-0518 Pharmacokinetics in HIV-Infected Subjects on a Stable Raltegravir-Containing Regimen	
TRIAL IDENTIFIERS:	Protocol Number:	824
	Clinical Phase:	1
	IND Number	69,928
TRIAL CENTER:	[redacted] M.D. [redacted] USA	
DESIGN:	This was a non-randomized, single-site, open-label, 4-period, fixed-sequence trial of 1200 mg MK-0518, alone or in combination with metal cation-containing antacids (TUMS® Ultra Strength (US, calcium carbonate) or MAALOX® Maximum Strength (MS, magnesium/aluminum hydroxide) (or generic equivalent) in HIV-infected male and female subjects 18 years of age or older.	
	Planned duration of main phase:	Approximately 8 weeks
Objectives	1. To evaluate the effect of co-administration of a single dose of a calcium carbonate antacid on the steady-state plasma pharmacokinetic profile of MK-0518 in HIV-infected subjects. 2. To evaluate the effect of staggered dosing of a single dose of a magnesium/aluminum hydroxide antacid given 12 hours after administration of MK-0518 on the steady-state plasma pharmacokinetic profile of MK-0518 in HIV-infected subjects. 3. To evaluate the effect of staggered dosing of a single dose of a calcium carbonate antacid given 12 hours after administration of MK-0518 on the steady-state plasma pharmacokinetic profile of MK-0518 in HIV-infected subjects.	
Hypotheses	1. The C_{24} of steady-state MK-0518 after co-administration of a single dose of a calcium carbonate antacid will be estimated. 2. The C_{24} of steady-state MK-0518 after staggered dosing of a single dose of magnesium/aluminum hydroxide antacid given 12 hours after administration of MK-0518 will be estimated. 3. The C_{24} of steady-state MK-0518 after staggered dosing of a single dose of calcium carbonate antacid given 12 hours after administration of MK-0518 will be estimated.	

Treatment groups	Pre-treatment (5 days prior to Period 1):	1200 mg QD MK-0518 (2 x 600 mg), n=20
	Between Periods:	1200 mg QD MK-0518 (2 x 600 mg)
	Period 1, Treatment A:	1200 mg QD MK-0518 alone (2 x 600 mg), n=20
	Period 2, Treatment B:	3 tablets of TUMS® Ultra Strength (US) 1000, and 1200 mg QD MK-0518 (2 x 600 mg), taken concomitantly, n=19
	Period 3, Treatment C:	20 mL MAALOX® Maximum Strength (MS) (or generic equivalent*) given 12 hours after administration of 1200 mg QD MK-0518 (2 x 600 mg), n=19 *Leader Antacid MS was used
	Period 4, Treatment D:	3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518 (2 x 600 mg), n=19

Clinical Supplies Dispensed to Subjects

Bulk Product Description	**Lot Number**
MK-0518 600 mg tablet	[redacted] (manufacturing)
TUMS® Ultra Strength (US) 1000 mg tablet†	5D126
Leader Antacid Maximum Strength (MS)‡	5EK0517

† TUMS® Ultra Strength (US) 1000 mg (lot number 5D126; expiration date APR-2020; GSK) was supplied by the investigator. Total of 3000 mg calcium carbonate.

‡Due to non-availability of MAALOX® Maximum Strength (MS) a generic equivalent was used. Leader Antacid Maximum Strength (MS) (lot number 5EK0517; expiration date MAR-2017; Leader), was supplied by the investigator. Each 20 mL dose contained 1600 mg magnesium hydroxide, 1600 mg aluminum hydroxide and 160 mg simethicone per the manufacturer.

Endpoints and definitions	**Primary Endpoints**	**Pharmacokinetics** AUC_{0-24}, C_{24}, C_{max} and T_{max} were calculated from the individual plasma concentrations of 1200 mg QD MK-0518 after administration alone or with a calcium carbonate antacid or with a staggered dose of a calcium carbonate antacid or magnesium/aluminum hydroxide antacid. **Safety** Adverse events (AEs), in addition to laboratory safety tests (hematology, serum chemistry and urinalysis), 12-lead electrocardiograms (ECGs) and vital signs were assessed.	
Database lock	06-NOV-2015, relock 02-FEB-2016	Trial status	23-JUN-2015 to 09-OCT-2015
RESULTS AND ANALYSIS:	All analyses for safety and pharmacokinetics were performed according to the protocol.		

Disposition of Subjects

Variable	Category	n	(%)
Screened	Yes	20	(100.0%)
Pre-treated	Yes	20	(100.0%)
Randomized	Yes	20	(100.0%)
Treatment A	Yes	20	(100.0%)
Treatment B	Yes	19	(95.0%)
	No	1	(5.0%)
Treatment C	Yes	19	(95.0%)
	No	1	(5.0%)
Treatment D	Yes	19	(95.0%)
	No	1	(5.0%)
Completed	Yes	18	(90.0%)
	No	2	(10.0%)
AST population size		20	

n (%) = Number (and percentage) of subjects in respective category
A: 1200 mg QD MK-0518 alone
B: 3 tablets of TUMS® Ultra Strength 1000 and 1200 mg QD MK-0518, given concomitantly
C: 20 mL MAALOX® Maximum Strength (or generic equivalent) given 12 h after administration of 1200 mg QD MK-0518
D: 3 tablets of TUMS® Ultra Strength 1000 given 12 h after administration of 1200 mg QD MK-0518

Analysis description	**Primary Analysis - Pharmacokinetics** Individual steady state AUC_{0-24}, C_{max} and C_{24} values for MK-0518 were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with a fixed effect term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). C_{24}, C_{max}, and T_{max} values were obtained directly from the plasma concentration-time data. AUC_{0-24} was calculated using the linear up/log down trapezoidal method from time zero to 24 hours. The estimation hypothesis was addressed by comparing AUC_{0-24} and C_{max} values for MK-0518 from administration of MK-0518 with antacid (either TUMS® US (Concurrent; Period 2) or MAALOX® MS (or generic equivalent) (12 hours after; Period 3) or TUMS® US (12 hours after; Period 4)) to those obtained from administration of MK-0518 alone (Period 1). A two-sided 90% confidence interval (CI) for the true mean difference [MK-0518 with antacid minus MK-0518 alone] for each antacid (and timing of administration) and parameter on the log scale was computed from the above linear-mixed effect model. The 90% CI was then exponentiated to obtain the 90% CI for the true geometric mean ratio (MK-0518 with antacid/MK-0518 alone) for each antacid and parameter, MK-0518 AUC_{0-24} and C_{max}. An analysis of the MK-0518 C_{24} data was performed similarly.
Analysis population and time point description	The following populations were defined for the analysis and reporting of data. *Per-Protocol (PP)*: The population included the subset of subjects who complied with the protocol sufficiently to ensure that generated data would reflect the effects of treatment, according to the underlying scientific model. This population was used for the PK analyses and included 20, 19, 19, and 19 HIV-infected subjects who received Treatment A, Treatment B, Treatment C, and Treatment D respectively.
Summary	**<u>Three (3) tablets of TUMS® Ultra Strength 1000 and 1200 mg QD MK-0518 given concomitantly relative to 1200 mg QD MK-0518 alone</u>** Statistical comparisons of MK-0518 PK after 1200 mg QD MK-0518 alone (Treatment A), and after 3 tablets of TUMS® Ultra Strength 1000 and 1200 mg QD MK-0518 given concomitantly (Treatment B) are presented in Table 3 below. Steady state C_{max}, AUC_{0-24} and C_{24} of MK-0518 decreased by approximately 74%, 72% and 48%, respectively, when 1200 mg QD

	MK-0518 is given concomitantly with 3 tablets of TUMS® Ultra Strength 1000. Median T_{max} remained unchanged. **Twenty (20) mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg QD MK-0518 relative to 1200 mg QD MK-0518 alone** Statistical comparisons of MK-0518 PK after 1200 mg QD MK-0518 alone (Treatment A) and after 20 mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg QD MK-0518 (Treatment C) are presented in Table 3 below. Steady state C_{max}, AUC_{0-24} and C_{24} of MK-0518 decreased by approximately 14%, 14% and 58%, respectively, when 20 mL MAALOX® MS (or generic equivalent) is given 12 hours after administration of 1200 mg QD MK-0518. Median T_{max} remained unchanged. **Three (3) tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg QD MK-0518 relative to 1200 mg QD MK-0518 alone** Statistical comparisons of MK-0518 PK after 1200 mg QD MK-0518 alone (Treatment A) and after 3 tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg QD MK-0518 (Treatment D) are presented in the table below. Steady state C_{max}, AUC_{0-24} and C_{24} of MK-0518 decreased by approximately 2%, 10% and 57%, respectively, when 3 tablets of TUMS® Ultra Strength 1000 is given 12 hours after administration of 1200 mg QD MK-0518. Median T_{max} remained unchanged.

Statistical Comparisons of Pharmacokinetic Parameters for MK-0518 after Administration of Treatments A, B, C and D to HIV-Infected Subjects

PK Parameter	Treatment	N	AUC_{0-24}‡ (h·µM)	C_{max}‡ (nM)	C_{24}‡ (nM)	T_{max}§ (h)
GM (95% CI)	A	20	53.7 (44.2, 65.2)	20000 (16500, 24300)	75.6 (55.3, 103)	1.50 (0.50, 3.00)
	B	19 [a]	14.8 (12.4, 17.7)	5240 (4230, 6490)	39.6 (29.9, 52.5)	1.50 (1.00, 2.00)
	C	19 [a]	46.3 (36.0, 59.6)	17300 (12800, 23300)	32.0 (23.7, 43.2)	1.50 (0.50, 3.00)
	D	19 [a]	48.5 (39.0, 60.3)	19500 (15900, 24000)	32.4 (24.6, 42.6)	1.50 (0.50, 3.00)
GMR (90% CI)	B/A		0.28 (0.24, 0.32)	0.26 (0.21, 0.32)	0.52 (0.45, 0.61)	
	C/A		0.86 (0.73, 1.03)	0.86 (0.65, 1.15)	0.42 (0.34, 0.52)	
	D/A		0.90 (0.80, 1.03)	0.98 (0.81, 1.17)	0.43 (0.36, 0.51)	
Pseudo Within Subject %CV†	A, B		28.5	35.4	25.9	
	A, C		30.5	50.4	36.8	
	A, D		22.6	32.8	31.0	

† Pseudo Within-Subject %CV = $100*(\sqrt{(\hat{\sigma}_X^2+\hat{\sigma}_Y^2-2\hat{\sigma}_{XY})/2})$, where $\hat{\sigma}_X^2$ and σ_Y^2 are the estimated variances on the log scale for the two treatment groups, and $\hat{\sigma}_{XY}^2$ is the corresponding estimated covariance, each obtained from the linear mixed effects model.

‡ Back-transformed least squares mean and confidence interval from ANOVA model performed on natural log-transformed values.

§ Median (min, max) reported for T_{max}.

GM=Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval; CV= Coefficient of variation.

[a] One (1) subject did not receive treatment B (Period 2), treatment C (Period 3) and treatment D (Period 4) due to consent withdrawal prior to receiving dose in Period 2.

Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg).
Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000 and 1200 mg QD MK-0518 (two tablets of 600 mg) given concomitantly.
Treatment C: 20 mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).
Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).

Analysis description	**Co-primary Analysis - Safety** The safety and tolerability were monitored by clinical assessment of adverse experiences and by repeated measurements of vital signs, physical examinations, ECGs, and selected laboratory safety values, as deemed clinically appropriate.

Analysis population and time point description	*All Subjects as Treated (AST)*: The population included all subjects who received at least one dose of the investigational drug MK-0518, with or without an antacid. This population was used for assessments of safety and tolerability. All 20 subjects were included in the AST population.
Summary	MK-0518, administered alone or with TUMS® Ultra Strength (US) and MAALOX® MS (or generic equivalent), was generally well-tolerated in HIV-infected male and female subjects, at least 18 years of age. Most adverse experiences (AEs) reported were generally transient and considered mild to moderate intensity by the investigator. In total, 15 subjects reported 37 AEs. The most frequently reported treatment emergent AEs were upper respiratory tract infection, diarrhoea and headache. One laboratory AE was reported of mild intensity during Treatment B that was considered to be reasonably related to study medication. Four (4) serious adverse experiences (SAEs) were reported by 1 subject in the study. This subject was briefly hospitalized for reported chest pain, dyspnoea, orthostatic hypotension and rash 9 days following dosing with MK-0518 and TUMS® Ultra Strength (US) 12 hours later (Treatment D, Period 4). Upon arrival at the hospital, the subject noted the rash started after receiving MK-0518 on Day -1 of Period 3, 2 days after receiving MK-0518 with TUMS® Ultra Strength (US) (Treatment B, Period 2). Each of the SAEs were of moderate intensity. The rash was considered reasonably related to the study medication and resolved 21 days after it started. The chest pain, dyspnoea and orthostatic hypotension were considered not reasonably related to the study medication. The dysponea and chest pain resolved after approximately 2 weeks. The orthostatic hypotension resolved after 2 days. This subject was lost to follow up. None of the subjects discontinued due to an AE.

CONCLUSIONS:	**Pharmacokinetics:** • Three (3) tablets of TUMS® Ultra Strength 1000 mg given concomitantly with 1200 mg QD MK-0518 decreased MK-0518 steady-state C_{max}, AUC_{0-24}, and C_{24} by approximately 74%, 72%, and 48%, respectively, compared to 1200 mg QD MK-0518 alone. • Twenty (20) mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg QD MK-0518 decreased MK-0518 steady-state C_{max}, AUC_{0-24}, and C_{24} by approximately 14%, 14%, and 58%, respectively, compared to 1200 mg QD MK-0518 alone. • Three (3) tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg QD MK-0518 decreased MK-0518 steady-state C_{max}, AUC_{0-24}, and C_{24} by approximately 2%, 10%, and 57%, respectively, compared to 1200 mg QD MK-0518 alone. • Results from the ongoing clinical studies will be used to determine the clinical significance of these findings. **Safety:** • Single oral doses of 1200 mg QD MK-0518 alone or in combination with TUMS® Ultra Strength and MAALOX® MS (or generic equivalent) were generally well tolerated.
REPORT DATE	21-MAR-2016

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-0518	
INDICATION:	HIV-1 infection	
PROTOCOL TITLE:	A Multiple Dose, Randomized, Double-blind, Placebo-controlled, 2-Treatment Study to Evaluate the Safety and Tolerability and to Assess the Pharmacokinetics of MK-0518 in healthy adult subjects	
TRIAL IDENTIFIERS:	Protocol Number:	293
	Clinical Phase:	1
	EudraCT Number:	[2013-002767-26]
	ISRCT number:	Not Applicable
	US IND Number	Not Applicable
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For trial audit information see [16.1.8]. The signature of the primary/coordinating investigator is in [16.1.5.1] and the signatures of the principal authors of this report are in [16.1.5.2].	
TRIAL CENTERS:	[redacted] MD This trial was conducted at 1 trial center in the Netherlands	
DESIGN:	A Single-site, Multiple Dose, Randomized, Double-blind, Placebo-controlled, 2-Treatment Study.	
	Planned duration of main phase:	The planned duration was approximately 9 weeks.
OBJECTIVES	**1.** To evaluate the safety and tolerability of 1800 mg reformulated raltegravir formulation when administered once-daily for 28 consecutive days in healthy subjects. **2.** To assess the pharmacokinetics (e.g., $AUC_{0\text{-}24hr}$, C_{max} and C_{24hr}) of raltegravir after multiple dose administration of raltegravir.	

HYPOTHESES	**1.** Administration of 1800 mg QD doses of reformulated raltegravir formulation is sufficiently safe and well-tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation. **2.** The pharmacokinetic parameters of raltegravir after administration of 1800 mg QD dose of reformulated tablets of raltegravir will be estimated.	
TREATMENTS GROUPS	Treatment A (N=18)	Administration of 1800 mg (3 x 600 mg) reformulated raltegravir tablets once a day for 28 days
	Treatment B (N=6)	Administration of matched placebo tablets once a day for 28 days

ENDPOINTS AND DEFINITIONS	**Pharmacokinetic Endpoints** The following pharmacokinetic parameters of raltegravir were estimated after administration of 1800 mg QD dose of reformulated tablets of raltegravir: $AUC_{0\text{-}24hr}$, C_{max}, C_{24hr}, and T_{max}.		
	Safety Endpoints Primary safety endpoints included all types of adverse events, in addition to physical examinations, vital signs (heart rate, blood pressure, and body temperature), 12-lead electrocardiogram (ECG), and laboratory safety tests.		
DATABASE LOCK	[redacted]20[redacted]	Trial status	first subject first visit (FSFV): [redacted]20[redacted] last subject last visit (LSLV): [redacted]20[redacted]
RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol. The Statistical Analysis Plan is provided in [16.1.9].		

PK ANALYSIS DESCRIPTION	Blood samples for PK evaluation were collected pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose on days 14 and 28. Trough samples collected on Days 7, 10, and 21 were obtained prior to dosing.
SAFETY ANALYSIS DESCRIPTION	The investigator evaluated the tolerability and safety of each treatment administered during the study. This evaluation took into account the recorded adverse events, vital signs, ECG parameters, clinical laboratory (including tests of liver function), physical examinations and any other parameter that is relevant for safety assessment.
ANALYSIS POPULATION	The following population was defined for the analysis and reporting of safety and tolerability.

AND TIME POINT DESCRIPTION

All Subjects as Treated (AST): All subjects who received at least one dose of the investigational drug.

The pharmacokinetic population (PP) included all subjects who had received at least 3 consecutive doses of raltegravir prior to Days 14 or 28 and had sufficient concentration-time data (at least 5 data points with a quantifiable plasma g raltegravir concentration value) on Days 14 or 28.

PK RESULTS

Twenty-four (24) subjects were enrolled in this study. Eighteen (18) and 6 subjects were randomized to Treatment A (1800 mg reformulated raltegravir tablets) and Treatment B (placebo) in this study, respectively. Seventeen (17) subjects among those (18 subjects) in Treatment A completed the study. One subject (293-01*) in Treatment A withdrew consent on Day 28. Therefore, 18 subjects on Day 14 and 17 subjects on Day 28 were included in the pharmacokinetic analysis population.

Table 2-1 provides the summary of pharmacokinetic parameters for raltegravir after multiple administration of raltegravir on Days 14 and 28. Table 2-2 shows the numbers and percentage of subjects with trough concentrations of raltegravir ≤45 nM and >45 nM after multiple administration of raltegravir on Days 7, 14, 21 and 28.

The mean values of C_{max}, C_{24hr}, AUC_{0-24hr} were 25300 nM, 110 nM, 60300 h·nM and 29000 nM, 88.5 nM, 74500 h·nM after multiple administration of raltegravir on Days 14 and 28 in healthy subjects, respectively. The median value of T_{max} was 1.5 hours after multiple administration of raltegravir on Days 14 and 28 in healthy subjects. It appears that the pharmacokinetics was comparable after multiple administration of raltegravir on Days 14 and 28 in healthy subjects. The percentage of subjects with trough concentrations of raltegravir >45 nM after multiple administration of raltegravir on Days 7, 10, 14, 21 and 28 ranged from 56 to 78%.

Table 2-1: Summary (Mean and SD) of Pharmacokinetic Parameters for Raltegravir after Multiple Administration of Raltegravir on Days 14 and 28.

	Day 14 (N=18)				Day 28 (N=17)			
Parameters	**AM**	**SD**	**GM**	**GCV%**	**AM**	**SD**	**GM**	**GCV %**
C_{max}, nM	25300	16900	20600	75	29000	13400	26300	50
C_{24hr}, nM	110	74.9	86.9	85	88.5	56.3	71.4	80
AUC_{0-24hr}, h·nM	60300	33200	52100	62	74500	35800	67600	47
T_{max}, h*	1.50 [0.50, 2.02]				1.50 [0.50, 2.00]			

AM: Arithmetic Mean; SD: Standard Deviation; GM: Geometric Mean; * T_{max} expressed as median [Range] ; GCV%: Geometric CV which is equal to 100 x sqrt($exp(s^2)$ - 1), where s^2 is the observed variance on the natural log-scale; N: Total Evaluable Subjects

Table 2-2: The Numbers and Percent of Subjects with Trough Concentrations of Raltegravir ≤ 45 nM and >45 nM after Multiple Administration of Raltegravir on Days 7, 10, 14, 21 and 28.

Parameters		Trough Concentration >45 nM		Trough Concentration ≤ 45 nM	
Day	N	Number (n)	Percent (%)	Number (n)	Percent (%)
7 (pre-dose)	18	10	55.6	8	44.4
10 (pre-dose)	18	13	72.2	5	27.8
14 (pre-dose)	18	11	61.1	7	38.9
14 (24 hours)	18	14	77.8	4	22.2
21 (pre-dose)	18	11	61.1	7	38.9
28 (pre-dose)	18*	11	61.1	7	38.9
28 (24 hours)	17**	13	76.5	4	23.5

Percent=100*n/N; N: Total Evaluable Subjects;

* Although 293-01* on Day 28 withdrew the consent, the subject did have an evaluable pre-dose concentration sample.

** 293-01* withdrew the consent on Day 28.

SAFETY RESULTS

MK-0518 was well tolerated. There were no deaths and no serious adverse events (SAEs). There were no clinically significant findings for vital signs or ECG data. A total of 23 subjects (95.8%) reported at least one adverse event: 17 subjects (94.4%) after Treatment A and 6 subjects (100%) after Treatment B. Two (2) subjects withdrew their consent at Day 28. No subjects discontinued the study due to adverse events.

Adverse events reported by >3 subjects include headache (9 subjects after active, 3 after placebo), dizziness (4 subjects after active, 1 after placebo), myalgia (8 subjects after active, 1 after placebo), back pain (4 subjects after active), musculoskeletal stiffness (4 subjects after active, 1 after placebo), abdominal pain (6 subjects after active, 2 subjects after placebo), oropharyngeal pain (5 subjects after active, 1 after placebo), fatigue (5 subjects after active, 1 after placebo), nasopharyngitis (4 subjects after active), and pollakiuria (4 subjects after active).

Five subjects (293-02*, 03*, 04*, 05* and 06*; all on reformulated raltegravir) showed elevations in CPK. Among the five subjects, four (293-02*, 03*, 04* and 05*) did not show elevations until after the dosing had been completed and the subjects were no longer domiciled. Of the five subjects, two (293-03* and 04*) experienced CPK >20 x ULN and one (293-06*) experienced ~9 x ULN; for these three subjects, the intensity of the event was rated as severe by the investigator and was considered related to the study drug. One subject (293-02*) experienced >2 x ULN CPK increase and one other subject (293-05*) experienced <2 x ULN CPK increase. As described above, 293-02* showed a CPK level of 508 U/L two days post last dose (CPK values were within

	normal limits (WNL) throughout dosing period, i.e., <200 U/L). 293-03* showed a CPK level of 6070 U/L at the 2-week follow-up post study visit. 293-04* showed a CPK level of 4220 U/L, also at the 2-week follow-up post-study visit. 293-05* showed a CPK level of 359 U/L at the 2-week follow-up post-study visit. The LFT panels were WNL throughout the dosing period for 293-03*, 04* and 05*. 293-06* first had a CPK level elevation (1870 U/L) on Day 13 (described above). All subjects were closely monitored by the clinical site until values returned to normal range or stabilized. No subjects experienced ALT >5x ULN in this study. One subject (293-02*) experienced ALT >3x ULN and one subject (293-06*) experienced ALT >2x ULN, both were in the reformulated raltegravir group. Five subjects experienced ALT <2x ULN (293-07*, 08*, 09*, 10* and 11*). 293-08* and 10* received a placebo and 293-02*, 06*, 07*, 09* and 11* recieved 1800 mg reformulated raltegravir QD. These changes were not considered clinically significant because of a lack of clinically significant symptoms, and observed improvements while on treatment. No subjects were discontinued because of these changes.

CONCLUSIONS:	**Pharmacokinetics:** 1. The mean values of C_{max}, C_{24hr}, AUC_{0-24hr} were 25300 nM, 110 nM, 60300 h·nM and 29000 nM, 88.5 nM, 74500 h·nM after multiple administration of raltegravir on Days 14 and 28 in healthy subjects, respectively. 2. The median value of T_{max} was 1.5 hours after multiple administration of raltegravir on Days 14 and 28 in healthy subjects. 3. The percentages of subjects with trough concentrations of raltegravir >45 nM after multiple administration of raltegravir on Days 7,10,14, 21 and 28 ranged from 56 to 78%. 4. It appears that the pharmacokinetics was comparable after multiple administration of raltegravir on Days 14 and 28 in healthy subjects. **Safety:** Overall, administration of 1800 mg QD doses of MK-0518 was safe and well tolerated in healthy subjects.
PUBLICATION(S):	Not applicable
REPORT DATE	[redacted]20[redacted]

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-0518, raltegravir, ISENTRESS® Raltegravir 1200 mg once daily (QD; 2 x 600 mg tablets) Raltegravir 400 mg twice daily (BID; 1 x 400 mg tablet)	
INDICATION:	Treatment of HIV-1 infection	
PROTOCOL TITLE:	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Reformulated Raltegravir 1200 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Each in Combination With TRUVADA™, in Treatment-Naïve HIV-1 Infected Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	292
	Clinical Phase:	3
	EudraCT Number:	2013-001939-47
TRIAL CENTERS:	One hundred fifty-one (151) centers were shipped drug and/or opened for screening for this study. Of these, 139 centers allocated subjects to study treatment. Three (3) centers were located in Argentina, 5 in Australia, 4 in Belgium, 7 in Canada, 4 in Chile, 5 in Colombia, 9 in France, 10 in Germany, 4 in Guatemala, 1 in Ireland, 5 in Israel, 9 in Italy, 4 in Malaysia, 3 in Peru, 1 in the Philippines, 5 in Portugal, 3 in Puerto Rico, 8 in Russia, 5 in South Africa, 1 in South Korea, 8 in Spain, 4 in Switzerland, 3 in Taiwan, 4 in Thailand, 5 in the United Kingdom, and 31 in the United States.	
DESIGN:	This is a multicenter, double-blind (with in-house blinding), randomized, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of raltegravir 1200 mg QD compared with raltegravir 400 mg BID when each is given in combination with TRUVADA™ in HIV-1 infected treatment-naïve subjects who were ≥18 years of age with a screening HIV RNA ≥1000 copies/mL within 60 days prior to study randomization. An external Data Monitoring Committee provided ongoing monitoring of safety data. In addition, one interim efficacy analysis was performed, when complete Week 24 data were available for approximately 375 subjects, for the sole purpose of stopping the study if there was a lack of efficacy as prespecified (futility).	
	Planned duration of main phase: Planned duration of run-in phase: Planned duration of extension phase:	48 weeks Not applicable 48 weeks
Objectives	The objectives and hypotheses as stated in the protocol are provided verbatim below, to be consistent with the protocol. Please note that "reformulated raltegravir 1200 mg QD" is the same as "raltegravir 1200 mg QD (2 x 600 mg tablets)". **Primary Objective** In HIV-1 positive treatment-naïve subjects with pre-treatment HIV-1 ribonucleic acid (RNA) ≥1,000 copies/mL: 1. To evaluate the antiretroviral activity of reformulated raltegravir 1200 mg QD, compared to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48.	

	Secondary Objectives In HIV-1 positive treatment-naïve subjects with pre-treatment HIV-1 RNA ≥ 1,000 copies/mL: 1. To evaluate the immunological effect of reformulated raltegravir 1200 mg QD, compared to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as measured by the change from baseline in CD4 cell count at Week 48. 2. To evaluate the antiretroviral activity and immunological effect of reformulated raltegravir 1200 mg QD, compared to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as measured by the following parameters at Week 96: ▪ Proportion of subjects achieving HIV-1 RNA <40 copies/mL. ▪ Change from baseline in CD4 cell count. 3. To evaluate the safety and tolerability of reformulated raltegravir 1200 mg QD, compared to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as assessed by review of the accumulated safety data at Week 48 and Week 96.	
Hypotheses	**Primary Hypothesis** 1. Reformulated raltegravir 1200 mg QD is non-inferior to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as assessed by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48. **Secondary Hypothesis** 2. Reformulated raltegravir 1200 mg QD is non-inferior to raltegravir 400 mg BID, each in combination with TRUVADA™, as assessed by proportion of subjects achieving HIV-1 RNA <40 copies/ml at Week 96.	
Treatment groups	Raltegravir QD	Raltegravir 1200 mg once daily (QD) + TRUVADA™ QD, ~500 Subjects
	Raltegravir BID	Raltegravir 400 mg twice daily (BID) + TRUVADA™ QD, ~250 subjects

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
FCT Emtricitabine / Tenofovir Disoproxil Fumarate (TRUVADA) 200 mg / 300 mg, 30 Count Bottle (ex-Germany) FCT Emtricitabine / Tenofovir Disoproxil Fumarate (TRUVADA) 200 mg / 300 mg, 30 Count Bottle (ex-UK) FCT MK-0518 (003E) 400 mg (Clinical Image) FCT MK-0518 (003E) 600 mg (Milled, Divi, Reformulated) FCT MK-0518 (003E) 600 mg (PhIII Clinical Image, Reformulated, Divi API) FCT MK-0518 400 mg Placebo (Clinical Image) FCT MK-0518 600 mg Placebo FCT MK-0518 600 mg Placebo (PhIII Clinical Image)	[redacted]

Data Source: [16.4]

Endpoints and definitions	Primary efficacy endpoint	HIV-1 RNA	The proportion of subjects achieving HIV-1 RNA < 40 copies/mL at Week 48
	Secondary efficacy endpoint	CD4	Change from baseline in CD4 count at Week 48
	Safety and Tolerability	Tier 1, Tier 2, Tier 3	For this protocol, there were no Tier 1 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE were considered Tier 2 endpoints. In addition, adverse experiences (specific terms as well as system organ class terms) and laboratory values that met predefined limits of change (PDLC) were classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 required that at least 1% of subjects in any treatment group exhibited the event; all other adverse experiences and laboratory values meeting PDLC were classified as Tier 3.
	Pharmacokinetic Endpoints	C_{all} C_{trough} C_{min}	Raltegravir concentrations in all samples from an individual subject Raltegravir concentrations in all samples for an individual subject collected between 22 and 26 hours post-dose for the QD arm and between 11 and 13 hours post-dose for the BID arm of the study Minimum concentration value of all samples for an individual subject
	Future Biomedical Research		Biomarker testing to address emergent questions.

Database lock	[redacted] 20[redacted]	Study status	The study is ongoing; this is an interim analysis report with complete data to address the primary hypothesis and objectives at Week 48.

RESULTS AND ANALYSIS:	With 500 subjects in the raltegravir QD arm and 250 subjects in the BID arm, the study had 90% power to demonstrate non-inferiority of raltegravir QD over raltegravir BID, each in combination with TRUVADA™. This assumes a true response proportion of 85% at Week 48 for the raltegravir 400 mg BID arm and no larger than a 1% lower response rate for the raltegravir 1200 mg QD arm using the NC=F approach as defined by the FDA "snapshot" approach. There are 2 data cutoffs in the CSR. The primary data cutoff includes data up to the Week 48 window for all subjects; tables using this data cutoff are denoted "Weeks 0-48". The second data cutoff includes all data that are available in the frozen database for events that began or procedures that occurred by [redacted] 20[redacted] for all subjects; tables using this data cutoff are denoted "All Data Available" and are supportive analyses. The database was frozen on [redacted] 20[redacted].

Subject Baseline Characteristics by Treatment Group

	Raltegravir 1200 mg QD (N = 531)	Raltegravir 400 mg BID (N = 266)	Total (N = 797)
Gender n (%)			
Male	440 (82.9)	234 (88.0)	674 (84.6)
Female	91 (17.1)	32 (12.0)	123 (15.4)
Race n (%)			
American Indian or Alaska Native	3 (0.6)	3 (1.1)	6 (0.8)
Asian	83 (15.6)	40 (15.0)	123 (15.4)
Black or African American	98 (18.5)	36 (13.5)	134 (16.8)
Multiple	46 (8.7)	14 (5.3)	60 (7.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.1)
White	301 (56.7)	172 (64.7)	473 (59.3)
Ethnicity n (%)			
Hispanic or Latino	126 (23.7)	52 (19.5)	178 (22.3)
Not Hispanic or Latino	380 (71.6)	205 (77.1)	585 (73.4)
Not Reported	19 (3.6)	8 (3.0)	27 (3.4)
Unknown	6 (1.1)	1 (0.4)	7 (0.9)
Region n (%)			
Africa	43 (8.1)	13 (4.9)	56 (7.0)
Asia/Pacific	86 (16.2)	46 (17.3)	132 (16.6)
Europe	200 (37.7)	112 (42.1)	312 (39.1)
Latin America	77 (14.5)	26 (9.8)	103 (12.9)
North America	125 (23.5)	69 (25.9)	194 (24.3)
Age (years)			
18 to 64	527 (99.2)	263 (98.9)	790 (99.1)
>=65	4 (0.8)	3 (1.1)	7 (0.9)
Mean (SD)	35.4 (10.3)	36.9 (11.0)	35.9 (10.5)
Median (min, max)	34.0 (18, 66)	35.0 (19, 84)	34.0 (18, 84)
Baseline CD4 Cell Count (cells/mm^3)			
N[†]	531	266	797
Mean (SD)	407.6 (213.7)	428.9 (217.3)	414.7 (215.0)
Median (min, max)	380.0 (19, 1836)	415.5 (19, 1130)	390.0 (19, 1836)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	9 (1.7)	6 (2.3)	15 (1.9)
>50 cells/mm^3 and <=200 cells/mm^3	60 (11.3)	31 (11.7)	91 (11.4)
>200 cells/mm^3	462 (87.0)	229 (86.1)	691 (86.7)
Baseline Plasma HIV RNA (log10 copies/mL)			
N[†]	531	266	797
Mean (SD)	4.6 (0.7)	4.6 (0.7)	4.6 (0.7)
Median (min, max)	4.6 (1.6, 6.6)	4.6 (2.7, 6.2)	4.6 (1.6, 6.6)

Subject Baseline Characteristics by Treatment Group

	Raltegravir 1200 mg QD (N = 531)	Raltegravir 400 mg BID (N = 266)	Total (N = 797)
Baseline Plasma HIV RNA (copies/mL)			
N[†]	531	266	797
Geometric Mean	40518.8	40733.2	40590.2
Median (min, max)	43890.0 (39, 3910386)	40631.0 (454, 1466713)	42424.0 (39, 3910386)
Baseline Plasma HIV RNA n (%)			
<=100,000 copies/mL	382 (71.9)	189 (71.1)	571 (71.6)
>100,000 copies/mL	149 (28.1)	77 (28.9)	226 (28.4)
Baseline Plasma HIV RNA n (%)			
<=500,000 copies/mL	506 (95.3)	251 (94.4)	757 (95.0)
>500,000 copies/mL	25 (4.7)	15 (5.6)	40 (5.0)
History of AIDS n (%)			
Yes	79 (14.9)	28 (10.5)	107 (13.4)
No	452 (85.1)	238 (89.5)	690 (86.6)
Stratum n (%)			
Screening HIV RNA<= 100,000	382 (71.9)	190 (71.4)	572 (71.8)
Hepatitis B and/or C Positive[††]	15 (2.8)	8 (3.0)	23 (2.9)
Baseline Hepatitis Status			
Hep B Positive Only	11 (2.1)	3 (1.1)	14 (1.8)
Hep C Positive Only	4 (0.8)	4 (1.5)	8 (1.0)
Both Hep B and Hep C Positive	0 (0.0)	1 (0.4)	1 (0.1)
Viral Subtype n (%)			
Clade B	335 (63.1)	186 (69.9)	521 (65.4)
Non-Clade B	194 (36.5)	77 (28.9)	271 (34.0)
Missing	2 (0.4)	3 (1.1)	5 (0.6)

[†] Subjects with missing results excluded.

[††] Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction(PCR) quantitative test for hepatitis C Virus. 19 subjects previously classified as hepatitis B or C positive were subsequently identified based on lab tests as being hepatitis B or C negative. 3 subjects previously classified as hepatitis B or C negative were subsequently identified based on lab tests as being hepatitis B or C positive.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

N = Number of patients randomized and treated in each treatment group.

n (%) = Number (percent) of patients in each sub-category.

Data Source: [16.4]

Subject Status by Treatment Group
Weeks 0-48

	Raltegravir 1200 mg QD		Raltegravir 400 mg BID		Total	
	n	(%)	n	(%)	n	(%)
Total Entered	533		269		802	
Not Treated	2	(0.4)	3	(1.1)	5	(0.6)
Treated	531	(99.6)	266	(98.9)	797	(99.4)
Discontinued Study	41	(7.7)	24	(8.9)	65	(8.1)
Adverse Event	6	(1.1)	6	(2.2)	12	(1.5)
Death	0	(0.0)	1	(0.4)	1	(0.1)
Lack Of Efficacy	4	(0.8)	1	(0.4)	5	(0.6)
Lost To Follow-Up	8	(1.5)	4	(1.5)	12	(1.5)
Non-Compliance With Study Drug	5	(0.9)	4	(1.5)	9	(1.1)
Physician Decision	4	(0.8)	0	(0.0)	4	(0.5)
Pregnancy	2	(0.4)	0	(0.0)	2	(0.2)
Withdrawal By Subject	12	(2.3)	8	(3.0)	20	(2.5)

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.
n (%)= Number (percent) of subjects in each sub-category.

Data Source: [16.4]

Analysis description	**Primary Analysis:** HIV-1 RNA *Statistical methodology:* The primary hypothesis on antiretroviral activity was assessed by the percentage of subjects achieving plasma HIV RNA <40 copies/mL at Week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to define non-inferiority. Raltegravir QD was concluded to be non-inferior to raltegravir BID if the lower bound of the two-sided exact 95% CI for the difference in response rate (raltegravir QD – raltegravir BID) remained above -10 percentage points. The NC=F approach as defined by FDA "snapshot" approach was used as the primary approach to analysis with respect to the proportion of subjects with virologic response (HIV-1 RNA <40 copies/mL). All missing data were treated as failures regardless of the reason. **Secondary Analysis:** CD4 *Statistical methodology:* The treatment difference of changes in CD4 cell counts at time points of interest was estimated between the two treatment groups. However, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, magnitude and direction of the CD4 changes seen in each treatment arm. The OF approach was used for the calculations of change from baseline in CD4 cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.
Analysis population and time point description	The primary population for efficacy analyses was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least one dose of study treatment and had baseline data for those analyses that require baseline data.
Summary	With respect to the primary efficacy endpoint, the proportion (%) of subjects achieving HIV RNA <40 copies/mL at Week 48 by the FDA Snapshot approach was 88.9% (472/531) and 88.3% (235/266) for raltegravir 1200 mg QD and raltegravir 400 mg BID, respectively. The treatment difference (QD – BID) was 0.510% with an associated 95% CI of (-4.204, 5.223), demonstrating non-inferiority of raltegravir 1200 mg QD treatment group versus raltegravir 400 mg BID treatment group, as the lower bound of the 95% CI for treatment difference was above the pre-defined non-inferiority bound of -10 percentage points. Regarding the secondary analysis, the raltegravir QD group had a similar mean change from baseline in CD4 cell count (232 cells/mm^3) compared with that in the raltegravir BID group (234 cells/mm^3), with a treatment difference (95% CI) of -2.1 (-30.9, 26.7).

Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (QD - BID)[‡]		Conclusion[§]
		Raltegravir 1200 mg QD n/N (%)	Raltegravir 400 mg BID n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Patients with HIV RNA <40 copies/mL	Snapshot (NC=F)	472/531 (88.9)	235/266 (88.3)	0.510	(-4.204, 5.223)	Non-inferior
Supportive						
Proportion of Patients with HIV RNA <40 copies/mL	OF	472/501 (94.2)	235/251 (93.6)	0.553	(-3.103, 4.209)	
Proportion of Patients with HIV RNA <50 copies/mL	Snapshot (NC=F)	477/531 (89.8)	240/266 (90.2)	-0.415	(-4.858, 4.027)	
Proportion of Patients with HIV RNA <50 copies/mL	OF	477/501 (95.2)	240/251 (95.6)	-0.432	(-3.633, 2.769)	
Proportion of Patients with HIV RNA <200 copies/mL	Snapshot (NC=F)	484/531 (91.1)	243/266 (91.4)	-0.212	(-4.428, 4.005)	
Proportion of Patients with HIV RNA <200 copies/mL	OF	484/501 (96.6)	243/251 (96.8)	-0.221	(-3.018, 2.576)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Secondary						
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	232.0 (214.6, 249.4)	234.1 (212.8, 255.3)	-2.1	(-30.9, 26.7)	

[†] NC=F: Non-Completer=Failure as defined by FDA snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA <=100,000 copies/mL or HIV-1 RNA >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] Raltegravir 1200 mg QD is concluded non-inferior to raltegravir 400 mg BID if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™

N = Number of subjects in each treatment group.

Data Source: [16.4]

Analysis description	**Supportive Analysis:** Virologic Outcome *Statistical methodology:* To provide a full picture of virologic outcome at a timepoint, besides the primary analysis of proportion of subjects achieving virologic success (HIV-1 RNA < 40 copies/mL) at Week 48, subjects who were not classified as virologic success were further categorized as virologic failure (HIV-1 RNA ≥40 copies/mL) or no virologic data at the time window with reasons of 1) discontinued study due to AE, 2) discontinued study for other reasons (including withdrawn consent, loss to follow-up, moved, etc.), or 3) on study but missing data in window.
Summary	The virologic outcomes of raltegravir QD are comparable to those of raltegravir BID, in regard to percent of subjects with HIV RNA < 40 copies/mL; >= 40 copies/mL; and no virologic data at Week 48 window. Overall, 472/531 (88.9%) and 235/266 (88.3%) in the QD and BID groups, respectively, had HIV RNA < 40 copies/mL at Week 48; 5.5% and 6.0% of QD and BID subjects, respectively, were classified as HIV RNA ≥ 40 copies/mL at Week 48; 5.6% in each group had no virologic data at Week 48 window.

Virologic Outcome at Week 48
FDA Snapshot Approach

Outcome	Raltegravir 1200 mg QD (N=531) n	(%)	Raltegravir 400 mg BID (N=266) n	(%)
HIV RNA <40 copies/mL	472	(88.9)	235	(88.3)
HIV RNA ≥ 40 copies/mL[†]	29	(5.5)	16	(6.0)
No Virologic Data at Week 48 Window	30	(5.6)	15	(5.6)
Reasons				
Discontinued study due to AE or Death[‡]	6	(1.1)	6	(2.3)
Discontinued study for Other Reasons[§]	20	(3.8)	7	(2.6)
On study but missing data in window	4	(0.8)	2	(0.8)

[†] Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV RNA equal to or above 40 copies/mL in the Week 48 window (relative day 295-378).

[‡] Includes subjects who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[§] Other Reasons includes: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, withdrawal by subject.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

n (%) = Number (Percent) of subjects in each category.

Data Source: [16.4]

Analysis description	**Supportive Analysis:** Subgroup Efficacy *Statistical methodology:* To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the efficacy endpoint was calculated within each category of the subgroup factors.
Summary	Similar high virologic suppression was noted for both raltegravir 1200 mg QD and raltegravir 400 mg BID, regardless of demographic or prognostic factors, including baseline RNA and CD4 count.

Analysis description	**Exploratory Analysis:** Protocol Defined Virologic failure *Statistical methodology:* The proportion of subjects with protocol-defined virologic failure was summarized by treatment group. The protocol definition of virologic failure is 1) non-responder: those subjects who never achieved HIV-1 RNA <40 copies/mL by Week 24; or 2) rebounder: those subjects who have two consecutive measurements of HIV-1 RNA ≥40 copies/mL at least one week apart after an initial response of HIV-1 RNA <40 copies/mL.
Summary	There were few virologic failures through Week 48, and raltegravir resistance was infrequent in both groups. NRTI resistance was also uncommon. Overall, the frequency of subjects with detectable resistance to integrase inhibitor is very low (<1%) for both QD(4/531 or 0.8%) and BID (0/266 or 0%) and comparable to that observed in previous large studies with raltegravir BID conducted in treatment-naïve and treatment-experienced subjects.

Analysis description	**Safety analysis**: Adverse events The safety objective was assessed by clinical review of the accumulated safety data. For this study, there were no pre-specified events of interest (i.e., no Tier-1 events); therefore, no p-values were supplied for the safety analyses. The treatment differences and the associated 95% confidence intervals were provided for the percentage of subjects with the following events based on specific AE categories (i.e., Tier-2 events): (1) at least one adverse experience; (2) drug related adverse experience; (3) serious adverse experience; (4) serious and drug related adverse experience; (5) discontinued study therapy due to an adverse experience. In addition, adverse experiences (specific terms as well as system organ class terms) and laboratory values that met predefined limits of change (PDLC) with incidence ≥1% in any treatment groups were classified as Tier-2 events. These analyses were performed using Miettinen and Nurminen method, an unconditional, asymptotic method.
Analysis population and time point description	The primary analyses of safety were based upon the All Subjects as Treated approach which included all randomized subjects who received one dose of study medication.
Summary	Raltegravir 1200 mg QD had similar overall clinical and laboratory AE profiles to raltegravir 400 mg BID. The frequencies of clinical AEs, drug-related clinical AEs, serious clinical AEs, drug-related serious clinical AEs, and clinical AEs were similar between the two treatment groups. Similar findings were noted for laboratory AEs. AE and laboratory abnormality profiles were generally similar regardless of age, gender, race, geographic region, hepatitis co-infection, or PPI/H2 blocker use.

Analysis of Adverse Event Summary
Clinical Adverse Events
Weeks 0-48

	Raltegravir 1200 mg QD		Raltegravir 400 mg BID		Difference in % vs Raltegravir 400 mg BID
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	531		266		
with one or more adverse events	439	(82.7)	231	(86.8)	-4.2 (-9.2, 1.3)
with no adverse events	92	(17.3)	35	(13.2)	4.2 (-1.3, 9.2)
with drug-related[‡] adverse events	130	(24.5)	68	(25.6)	-1.1 (-7.6, 5.1)
with serious adverse events	31	(5.8)	25	(9.4)	-3.6 (-8.0, 0.2)
with serious drug-related adverse events	1	(0.2)	2	(0.8)	-0.6 (-2.5, 0.4)
who died	2	(0.4)	1	(0.4)	0.0 (-1.7, 1.0)
discontinued[§] due to an adverse event	4	(0.8)	6	(2.3)	-1.5 (-4.1, 0.1)
discontinued due to a drug-related adverse event	0	(0.0)	2	(0.8)	-0.8 (-2.7, -0.0)
discontinued due to a serious adverse event	3	(0.6)	2	(0.8)	-0.2 (-2.2, 1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

Data Source: [16.4]

Analysis of Adverse Event Summary
Laboratory Adverse Events
Weeks 0-48

	Raltegravir 1200 mg QD		Raltegravir 400 mg BID		Difference in % vs Raltegravir 400 mg BID
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	531		266		
with one or more adverse events	37	(7.0)	30	(11.3)	-4.3 (-9.1, -0.2)
with no adverse events	494	(93.0)	236	(88.7)	4.3 (0.2, 9.1)
with drug-related[‡] adverse events	8	(1.5)	4	(1.5)	0.0 (-2.4, 1.7)
with serious adverse events	2	(0.4)	0	(0.0)	0.4 (-1.1, 1.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)
who died	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)
discontinued[§] due to an adverse event	2	(0.4)	0	(0.0)	0.4 (-1.1, 1.4)
discontinued due to a drug-related adverse event	2	(0.4)	0	(0.0)	0.4 (-1.1, 1.4)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

Data Source: [16.4]

Analysis description	**Safety analysis**: Predefined Limits of Change (PDLC) All laboratory values were assessed per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Criteria).
Summary	In general, the laboratory abnormalities were uncommon, not of clinical significance, and occurred at similar frequencies in both treatment groups.

CONCLUSIONS:	**Efficacy** Raltegravir 1200 mg QD has potent and durable efficacy comparable to raltegravir 400 mg BID in HIV-1 treatment-naïve subjects, each in combination with TRUVADA™. In particular, raltegravir 1200 mg QD: ▪ Has statistically non-inferior antiretroviral activity (HIV RNA <40 copies/mL) compared to raltegravir 400 mg BID at Week 48 with - similar rapid viral suppression, - similar potent efficacy, regardless of demographic or prognostic factors, including baseline RNA and CD4 count, - a low frequency of resistance to raltegravir, similar to the frequency observed with raltegravir BID. ▪ Has comparable and robust immunologic efficacy, as measured by increases at Week 48 from baseline CD4 cell counts. **PK** ▪ Based on the observed sparse concentration of raltegravir (collected up to treatment week 24), the geometric mean and corresponding 95% CI of C_{all}, C_{trough} and C_{min} after administration of multiple doses of 1200 mg QD were 963.52 nM (887.85, 1045.64) 122.08 nM (109.97, 135.53), and 79 nM (71.28, 87.54), respectively. The values of PK exposure endpoints, particularly C_{trough} and C_{min}, of raltegravir 400 mg BID observed in this study were generally consistent with those previously observed in the raltegravir BID development program. ▪ No clinically significant association was found between PK exposures and the primary and secondary efficacy endpoints (HIV RNA <40 copies/mL and change in baseline CD4 cell counts) for raltegravir data from PN292. Maximum response was likely achieved across the PK exposure range for both raltegravir 1200 mg QD and raltegravir 400 mg BID treatment regimens. ▪ Overall, the concentrations of raltegravir achieved in raltegravir 1200 mg QD result in highly effective and well-tolerated raltegravir once-daily treatment among HIV treatment-naïve patients.

	Safety ▪ Raltegravir 1200 mg QD has a favorable safety profile, with a safety profile similar to that of raltegravir 400 mg BID in HIV-1 treatment-naïve subjects in this study, and consistent with the established safety profile of ISENTRESS® BID. There are no new safety concerns for the raltegravir 1200 mg QD regimen. ▪ The most frequently reported (incidence >2%) drug-related AEs in either group (shown as % for QD, % for BID) were nausea (7.3%, 6.8%), headache (3.0%, 4.5%), and dizziness (2.3%, 3.0%). ▪ No deaths were considered related to study drug, and serious drug-related AEs and AEs leading to discontinuation were rare. ▪ The rates of treatment-emergent laboratory abnormalities are low and generally similar for raltegravir 1200 mg QD and raltegravir 400 mg BID. ▪ Both raltegravir 1200 mg QD and raltegravir 400 mg BID have favorable safety profiles in key baseline demographic or prognostic groups. ▪ Exploratory safety analysis based on PK exposure quartiles ($AUC_{0\text{-}24h}$ and C_{max}) confirmed the lack of any potential increased risks associated with the highest exposures from the raltegravir 1200 mg QD regimen. Additionally, the safety profile of raltegravir 1200 mg QD is comparable among subjects in the lowest and highest PK quartiles.
REPORT DATE:	[redacted]-20[redacted]