CTD 第 2 部

2.7　臨床概要

2.7.6　個々の試験のまとめ

MSD 株式会社

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Table of all Clinical Trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	MK-1439-037-01 [Ref. 5.3.1.1: P037]	p037.pdf [5.3.1.1 - Bioavailability (BA) Study Reports]	Determine bioavailability of a new (generic) drug product under fasted and fed conditions	Randomized, open-label, 2-period, 2-treatment, crossover	One Tablet, MK-1439 100 mg, Oral	14 (14 completed)	Healthy Subjects	Single-dose	Complete; Full Report

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Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
P044 [Ref. 5.3.1.1: P044]	1	USA	A Study of the Pharmacokinetics of the Intravenous Microdose Formulation of MK-1439 in Healthy Adults	Single-dose, single-period, open-label pharmacokinetic study	MK-1439: single intravenous (IV) 100 µg dose, administered via infusion syringe over a period of 15 minutes.	Males/females Age: 18-55 years Healthy subjects	100 µg of MK-1439

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
Protocol # (P029-00) [Ref. 5.3.1.1: P029]	I	CAN	A Study of the Comparative Fed and Fasted Bioavailability of MK-1439A in Healthy Subjects Type of Trial: BE, Safety Indication: Indication: Treatment of human immunodeficiency virus type 1 (HIV-1) infection	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative fed and fasted bioavailability study	A: MK-1439A 100 mg/300 mg/300 mg Tablets; po (fed) B: MK-1439A 100 mg/300 mg/300 mg Tablets; po (fasted)	Males and Females Age: 18-65 years	A: MK-1439A 100 mg/300 mg/300 mg: 14, open-label B: 100 mg/300 mg/300 mg: 13, open-label

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	MK-1439-PN039 [Ref. 5.3.1.2: P039]	5.3.1.2 Biocomparison/Bioequivalence Studies p039.pdf	Determine bioequivalence between a new drug product and its after-market image under fasting conditions	Crossover	One Uncoated Tablet, MK-1439 100 mg, Oral	24 (24 completed)	Healthy Subjects	Single-dose	Complete; Full Report

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
MK-1439-043 [Ref. 5.3.1.2: P043]	I	USA	A Study to Evaluate the Comparative Bioavailability of the Investigational Oral Pediatric Minitablet Formulation of MK- 1439 Compared to the Adult Formulation of MK-1439 in Healthy Adult Subjects	Open-Label, Single-Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Crossover Study (Fasted)	Treatment A: Single oral dose of MK-1439 100 mg Tablets Treatment B: 125 x MK-1439 0.8 mg [equivalent to 100 mg MK-1439 tablet] Oral Pediatric Formulation Minitablets	Healthy Adult Males/females Age: 24 - 53	24

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-049-00 *(P049)* [Ref. 5.3.1.2: P 049MK1439]	*I*	*USA*	A study of the Comparative Bioavailability of the Investigational Pediatric Oral Granules Formulation of MK-1439 Compared to the Adult Formulation under Fed and Fasted Conditions	*Open-label, single-dose, partially randomized, three-period, four-treatment, four-sequence, crossover, comparative bioavailability study*	A: 100 mg MK-1439 (1 adult tablet); po, administered under fasted conditions. B: 100 mg MK-1439 (125 x 0.8 mg oral pediatric granules); po, administered under fasted conditions. C: 125 mg MK-1439 (156 x 0.8 mg oral pediatric granules); po, administered in with vanilla yogurt under fasted conditions after an overnight fast. D: 100 mg MK-1439 (125 x 0.8 mg oral pediatric granules); po, administered with vanilla pudding after an overnight fast in vanilla pudding under fasted conditions.	*Males/Females* *Age: 22-53 years*	*ABC/BAC: 325 mg MK-1430 (12)* *ABD/BAD: 300 mg MK-1439 (12)*

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
Protocol # (P052-00) [Ref. 5.3.1.2: P052MK1439]	I	CAN	A Study of the Comparative Bioavailability of Two Second-Generation Investigational Pediatric Oral Granule Formulations of MK-1439 Compared to the Adult Formulation Type of Trial: BE, Safety Indication: Treatment of human immunodeficiency virus type 1 (HIV-1) infection	Open-label, single-dose, partially randomized, five-period, seven-treatment, six-sequence, crossover, comparative bioavailability study	A: 1 x 100 mg MK-1439 adult tablet; po (fasting) B: 125 x 0.8 mg MK-1439 pediatric uncoated granules; po (fasting) C: 125 x 0.8 mg MK-1439; po (fasting) W: 125 x 0.8 mg MK-1439 pediatric uncoated granules; po (administered with vanilla pudding) X: 125 x 0.8 mg MK-1439 pediatric uncoated granules; po (administered with apple sauce) Y: 125 x 0.8 mg MK-1439 pediatric coated granules; po (administered with vanilla pudding) Z: 125 x 0.8 mg MK-1439 pediatric coated granules; po (administered with apple sauce)	Gender: Males/Females Age: 18-55 years Indication: Treatment of HIV-1 infection	A: MK-1439 100 mg: 23, open label B: MK-1439 100 mg: 24, open label C: MK-1439 100 mg: 24, open label W: MK-1439 100 mg: 12, open label X: MK-1439 100 mg: 12, open label Y: MK-1439 100 mg: 10, open label Z: MK-1439 100 mg: 11, open label

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
Protocol # (P014-00) [Ref. 5.3.1.2: P014]	I	CAN	A Fasted Bioavailability Study of Two Probe MK-1439A Formulations in Healthy Subjects Type of Trial: BE, Safety Indication: Indication: Treatment of human immunodeficiency virus type 1 (HIV-1) infection	Open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover, comparative fasted bioavailability study	A: MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets; po (fasted) B: MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets; po (fasted) C: MK-1439 100 mg Oral Compressed Tablets co-administered with Epivir® 300 mg Tablets and Viread® 300 mg Tablets; po (fasted)	Males and Females Age: 18-55 years	A: MK-1439A 50 mg/150 mg/150 mg: 24, open-label B: MK-1439A 100 mg/300 mg/300 mg: 24, open-label C: MK-1439 100 mg, Epivir® 300 mg,Viread® 300 mg: 23, open-label

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
Protocol # (P015-00) [Ref. 5.3.1.2: P015]	I	CAN	A Fasted Bioavailability Study of a Probe MK-1439A Formulation in Healthy Subjects Type of Trial: BA, Safety Indication: Indication: Treatment of human immunodeficiency virus type 1 (HIV-1) infection	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative fasted bioavailability study	A: MK-1439A 100 mg/300 mg/300 mg Tablets; po (fasted) C: MK-1439 100 mg Oral Tablets co-administered with Epivir® 300 mg Tablets and Viread® 300 mg Tablets; po (fasted)	Males and Females Age: 18-55 years	A: MK-1439A 100 mg/300 mg/300 mg: 24, open-label C: MK-1439 100 mg, Epivir® 300 mg,Viread® 300 mg: 24, open-label

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	026-00 [Ref. 5.3.1.2: P026]	026-00.pdf	Determine bioequivalence between a new (generic) drug product and a marketed reference product under fasted conditions	Crossover	One Tablet, 100 mg/300 mg/300 mg, Oral	24 (24 completed)	Healthy Subjects	Single-dose	Complete; Full Report

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
MK-1439-034 [Ref. 5.3.1.2: P034]	*I*	*USA*	*An Open-Label, Single-Dose, Fixed-Sequence Study to Evaluate the Comparative Bioavailability of Two Nanoparticle Formulations of MK-1439 to the Current Market Image Tablet*	*Open-label, 3-period, fixed-sequence, single-dose trial*	Large nanoparticles: A single oral dose of 100 mg MK-1439 as large nanoparticles (LN) in an on-site formulation suspension (4 mL of 25 mg/mL) on Day 1 of Period 1 Small Nanoparticles: A single oral dose of 100 mg MK-1439 as small nanoparticles (SN) in an on-site formulation suspension (4 mL of 25mg/mL) on Day 1 of Period 2. Market Image Tablet: A single oral dose of 100 mg MK-1439 as a market image tablet (MIT) (1 x 100 mg tablet) on Day 1 of Period 3	*Healthy Adult Males/females Age: 21-51*	*MK-1439 LN: 18* *MK-1439 SN: 18* *MK-1439 MIT: 17*

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
P046 [Ref. 5.3.1.2: P 046MK1439]	I	UK	A Rapid Pharmacokinetic Trial of the Bioavailability of Four MK-1439 Nano Formulations in Healthy Adults	Single center, open-label, 5-period, fixed sequence	Single dose: **Period 1:** • MK-1439 nanoparticle formulation Type 1 dose (150 mg tablet [[redacted] % drug loaded [redacted]]) **Period 2:** • MK-1439 100 mg film coated tablet **Period 3:** • MK-1439 nanoparticle formulation Type 2 dose (150 mg tablet [[redacted] % drug loaded [redacted]]) **Period 4:** • MK-1439 nanoparticle formulation Type 3 dose (150 mg tablet [[redacted] % drug loaded [redacted]]) **Period 5:** • MK-1439 nanoparticle formulation Type 4 dose (100 mg tablet [[redacted] % drug loaded [redacted]])	Healthy male/female subjects between the ages of 18 and 55 years (inclusive)	Period 1: N = 16 Period 2: N = 16 Period 3: N = 16 Period 4: N = 16 Period 5: N = 16

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-001 [Ref. 5.3.3.1: P001V01]	I	Belgium	A Single and Multiple Dose Study to Evaluate the Safety and Pharmacokinetics of Doravirine (MK-1439) and to Evaluate the Effect of Multiple Doses of Doravirine on Midazolam	This was a three-part, double-blind, randomized, placebo-controlled study Part I: alternating-panel, single-rising-dose. Panel A and B. 14 weeks Part II: serial-panel, rising-multiple-dose Panels C, D and F: 8 weeks Part III: fixed-sequence, 4-period study. Panle G. 14 weeks	Part I: Two alternating panels, Panels A and B, subjects were randomized to receive rising single oral dose of doravirine (n=6) or matching placebo (n=2) in up to 5 (Panel A) and 4 (Panel B) treatment periods. The doses for Panel A were, 6-, 25-, 100-, 300-, and 450-mg dosed in the fasted state. The doses for Panel B were 12-, 50-, and 150-mg dosed in the fasted state and 50 mg dosed with food. At least 3 days elapsed between administrations at each dose level. Within each panel, the washout between study drug administration in Periods 1 and 2 was at least 7 days, and at least 14 days between subsequent doses. Part II: Four serial rising-dose panels Subjects in Panels C, D, and F were randomized to receive rising multiple-doses of doravirine (n=6) or matching placebo (n=2) once-daily (QD) for 10 days. Subjects in Panel E received multiple-doses of doravirine (n=8) or matching placebo (n=2) QD for 14 days, and all subjects (n=10) received a single oral dose of 2.0 mg midazolam hydrochloride (HCL) syrup (2 mg/mL) on Days -1 and 13. .The doses for Panel C, D, E and F were 30-, 60-, 120-, and 240-mg, respectively. At least 3-days elapsed between panels._. Part III: One panel G, subjects were randomized to receive single oral dose of doravirine (n=6) or matching placebo (n=2) in up to 4 periods. Subjects randomized to receive matching placebo received placebo in all 4 periods. Period 1, subjects received a single 50 mg dose of the tablet formulation in the fasted state. Periods 2 and 3, subjects received single 50 mg doses of the capsule formulation in the fasted and fed states, respectively. In Period 4, subjects received a single dose of 300 mg of doravirine as the capsule formulation in the fasted state. For each subject, there was at least a 2-week washout between study drug administrations in each period	Males Ages: 18 to 50 years	Part I 6 mg doravirine: 6 12 mg doravirine: 6 25 mg doravirine: 6 50 mg doravirine: 6 100 mg doravirine: 6 150 mg doravirine: 6 300 mg doravirine: 6 450 mg doravirine: 6 Part II 30 mg doravirine QD: 6 60 mg doravirine QD: 6 120 mg doravirine QD: 8 240 mg doravirine QD: 6 2 mg midazolam: 10 Part III 50 mg doravirine: 6 300 mg doravirine: 6

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
1439-006 [Ref. 5.3.3.1: P 006MK1439]	I	Europe	A Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Doravirine (MK-1439)	Double-blind, randomized, placebo-controlled, single-rising and multiple dose study	Panel A Period 1: single oral dose of doravirine 600 mg or matching placebo Period 2: single oral dose of doravirine 800 mg or matching placebo Period 3: multiple, once daily oral doses of doravirine 450 mg or matching placebo for 10 days Panel B Period 1: single oral dose of doravirine 1000 mg or matching placebo Period 2: single oral dose of doravirine 1200 mg or matching placebo Period 3: multiple, once daily oral doses of doravirine 750 mg or matching placebo for 10 days	Healthy male subjects, 18 to 50 years of age	Doravirine: 16 subjects

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
Drug: MK-1439 Protocol 008 [Ref. 5.3.3.1: P008]	I	USA	A Study to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of MK 1439	Open-label, Single-dose, ADME study. 23 days.	Single oral dose of 351 mg (~211 µCi) dose of [^{14}C]MK-1439. Actual doses ranged from 349 mg – 353 mg [210 - 212 µCi] [^{14}C]MK-1439.	Males Age: 23-42 Healthy, non-smoking volunteers	[^{14}C]MK-1439:6

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
Protocol # (P031-03) [Ref. 5.3.3.1: P031MK1439]	I	CAN	A Single-Dose, Parallel, Pharmacokinetic, Safety and Tolerability Study of MK-1439 Long Acting Parenteral (LAP) Intramuscular Injections Type of Trial: PK, Safety, Tolerability Indication: human immunodeficiency virus type 1 (HIV-1) infection	**Part 1:** open-label, non-randomized, multiple-dose, single-period, single-treatment safety study **Part 2:** open-label, randomized, single-dose, single-period, three-treatment, parallel PK, safety, tolerability study	**Part 1:** MK-1439 100 mg Tablet; po; QD for 14 days **Part 2:** A: 200 mg MK-1439 (one 1 mL [20% suspension] IM injection) administered in the deltoid muscle; or B: 200 mg MK-1439 (one 0.66 mL [30% suspension] IM injection) administered in the deltoid muscle; or C: 200 mg MK-1439 (two 0.5 mL [20% suspension] IM injections) administered in the deltoid muscles (one injection of 100 mg to each deltoid muscle).	Healthy Males/Females Age: 18-65 years Indication: human immunodeficiency virus type 1 (HIV-1) infection	**Part 1:** 1400 mg MK-1439 QD for 14 days: 41 subjects 700 mg MK-1439 QD for 7 days: 1 subject **Part 2**: A: 200 mg MK-1439: 12 subjects B: 200 mg MK-1439: 12 subjects C: 200 mg MK-1439: 12 subjects

Type of the Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)	Test Product Dose Regimen Route of Administration	No of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Bioavailability	MK-1439-009 [Ref. 5.3.3.3: P009]	Module 5.3.3.3 - Intrinsic Factor PK Study Reports	To assess the relative bioavailability of MK-1439 between healthy elderly male and female subjects and to assess the safety and tolerability of MK-1439 after administration of a single 100 mg dose of MK-1439 to healthy elderly male and female subjects and young adult female subjects	An Open-Label, One-Period, Parallel-Group Study in Healthy Elderly Male and Female Subjects	MK-1439 as a 100 mg tablet, Formulation No. [redacted], Control No. [redacted]	MK-1439 was administered as a single oral dose 100 mg tablet with 240 mL of water after fasting overnight for at least 8 hrs.	Total: 36 subjects 12 per group (Gp1: 12 elderly male, Gp2: 12 elderly female, Gp3: 12 young female) completed all the periods) (12M/24F) Healthy subjects mean ages: 70.5 yrs for Grp 1-elderly males; 70.4 yrs for Grp 2 elderly females; 33.3 yrs for Gp 3 young female	Healthy, adult, subjects	single oral dose

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-019 [Ref. 5.3.3.3: P019]	I	USA	A 2-Part, Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of MK-1439	Non-randomized, 2-part, single-dose, open-label Hepatic Insufficiency Subjects: 7 weeks. Healthy Matched Control Subjects: 6 weeks	Part 1 Single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on the morning of Day 1, at Hour 0. Part 2 was not initiated.	Moderate Hepatic Males and Females Healthy Matched Control Males and Females Age 44-64 years	MK-1439 100 mg: 16

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
1439-051 [Ref. 5.3.3.3: P 051MK1439]	*1*	*USA*	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-1439 (Doravirine) in Subjects With Severe Renal Impairment	Pharmacokinetic, safety, tolerability, parallel assignment, open-label treatment *6 weeks*	On Day 1 at Hour 0, all subjects received a single oral dose of 100 mg (1 x 100 mg coated tablet) doravirine following an overnight fast.	*Male and female subjects with severe renal impairment: 8* Age: 51 - 69 *Healthy mean age- and weight-matched male and female control subjects: 8* *Age: 52 – 69*	100 mg doravirine: 16

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-002 [Ref. 5.3.3.4: P002MK1439]	I	Belgium	A Study to Evaluate the Effect of Multiple Doses of Ritonavir on the Single Dose Pharmacokinetics of Doravirine (MK-1439)	Open-label, fixed-sequence, 2-period study 10 weeks	Period 1: 50 mg doravirine single dose Day 1, Period 2: 100 mg b.i.d. ritonavir Days 1 – 20 and 50 mg doravirine single dose on Day 14	Males Age: 21-46 years	8 subjects

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439 P003 [Ref. 5.3.3.4: P003]	1	USA	A Study to Evaluate the Effect of Multiple Doses of Tenofovir on the Single-Dose Pharmacokinetics of MK-1439	Open-label, 2-period, fixed-sequence study in eight young healthy male subjects. The duration of the study was approximately 9 weeks per subject.	Period 1: Single oral dose of 100 mg MK-1439 Period 2: 300 mg tenofovir disoproxil fumarate (TDF) for 18 days with coadminstration of a single dose of 100 mg MK-1439 on Day 14.	Males Age: 18-65 years	8 subjects

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range (yrs)	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.3.4: P010]	[redacted] (P010)	Open-label, 2-period, fixed-sequence	8	2	22 to 50 48 to 49	Ten healthy, adult, non-tobacco using adult male and female (weighing at least 52 kg) and female (weighing at least 45 kg) subjects between 19 and 50 years of age (inclusive) with a body mass index between 18.5 and 32.0 kg/m^2 (inclusive) were enrolled in the study.	In Treatment A (Period 1), subjects received a single oral dose of 100 mg MK-1439 on Day 1. In Treatment B (Period 2), subjects received oral doses of 400 mg ketoconazole once daily (QD) for 10 days, with co-administration of a single oral dose of 100 mg MK-1439 on Day 2. There were 7 days between Period 1 dosing and the first dose of ketoconazole in Period 2. The total duration of the study (from screening to follow-up) was approximately 6 weeks.	Pharmacokinetics: Blood samples for determination of MK-1439 concentrations were collected at predose and at specified time points over 72 hours following MK-1439 dosing in Period 1 and over 216 hours following MK-1439 dosing in Period 2. The plasma pharmacokinetic parameters calculated were: AUC0-∞, Cmax, C24, CL/F, Tmax, and apparent terminal t½. Safety: Physical examinations, vital signs, electrocardiograms, and laboratory safety evaluations were obtained prestudy and at pre-specified time points along with monitoring for adverse events throughout the study.	• Administration of multiple doses of ketoconazole 400 mg with a single 100 mg dose of MK-1439 increases the plasma AUC0-∞ of MK-1439 by approximately 3-fold. The MK-1439 AUC0-∞ geometric mean ratio (MK-1439 + ketoconazole/MK-1439 alone) and 90% confidence interval are 3.06 (2.85, 3.29). • Single oral doses of MK-1439 were generally well tolerated when administered alone or with multiple oral doses of ketoconazole in the healthy males and females in this study.

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
Drug: MK-1439 Protocol 011-00 [Ref. 5.3.3.4: P011V01]	I	USA	A Study to Assess the Effects of Single and Multiple Doses of Rifampin on the Single-Dose Pharmacokinetics of MK-1439 in Healthy Adult Subjects.	Open-label, 2-period, fixed-sequence study. 12 weeks.	Period 1 Single oral dose of 100 mg MK-1439. Period 2 Single oral dose of 600 mg rifampin co-administered with a single oral dose of 100 mg MK-1439 on Day 1, followed by multiple oral once-daily (QD) doses of 600 mg rifampin for 15 days (Day 4 to Day 18), and co-administered with a single oral dose of 100 mg MK-1439 on Day 17. There was a washout of at least 7 days between dosing in Period 1 and the first dose in Period 2.	Males Age: 22-52 Antiviral treatment for HIV-1 infection	Period 1 MK-1439: 100 mg: in healthy subjects: 11 Period 2 MK-1439: 100 mg + SD rifampin: 600 mg in healthy subjects: 11 MK-1439: 100 mg + MD rifampin: 600 mg in healthy subjects: 10

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range (yrs)	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.3.4: P012]	[redacted] (012)	Open-label, 2-period, fixed-sequence study	NA	20	NA 42 to 65	Twenty (20) healthy, non-smoking adult oophorectomized or postmenopausal females ≥ 18 and ≤ 65 years of age, weighing a minimum of 45 kg and having a BMI ≥ 18.5 and ≤ 32.0 kg/m^2 at the prestudy visit were enrolled in the study.	**In Period 1 (Treatment A), subjects received a single oral dose of 0.03 mg EE/0.15 mg LNG (Nordette®-28) on Day 1. In Period 2 (Treatment B), subjects received multiple oral doses of 100 mg MK-1439 QD for 17 consecutive days, with a single oral dose of 0.03 mg EE/0.15 mg LNG (Nordette®-28) co-administered with MK-1439 on Day 14. There was a washout of at least 7 days between dosing in Period 1 and the first dose in Period 2.**	PK: Blood samples for determination of plasma EE and LNG were obtained at predose and specified time points for 96 hrs postdose in Period 1 following a single oral dose of **Nordette®-28** alone on Day 1. Blood samples for the determination of plasma EE and LNG following multiple oral doses of 100 mg MK-1439 QD for 17 days with a single dose of **Nordette®-28** co-administered on Day 14 were obtained at predose and specified time points for 96 hrs postdose in Period 2. **The plasma pharmacokinetic parameters (AUC0-∞, AUC0-last, Cmax, Tmax, and the apparent terminal t½) of** EE and LNG were calculated following a single oral dose of **Nordette®-28** alone on Day 1 in Period 1 and following multiple oral doses of MK-1439 for 17 days with a single dose of **Nordette®-28** co-administered on Day 14 in Period 2. Safety: Physical exams, vital signs, 12-lead ECGs, and lab safety tests were obtained at prestudy, predose, and at specified time points along with monitoring for adverse experiences throughout the study.	(1) Multiple-dose administration of MK-1439 does not substantially alter the single-dose plasma AUC0-∞ and Cmax of EE after co-administration of Nordette®-28. (2) Multiple-dose administration of MK-1439 increases the single-dose plasma AUC0-∞ of LNG by 21% after co-administration of Nordette®-28, but does not substantially alter the Cmax. (3) The concomitant administration of multiple 100 mg oral doses of MK-1439 with a single oral dose of an oral contraceptive (0.03 mg EE/0.15 mg LNG) is generally well-tolerated in healthy female subjects.

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-016-00 [Ref. 5.3.3.4: P016]	I	USA	A 2-way Steady State Interaction Study of MK-1439 and Dolutegravir	Open-label, 3 period, fixed sequence	**Period 1:** 50 mg dolutegravir once daily for 7 days **Period 2:** 200 mg MK-1439 once daily for 7 days **Period 3:** 50 mg dolutegravir + 200 mg MK 1439 once daily for 7 days	Males/females Age: 18-45 (inclusive) years	**Period 1:** 12 subjects received 50 mg dolutegravir once daily for 7 days, per protocol, 1 subject discontinued after Period 1 **Period 2:** 11 subjects received 200 mg MK-1439 once daily for 7 days **Period 3:** 11 subjects received 50 mg dolutegravir + 200 mg MK-1439 once daily for 7 days

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-020 [Ref. 5.3.3.4: P020]	I	USA	An Open-label, Multiple-Dose Study to Investigate the Effect of Switching From Efavirenz Therapy to MK-1439 on the Pharmacokinetics of MK-1439	open-label, 3-period, fixed-sequence, multiple-dose Approximately 9 weeks	Period 1 Multiple oral doses of 100 mg MK-1439 QD from Days 1 to 5. Period 2 Multiple oral doses of 600 mg efavirenz (1 x 600 mg tablet) QD from Days 1 to 14. Period 3 Multiple oral doses of 100 mg MK-1439 (1 x 100 mg tablet) QD from Days 1 to 14.	Males and Females Age: 21-53	100 mg MK 1439: 20 600 mg efavirenz: 19

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
20[redacted]-3732 [Ref. 5.3.3.4: P035]	I	USA	A Study to Evaluate the Effect of Multiple Doses of Rifabutin on the Single-Dose Pharmacokinetics of Doravirine (MK-1439) in Healthy Subjects	This was an open-label, single- and multiple-dose, two-period, two-treatment, fixed-sequence, PK drug interaction study.	A: Doravirine (MK-1439) 100 mg Tablet; po B: Doravirine (MK-1439) 100 mg Tablet (Day 14) and Mycobutin® (rifabutin) 300 mg Capsules (Day 1-16); po	Males/Females Age: 18-65 years	A: MK-1439 100 mg: 100 mg – 18 subjects B: Doravirine: 100 mg: 100 mg and Rifabutin: 300 mg: 4800 mg – 18 subjects

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
DDI	MK-1439-036-00 [Ref. 5.3.3.4: P036]	p036.pdf	Primary Objective: To evaluate the effect of MK-1439 100 mg tablets at steady-state on the pharmacokinetics of atorvastatin after a single-dose (C_{max}, AUC_{0-inf}) in healthy subjects. Secondary Objective: To evaluate the safety and tolerability of atorvastatin when administered alone and when co-administered with MK-1439 100 mg tablets in healthy subjects.	Open-label, two-period, two-treatment, fixed-sequence	MK-1439: One Tablet, 100 mg, Oral, Once daily from Days 1 to 8 in Period 2. Atorvastatin: One Tablet, 20 mg, Oral, Once on Day 1 in Period 1 and once on Day 5 in Period 2	16 (14 completed)	Healthy Subjects	Single-dose and Multiple-dose	Complete; Full Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	038-01 [Ref. 5.3.3.4: P038V01]	p038.pdf [5.3.3.4 Extrinsic Factor PK Study Reports]	Determine comparative bioavailability between a new (generic) drug product and marketed reference products under fasting conditions	Crossover	One Tablet, MK-1439 100 mg, Oral	15 (15 completed)	Healthy Subjects	Single-dose	Complete; Full Report

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-042-01 [Ref. 5.3.3.4: P042]	I (DDI)	USA	A Study to Evaluate the Effect of an Aluminum- and Magnesium-Containing Antacid and a Proton-Pump Inhibitor on the Single-Dose Pharmacokinetics of Doravirine (MK-1439) in Healthy Subjects	Open-label, single-dose and multiple-dose, three-period, three-treatment, fixed-sequence, pharmacokinetic drug interaction study	A: 100 mg MK-1439; po B: 100 mg MK-1439; po + 20 mL antacid oral suspension containing 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone; po C: 40 mg pantoprazole sodium od on Days 1 to 4; po 100 mg MK-1439; po + 40 mg pantoprazole sodium on Day 5; po	Males/Females Age: 18-65 years	A: MK-1439 100 mg: 14 B: MK-1439 100 mg + 20 mL antacid oral suspension: 14 C: : Pantoprazole 40 mg x 5 days + MK-1439 100 mg: 13

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
1439-045 [Ref. 5.3.3.4: P045]	I	USA	A Multiple-Dose Clinical Trial to Study the Effect of MK-1439 (doravirine) on Methadone Pharmacokinetics	Open label, pharmacokinetic, safety, fixed-sequence, single-group assignment	Oral methadone once daily (QD) on Days 1-7 and oral MK-1439 mg QD on Days 2-6	Males/females Age: 18-65(20-59 actual) Healthy volunteers on a stable oral methadone maintenance therapy 20-200 mg (20-180 mg actual) QD.	MK-1439 100 mg: 14 Methadone 20-200 mg: 14

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-048-00 [Ref. 5.3.3.4: P048]	I	Canada	A Study to Evaluate the Effect of Multiple Doses of MK-1439 (Doravirine) on Metformin Pharmacokinetics in Healthy Subjects	This was a fixed-sequence, open-label, 2-period, pharmacokinetic study in healthy subjects.	A: 1000 mg Metformin Tablets; po B: 1000 mg Metformin Tablet on Day 5 / 100 mg MK-1439 QD for 7 days; po	Males/Females Age: 18-55 years	A: 1000 mg Metformin: 14 B: 700 mg MK-1439 & 1000 mg Metformin: 14

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
1439-050 [Ref. 5.3.3.4: P 050MK1439]	1	USA	Drug-Drug Interaction Study of MK-1439 (Doravirine) with MK-8742 + MK-5172 (Elbasvir + Grazoprevir)	Nonrandomized, fixed-sequence, single-site, open-label trial	100 mg doravirine was administered once daily (QD) on Days 1 to 5 of Period 1. A 50 mg dose of elbasvir and 200 mg dose of grazoprevir were co-administered QD on Days 1 to 10 of Period 2. Doses of 100 mg doravirine, 50 mg elbasvir, and 200 mg grazoprevir were co-administered QD on Days 1 to 5 of Period 3.	Males/females Age: 19-55	12 subjects

Trial ID	Phase	Country	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
1439-053 [Ref. 5.3.3.4: P053]	*1*	*USA*	A Randomized, Open-Label, 3-Period Crossover Study to Evaluate the Pharmacokinetic Interaction of MK-1439 (Doravirine) and Ledipasvir/Sofosbuvir in Healthy Adult Subjects	*Open-label, randomized, 3-period crossover Duration of the study from screening to follow-up was approximately 9 weeks*	Subjects (14) were randomized to receive 3 treatments over 3 periods: a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir, coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg doravirine, and a single oral dose of 100 mg doravirine. Periods were separated by a washout interval of 14 days.	Healthy male and female Age: 25 – 60	*90 mg ledipasvir: 14* *400 mg sofosbuvir: 14* *100 mg doravirine: 14*

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
1439-005 [Ref. 5.3.4.1: P005V01]	1	Germany	A Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiretroviral Activity of MK-1439 in HIV-1 Infected Patients	Double-blind, randomized, placebo-controlled, multiple-panel study	Doravirine: 25 mg tablet orally once daily for 7 days 200 mg tablet orally once daily for 7 days Matching placebo orally once daily for 7 days	HIV-1-infected male subjects Age: 24 to 45 years-of-age, inclusive	Doravirine: 25 mg: 6 200 mg: 6 Placebo: 6

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439-017-00 [Ref. 5.3.4.1: P017]	I	USA	A Single Dose Trial to Assess the Effect of MK-1439 on QTc Interval in Healthy Adult Volunteers	Single center, randomized, 3-period, 6-sequence, crossover, placebo-controlled and double-blinded trial with respect to MK-1439, and open-label with respect to moxifloxacin	**Period A:** Single dose 1200 mg oral MK-1439 (supra-therapeutic dose) **Period B:** Single dose 400 mg oral moxifloxacin **Period C:** Single dose matching oral placebo for MK-1439	Males/females Age: 18-55 (inclusive) years	**Period A:** 41 subjects received single dose 1200 mg oral MK-1439 (supra-therapeutic dose) **Period B:** 41 subjects received single dose 400 mg oral moxifloxacin **Period C:** 39 subjects received single dose matching oral placebo for MK-1439

Trial ID	Phase	Region (Country)	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439 [Ref. 5.3.5.1: P 007MK1439]	2b	N. America (USA including Puerto Rico, Canada); Oceania (Australia); Europe (Belgium, France, Germany, Netherlands, Poland, Romania, Russia, Spain)	Multicenter, Double-Blind, Randomized, 2-Part, Dose Ranging Study to Compare the Safety, and Antiretroviral Activity of MK-1439 Plus TRUVADA™ Versus Efavirenz Plus TRUVADA™ in Antiretroviral Treatment-Naïve, HIV-1 Infected Patients	Efficacy, safety, tolerability, pharmacokinetics, dose response, parallel assignment, double-blind, active comparator treatment study	Part I Doravirine: 25, 50, 100, or 200 mg po QD + TRUVADA™ po QD; or Efavirenz: 600 mg po QD + TRUVADA™ po QD for at least 24 weeks After dose selection of 100 mg doravirine based on 24 week data, all subjects randomized to any dose of doravirine in Part I received doravirine 100 mg po QD + TRUVADA™ for the remainder of the 96 week study Part II Doravirine 100 mg po QD + TRUVADA™ po QD; or Efavirenz: 600 mg po QD + TRUVADA™ po QD for a total of 96 weeks of treatment for all subjects enrolled in Part II	Males/females Age: 19-69 HIV-1 infected subjects	Part I/II Combined Doravirine 25 mg: 40 Doravirine 50 mg: 43 Doravirine 100 mg: 108 Doravirine 200 mg: 41 Efavirenz 600 mg: 108 TRUVADA™: 340 Note: Subjects in Part I randomized to Doravirine 25, 50, and 200 mg were switched to Doravirine 100 mg between Week 36 and Week 72

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439 [Ref. 5.3.5.1: P018V01MK 1439]	3	United States Argentina; Australia; Austria; Canada; Chile; Denmark; France; Germany; Italy; Romania; Russia; South Africa; Spain; United Kingdom	A Phase 3 Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Doravirine (MK-1439) 100 mg Once Daily Versus Darunavir 800 mg Once Daily Plus Ritonavir 100 mg Once Daily, Each in Combination with TRUVADA™ or EPZICOM™/ KIVEXA™, in Treatment-Naïve HIV-1 Infected Subjects	Multicenter, double-blind, randomized, active-comparator-controlled trial to evaluate the safety, efficacy, and pharmacokinetics of doravirine (DOR; MK-1439) compared with ritonavir-boosted darunavir (DRV+r), each given in combination with emtricitabine plus tenofovir disoproxil fumarate (FDC/TDF) (supplied as TRUVADA™) or abacavir plus lamivudine (ABC/3TC) (supplied as EPZICOM™ or KIVEXA™)	DOR single 100-mg oral compressed tablet administered QD for 96 weeks. Darunavir 800-mg tablet, in combination with ritonavir 100-mg tablet, administered QD for 96 weeks.	HIV–1-infected, treatment-naïve male and female adults ≥18 years of age	DOR 100 mg: 383 treated subjects (mean duration of exposure = 388 days) DRV+r (800 mg / 100 mg): 383 treated subjects (mean duration of exposure to both DRV and RTV = 379 days)

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-1439A [Ref. 5.3.5.1: P021V01MK 1439A]	3	United States; South Africa; Russia; United Kingdom; Peru; Germany; Taiwan; Thailand; Portugal; Canada; Chile; Guatemala; Spain; Belgium; Colombia; Puerto Rico; Switzerland; Mexico; Australia; Denmark; Israel; Honduras; and New Zealand.	Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects	Efficacy, safety, tolerability, pharmacokinetics, general health-related work productivity and activity impairement outcomes, randomized, double-blind, parallel-group, active-comparator-controlled study	DOR/3TC/TDF single oral tablet FDC containing DOR 100 mg, 3TC 300 mg, and TDF 300 mg, administered QD for 96 weeks. EFV/FTC/TDF is a single oral tablet FDC containing EFV 600 mg, FTC 200 mg, and TDF 300 mg (equivalent to 245 mg of tenofovir disoproxil), administered QD for 96 weeks.	Males/females Age: 18-≥ 65 Treatment- naïve HIV-1 infected subjects	Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg: 364 Doravirine 200 mg/lamivudine 600 mg/TDF 600 mg: 43 Efavirenz 600 mg/emtricitabine 200 mg/TDF 300 mg: 363 Efavirenz 1200 mg/emtricitabine 400 mg/TDF 600 mg: 54 Efavirenz 1800 mg/emtricitabine 600 mg/TDF 900 mg: 4

[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Title of Study:
A Study of the Comparative Fed and Fasted Bioavailability of MK-1439 in Healthy Subjects

Investigators:
[redacted] MD, PhD, FRCP(C)
MD, MSc, CCFP
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 I

Study Periods:
Period 1: December 12, 2014
Period 2: December 19, 2014

Objective:
The objective of this study was to evaluate the comparative bioavailability of:
- MK-1439 100 mg Tablets from Merck Sharp & Dohme Corp., USA under fasted and high-fat fed conditions.

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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Methodology:

- This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.
- This study was designed to evaluate the comparative bioavailability of MK-1439 100 mg tablets in healthy male and female subjects under fasted and high-fat fed conditions.
- Concentrations of MK-1439 were measured from the samples collected over a 72-hour interval after dosing in each period.
- The pharmacokinetic parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, C_{24}, $t_{½}$, CL/F, and V_d/F were estimated using a non-compartmental approach.

Number of subjects:

- Planned for inclusion: 14 subjects.
- Total number of subjects that completed the study: 14 subjects.
- Included in the safety dataset: 14 subjects.
- Included in the pharmacokinetic (PK) dataset: 14 subjects.
- Included in the statistical dataset: 14 subjects.

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 65 years of age, with a BMI from 19.0 to 33.0 kg/m^2, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements.

Study Drug Product (Treatment A and Treatment B):
MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Use by End Date: 02/2017
Dose: 100 mg
Mode of Administration: Oral under fasted (Treatment A) and high-fat fed (Treatment B) conditions

Duration of treatment:
Single-dose treatment

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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Safety Results:

		Pre-dose	Trt A	Trt B	Total
Severity	Mild	3	2	9	14
	Moderate	0	0	0	0
	Severe	0	0	0	0
Relationship to Study Drug	Definitely Related	0	0	0	0
	Probably Related	0	0	0	0
	Possibly Related	0	2	7	9
	Probably Not Related	0	0	0	0
	Definitely Not Related	3	0	2	5
Action Taken	Dose Increased	0	0	0	0
	Dose Not Changed	3	1	8	12
	Dose Reduced	0	0	0	0
	Drug Interrupted	0	0	0	0
	Drug Withdrawn	0	0	0	0
	Not Applicable	0	1	1	2
	Unknown	0	0	0	0

There were 14 adverse events (AEs) involving 5 subjects in the study. All AEs were judged to be mild in severity. There were 3 pre-dose AEs involving 2 subjects in the study. All pre-dose AEs were judged to be mild in severity. Action Taken was Not Applicable for two AEs since the time of onset occurred after the last available dosing of the study drug and no subsequent dosing was planned.

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.

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

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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Statistical Methods:

The PK parameters (C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$) for MK-1439 after administration of MK-1439 under fasted conditions and under high-fat fed conditions were estimated using a linear mixed-effects model appropriate for a 2-period crossover design. The endpoints C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$ were natural log-transformed prior to analysis and were analyzed with a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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).

A two-sided 90% confidence interval (CI) for the true mean difference (Fed – Fasted) for MK-1439 C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$ on the log scale was computed from the above linear-mixed effect model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (Fed/Fasted) for MK-1439 C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$. Ninety-five percent (95%) CIs were also generated from the above mixed-effects model for the geometric means (GMs) by treatment for MK-1439 C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$. Plots with the individual ratios, GMRs and 90% CIs were provided for MK-1439 C_{max}, $AUC_{0\text{-}inf}$, C_{24}, and $AUC_{0\text{-}last}$.

Individual values were listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) – 1), where s^2 is the observed variance on the natural log-scale).

Criteria for Evaluation:

The GMRs and their 90% confidence intervals of the MK-1439 $AUC_{0\text{-}inf}$ and C_{max} were used to assess the food effect on the bioavailability of the study drug product.

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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Results:

Pharmacokinetic Results:

Summary of Statistical Analysis Based on Plasma MK-1439 Levels

	FED: MK-1439 100 mg Tablets			*FASTED: MK-1439 100 mg Tablets*			*FED: MK-1439 100 mg Tablets / FASTED: MK-1439 100 mg Tablets*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	14	40.9	(33.7, 49.7)	14	35.4	(30.0, 41.7)	1.16	(1.06, 1.26)	12.8
$AUC_{0\text{-}last}$ (hr·µM)†	14	40.1	(33.2, 48.4)	14	34.0	(29.1, 39.7)	1.18	(1.08, 1.29)	13.5
C_{max} (nM)†	14	2010	(1740, 2310)	14	1940	(1670, 2260)	1.03	(0.89, 1.19)	21.3
C_{24hr} (nM)†	14	661	(520, 839)	14	487	(381, 622)	1.36	(1.19, 1.55)	19.4
T_{max} (hr)	14	4.00	(2.00, 12.00)	14	2.50	(1.00, 6.00)			
$t_{½}$ (hr)	14	11.75	18.6	14	14.35	31.0			
CL/F (L/hr)	14	5.74	32.1	14	6.63	31.7			
V_d/F (L)	14	97.3	22.5	14	137	32.6			

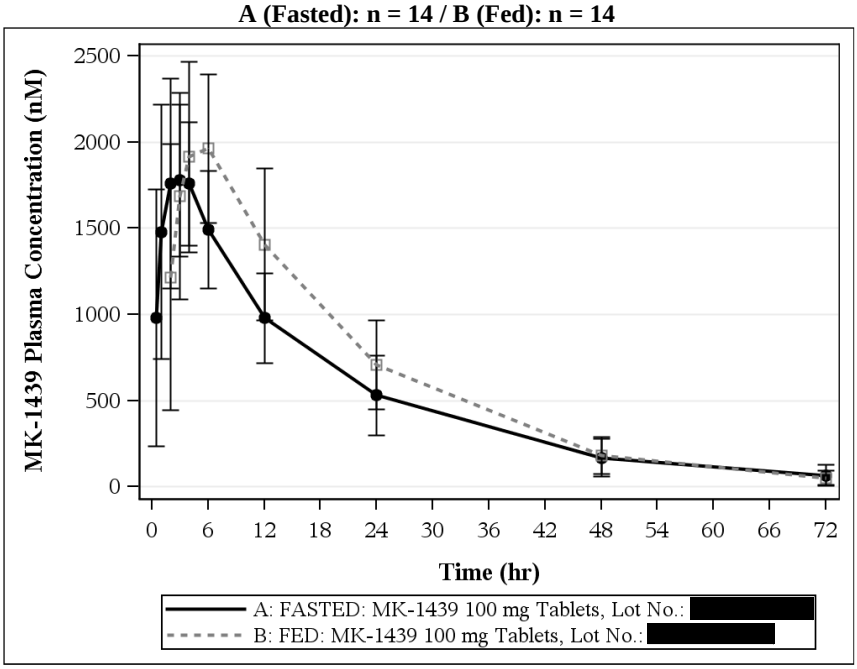
†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
‡ Estimated based on the elements of the variance-covariance matrix as:
$CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
Statistics for T_{max}: Median and Range (Minimum, Maximum)
*Statistics for $t_{½}$, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

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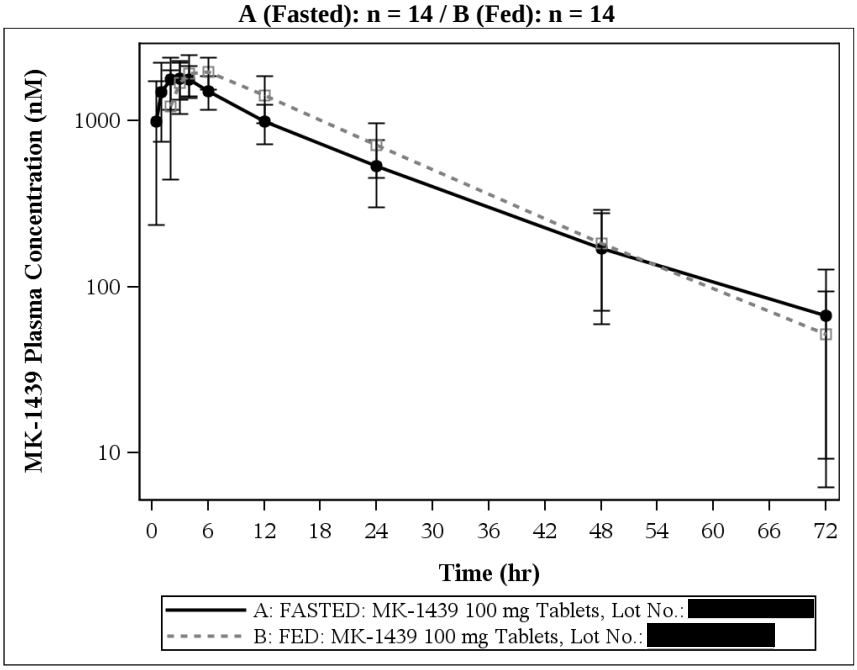
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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Mean (± SD) MK-1439 Plasma Concentration-Time Profiles (Linear Scale)
A (Fasted): n = 14 / B (Fed): n = 14



Mean (± SD) MK-1439 Plasma Concentration-Time Profiles (Semi-log Scale)
A (Fasted): n = 14 / B (Fed): n = 14



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[redacted] – Study Report
MK-1439 Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3707
Protocol Number: MK-1439-037-01

Conclusions:
The results of this food-effect study involving the administration of MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA) to healthy volunteers under fasted and high-fat fed conditions indicate that AUC_{inf} increased by 16%, while the C_{max} remained essentially unchanged. This increase in exposure is not considered to have any clinically meaningful effect.

Date of Report: Final Report: April 2015

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SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection	
PROTOCOL TITLE:	A Study of the Pharmacokinetics of the Intravenous Microdose Formulation of MK-1439 in Healthy Adults	
TRIAL IDENTIFIERS:	Protocol Number:	044
	Clinical Phase:	1
	IND Number:	112,796112,796
TRIAL CENTER:	[redacted]	
DESIGN:	This was a single-dose, single-period, open-label trial of MK-1439 in healthy male and female subjects, between the ages of 18 and 55 years (inclusive). Each subject received a single intravenous (IV) dose of 100 µg MK-1439 administered via infusion syringe over a period of 15 minutes.	
	Planned duration of main phase:	Approximately 6 weeks
Objectives	Primary: To evaluate the pharmacokinetics of a 100 µg IV dose of MK-1439.	
Hypotheses	The area under the concentration-time curve (AUC) from time 0 hours to infinity ($AUC_{0\text{-}inf}$), the AUC from time 0 hours to the last quantifiable concentration ($AUC_{0\text{-}last}$), terminal elimination half-life ($t_{1/2}$), maximum concentration at the end of the infusion (C_{max} [C_{eoi}]), clearance (CL), and volume of distribution at steady state (Vdss) of an IV microdose of MK-1439 were estimated.	
Treatment group	Enrolled subjects	A single IV dose of 100 µg MK-1439 microdose solution was administered via infusion syringe over a period of 15 minutes.

Product Description			
Product Name	Amount Supplied	API Lot Number	Site of Manufacture
MK-1439 API	500 mg	[redacted]	Merck &Co.;
The following ingredients were provided by Merck and were used to prepare the MK1439 Sterile IV solution: a) Tween 80. (manufactured by [redacted]) b) Sodium Chloride, Compendial, [redacted] [hemodialysis/Injectable Use] (manufactured by [redacted])			

Clinical Supplies Available to be Dispensed			
Product Name and Dosage Form	Batch/Lot Number	Potency or Dosage Strength of Dosage	Site of Manufacture
MK-1439 Sterile IV Solution	[redacted]	10 µg/mL	[redacted]

Endpoints and definitions	Pharmacokinetic endpoints	$AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max} (C_{eoi}), CL, Vdss, $t_{1/2}$	
Database lock	18 December 2015	Trial status	19 October 2015 to 11 November 2015 Completed
RESULTS AND ANALYSIS:	All analyses for pharmacokinetics and safety were performed according to the protocol. Eleven (11) of the 12 subjects enrolled completed the study. One subject (Subject MK-1439-044-1007) was withdrawn from the study due to line occlusion preventing the full dose of 10 mL to be administered intravenously. The majority of this subject's dose was administered subcutaneously. Data from 12 subjects were used in the safety analysis and data for the 11 subjects who completed the study were included in the pharmacokinetic analysis.		

Subject Disposition (enrolled subjects)

Parameter	Overall (N=12)
All Subjects as Treated	
Included	12 (100.0%)
Excluded	0 (0.0%)
Did subject complete the study?	
Yes	11 (91.7%)
No	1 (8.3%)

Summary of Demographic Characteristics

Parameter	Statistic	Overall (N=12)
Age (years) at Screening	Mean	38.6
	Std.Dev.	7.48
	Minimum	25
	Maximum	50
Gender		
Male	N (%)	4 (33.3%)
Female	N (%)	8 (66.7%)
Ethnicity		
Hispanic or Latino	N (%)	8 (66.7%)
Not Hispanic or Latino	N (%)	4 (33.3%)
Race		
Black or African American	N (%)	2 (16.7%)
White	N (%)	10 (83.3%)

Analysis description	**Primary Analysis: Pharmacokinetics** A natural log transformation was applied to AUC0-inf, AUC0-last, Cmax (Ceoi), CL, and Vdss and back-transformed summary statistics based on the t-distribution were provided. Geometric mean (GM) and 95% CI for MK-1439 $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max} (C_{eoi}), CL, and Vdss were reported.
Analysis population and time point description	All subjects who complied with the protocol sufficiently to ensure that generated data were likely to exhibit the effects of treatment, according to the underlying scientific model, were included in the primay anlysis dataset.

Summary	After IV administration of 100 µg MK-1439 as an infusion over 15 minutes, maximum MK-1439 plasma concentrations were achieved at 0.25 h and declined rapidly in a biexponential manner. The geometric mean (CV%) C_{eoi} value was 8.47 nM (30.1%). Geometric mean MK-1439 $AUC_{0\text{-}inf}$ was 63.1 h*nM (28.3%). Geometric mean CL, Vdss, and terminal $t_{1/2}$ values for MK-1439 were 3.73 L/h (28.3%), 60.5 L (18.5%), and 12.16 h (25.3%), respectively. Results of the pharmacokinetic analysis are shown below.

Summary Statistics for MK-1439 Plasma Pharmacokinetics Following a Single 100 µg intravenous dose of MK-1439 to healthy subjects

Parameter	**Treatment: 100 µg IV MK-1439**							
	n	**Min**	**Median**	**Max**	**GM**	**GCV%**	**95% CI of GM**	
							Lower	**Upper**
C_{max} (Ceoi) (nM)	11	5.14	8.52	14.4	8.47	30.1	6.95	10.3
$AUC_{0\text{-}last}$ (h*nM)	11	45.4	55.7	90.9	61.1	28.3	50.7	73.6
$AUC_{0\text{-}inf}$ (h*nM)	11	46.3	57.0	93.6	63.1	28.3	52.3	76.0
$t_{1/2}$ (h)	11	8.42	13.25	17.75	12.16	25.3	10.29	14.37
CL (L/h)	11	2.51	4.12	5.08	3.73	28.3	3.09	4.49
Vdss (L)	11	45.0	61.1	75.8	60.5	18.5	53.7	68.4
T_{max} (h)	11	0.17	0.25	0.25				

GM = Geometric Mean; Min = Minimum; Max = Maximum; CI = Confidence Interval; GCV%=Geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale)

Analysis description	**Safety:** The number of subjects with AEs was listed and descriptively summarized.
Analysis population and time point description	All 12 subjects were included in the assessment of safety and tolerability.
Summary	A single dose of 100 µg MK-1439 IV was generally well tolerated. One treatment-emergent adverse event (headache) was reported by 1 (8.3%) subject during the study. The headache was mild in severity and not related to the study treatment. The AE resolved by study completion. There were no serious adverse events, no adverse events of clinical interest, and no adverse events that led to a study discontinuation or death. No clinically significant observations or changes in safety parameters were identified in the subject population during the study conduct

CONCLUSIONS:	1. Following IV administration of 100 µg MK-1439, the geometric mean (CV%) MK-1439 C_{eoi} was 8.47 nM (30.1%). Geometric mean MK-1439 $AUC_{0\text{-}inf}$ was 63.1 h*nM (28.3%). Geometric mean CL, Vdss, and terminal $t_{1/2}$ values for MK-1439 were 3.73 L/h (28.3%), 60.5 L (18.5%), and 12.16 h (25.3%), respectively. 2. Overall, MK-1439 was generally well-tolerated when administered as a single IV 100 µg dose via infusion syringe over a period of 15 minutes.
REPORT DATE	**13 July 2016**
REVISED REPORT DATE:	**02 August 2017**

[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Title of Study:
A Study of the Comparative Fed and Fasted Bioavailability of MK-1439A in Healthy Subjects

Investigators:
[redacted] MD, PhD, FRCP(C)
MD, MSc, CCFP
MD, FRCP(C), MSc
[redacted] MD, MSc, CCFP

Study Centre(s):

Clinical Facility: [redacted] Canada, [redacted]

Clinical Laboratory Facility: [redacted] Canada, [redacted]

Bioanalytical Facilities:
MK-1439
[redacted]
The Netherlands

Lamivudine and Tenofovir
[redacted] Canada, [redacted]

Pharmacokinetic and Statistical Facility: [redacted] Canada, [redacted]

Report Issuing Facility: [redacted] Canada, [redacted]

Phase of Development: Phase I

Study Periods:
Period 1: [redacted], 20[redacted]
Period 2: [redacted], 20[redacted]

Confidential Information
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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Objective:
The objective of this study was to evaluate the comparative bioavailability of:

- MK-1439A 100 mg/300 mg/300 mg Tablets from Merck Sharp & Dohme Corp., USA under high-fat fed and fasted conditions.

Hypothesis (estimation):
The $AUC_{0\text{-}inf}$ and C_{max} GMR (geometric mean ratio) of MK-1439A after administration under fed and fasted conditions will be estimated.

Methodology:

- This was an open-label, single-dose, randomized, two-period, two-treatment, crossover study.
- This study was designed to evaluate the comparative bioavailability of MK-1439A 100 mg/300 mg/300 mg fixed-dose combination tablets in healthy male and female subjects administered under high-fat fed (Treatment A) and fasted conditions (Treatment B).
- Concentrations of MK-1439, lamivudine, and tenofovir were measured from the samples collected over a 72-hour interval after dosing in each period.
- The pharmacokinetic (PK) parameters $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, T_{half}, CL/F, V_d/F and C_{24} were estimated using a non-compartmental approach.

Number of subjects:

- Planned for inclusion: 14 subjects
- Total number of subjects that completed the study: 13 subjects
- Included in the safety dataset: 14 subjects
- Included in the PK and statistical datasets: 14 subjects
    - Subject 0008 was dismissed from the study in Period 1; therefore, data from this subject only for Treatment A is available and included in the PK and statistical analyses.

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 65 years of age, with a BMI from 19.0 to 33.0 kg/m^2, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements.

Study Drug Product (Treatment A and Treatment B):
MK-1439A 100 mg/300 mg/300 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency (% of label claim):

- 99.4% (MK-1439);
- 101.8% (lamivudine);
- 101.4% (tenofovir disoproxil fumarate).

Use by End Date: [redacted]/20[redacted]
Dose: FDC of 100 mg MK-1439; 300 mg lamivudine; 300 mg tenofovir disoproxil fumarate
Mode of Administration: Oral under high-fat fed (Treatment A) and fasted (Treatment B) conditions

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Duration of treatment:
Single-dose treatment

Version 2 Report: Version 2 of this report was generated to update the reason for discontinuation of one (1) subject from health complaints (toothache) to adverse event (AE). This update was requested by the Sponsor after review of the data during data migration.

Safety Results:

		Pre-dose	Trt A	Trt B	Total
Severity	Mild	1	8	7	16
	Moderate	0	1	0	1
	Severe	0	0	0	0
Relationship to Study Drug	Related	0	1	6	7
	Not Related	1	8	1	10

There were 16 AEs involving 6 subjects in the study. One AE was judged to be moderate in severity while all the others were mild. There was one non treatment emergent adverse event (NTEAE) involving one subject in the study. The NTEAE was judged to be mild in severity.

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.

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

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Statistical Methods:

The primary PK endpoints $AUC_{0\text{-}inf}$ and C_{max} were natural log-transformed prior to analysis and analyzed (SAS PROC MIXED) with a linear-mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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.

A two-sided 90% confidence interval (CI) for the true mean difference (Fed – Fasted) was generated on the log-scale from the linear-mixed effect model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (fed/fasted) for MK-1439, lamivudine and tenofovir $AUC_{0\text{-}inf}$ and C_{max}.

Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439, lamivudine, and tenofovir, $AUC_{0\text{-}inf}$ and C_{max}. Plots with the individual ratios, GMRs and 90% CIs were provided for MK-1439, lamivudine, and tenofovir $AUC_{0\text{-}inf}$ and C_{max}.

MK-1439 C_{24} and $AUC_{0\text{-}last}$ and lamivudine and tenofovir $AUC_{0\text{-}last}$ were also analyzed in a similar manner.

Individual values were listed for each PK parameter by treatment and analyte, and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data); arithmetic mean; standard deviation; arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean); median; minimum; maximum; geometric mean; and geometric percent CV (calculated as 100 x sqrt(exp(s^2) – 1), where s^2 was the observed variance on the natural log-scale).

Criteria for Evaluation:

The GMRs and their 90% confidence intervals of the MK-1439, lamivudine, and tenofovir $AUC_{0\text{-}inf}$ and C_{max} were used to assess the food effect on the bioavailability of the study drug product.

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Results:

Pharmacokinetic Results:

Summary Statistical Analysis Based on Plasma MK-1439 Levels

	FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets			***FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***			***FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets / FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	14	41.4	(34.8, 49.4)	13	37.7	(31.2, 45.5)	1.10	(1.01, 1.20)	12.0
$AUC_{0\text{-}last}$ (hr·µM)†	14	40.1	(33.8, 47.5)	13	36.3	(30.2, 43.6)	1.10	(1.01, 1.20)	12.0
C_{max} (nM)†	14	1850	(1610, 2120)	13	1950	(1600, 2380)	0.95	(0.80, 1.12)	23.1
C_{24} (nM)†	14	680	(548, 843)	13	539	(424, 684)	1.26	(1.13, 1.41)	15.9
T_{max} (hr)	14	6.00	(0.50, 6.00)	13	3.00	(0.50, 6.00)			
$t_{½}$ (hr)	14	13.15	23.2	13	14.18	29.3			
CL/F (L/hr)	14	5.67	30.9	13	6.16	33.7			
V_d/F (L)	14	108	25.2	13	126	35.2			

†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
*‡ Estimated based on the elements of the variance-covariance matrix as: CV(%) = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*
Statistics for Tmax: Median and Range (Minimum, Maximum)
*Statistics for t½, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Summary Statistical Analysis Based on Plasma Lamivudine Levels

	FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets			***FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***			***FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets / FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·ng/mL)†	14	12400	(11400, 13400)	13	13300	(12000, 14600)	0.93	(0.84, 1.03)	14.1
$AUC_{0\text{-}last}$ (hr·ng/mL)†	14	12100	(11200, 13100)	13	13100	(11800, 14400)	0.93	(0.84, 1.02)	14.2
C_{max} (ng/mL)†	14	2000	(1680, 2390)	13	2480	(2120, 2900)	0.81	(0.65, 1.01)	32.0
T_{max} (hr)	14	3.00	(1.00, 4.02)	13	1.00	(1.00, 4.00)			
$t_{½}$ (hr)	14	17.75	45.1	13	17.76	48.9			
CL/F (L/hr)	14	24.3	15.0	13	22.6	15.1			
V_d/F (L)	14	621	44.6	13	579	46.4			

†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
*‡ Estimated based on the elements of the variance-covariance matrix as: CV(%) = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*
Statistics for Tmax: Median and Range (Minimum, Maximum)
*Statistics for t½, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s²)-1), where s² is the observed between-subjects variance on the natural log-scale.*

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Summary Statistical Analysis Based on Plasma Tenofovir Levels

	FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets			***FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***			***FED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets / FASTED: MK-1439A 100 mg/300 mg/300 mg FDC Tablets***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·ng/mL)†	14	3100	(2730, 3530)	13	2450	(2190, 2740)	1.27	(1.17, 1.37)	11.3
$AUC_{0\text{-}last}$ (hr·ng/mL)†	14	2900	(2550, 3290)	13	2300	(2060, 2560)	1.26	(1.17, 1.36)	11.0
C_{max} (ng/mL)†	14	240	(191, 302)	13	272	(231, 320)	0.88	(0.74, 1.04)	24.7
T_{max} (hr)	14	3.00	(1.00, 6.00)	13	1.00	(0.50, 2.02)			
$t_{½}$ (hr)	14	19.08	15.5	13	19.33	13.6			
CL/F (L/hr)	14	43.8	22.6	13	54.8	18.5			
V_d/F (L)	14	1210	21.7	13	1530	19.5			

†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
*‡ Estimated based on the elements of the variance-covariance matrix as: CV(%) = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*
Statistics for Tmax: Median and Range (Minimum, Maximum)
*Statistics for $t_{½}$, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

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[redacted] – Version 2 Study Report
MK-1439A Fed/Fasted Bioavailability Study
[redacted] Study Number: 20[redacted]-3705
Protocol Number: MK-1439A-PN029-00

Conclusions:

1. MK-1439 $AUC_{0\text{-}inf}$ and C_{max} were generally similar after administration with a high fat meal or in the fasted state, while C_{24} was increased by 26% after high fat fed administration.

2. Lamivudine $AUC_{0\text{-}inf}$ was generally similar after administration with a high fat meal or in the fasted state, while C_{max} was decreased by 19% after high fat fed administration.

3. Tenofovir $AUC_{0\text{-}inf}$ was increased by 27% and C_{max} was decreased by 12% after administration with a high fat meal compared to fasted administration.

Date of Version 2 Report: Final Report: [redacted] 20[redacted]

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[redacted] [redacted] –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Title of Study:
A Study to Determine the Bioequivalence of MK-1439 Coated and Uncoated Tablets in Healthy Adult Subjects

Investigators:
[redacted] MD, PhD, FRCP(C)
MD, MSc, CCFP

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 I

Study Periods:
Period 1: [redacted], 20[redacted]
Period 2: [redacted], 20[redacted]

Objective:
To evaluate the bioequivalence between:
- MK-1439 100 mg Uncoated Tablets (Merck Sharp & Dohme Corp., USA) and
- MK-1439 100 mg Coated Tablets (Merck Sharp & Dohme Corp., USA)

after a single-dose in healthy subjects under fasted conditions.

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[redacted] [redacted] –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Hypothesis:
The MK-1439 uncoated tablet and MK-1439 coated tablet will be bioequivalent based on the assessment of $AUC_{0\text{-}inf}$ and C_{max} for MK-1439 (i.e., the true GMR (geometric mean ratio) for the $AUC_{0\text{-}inf}$ and C_{max} of MK-1439 will be contained within [0.80, 1.25]).

Methodology:
- This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.
- This study was designed to evaluate the bioequivalence between the MK-1439 coated and uncoated tablets in healthy male and female subjects under fasted conditions.
- Concentrations of MK-1439 were measured from the samples collected over a 72-hour interval after dosing in each period.
- The following pharmacokinetic (PK) parameters were estimated after administration of MK-1439 using a non-compartmental approach:
    - $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, apparent terminal $t_{1/2}$, C_{24}, CL/F and V_d/F.

Number of subjects:
- Planned for inclusion: 24 subjects
- Total number of subjects that completed the study: 24 subjects
- Included in the safety data analyses: 24 subjects
- Included in the PK data analyses: 24 subjects
- Included in the statistical data analyses: 24 subjects

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 64 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, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements.

Test Product 1:
MK-1439 100 mg Uncoated Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: 98.9% of label claim
Use by End Date: [redacted]/20[redacted]
Dose: 100 mg
Mode of Administration: Oral under fasted conditions

Test Product 2:
MK-1439 100 mg Coated Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: 99.0% of label claim
Use by End Date: [redacted]/20[redacted]
Dose: 100 mg
Mode of Administration: Oral under fasted conditions

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[redacted]

PHARMA MEDICA RESEARCH INC. –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Duration of treatment:
Single-Dose treatment

Safety Results:

		Pre-dose	Trt A	Trt B	Total
Severity	Mild	1	4	2	7
	Moderate	0	0	0	0
	Severe	0	0	0	0
Relationship to Study Drug	Related	0	2	2	4
	Not Related	1	2	0	3

There were 6 adverse events (AEs) involving 5 subjects in the study. All AEs were judged to be mild in severity. The most common AE across all treatments was sleepiness (one event during Treatment A, one event during Treatment B). Both events resolved.

There was one non-treatment emergent adverse event (NTEAE) involving one subject that occurred prior to administration of any drug product. This event was judged to be mild in severity.

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.

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

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[redacted] –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Statistical Methods:
The pharmacokinetics (PK) of MK-1439 ($AUC_{0\text{-}inf}$ and C_{max}) after administration of MK-1439 100 mg Uncoated Tablets and MK-1439 100 mg Coated Tablets were natural log-transformed prior to analysis and evaluated separately using a linear mixed-effect model appropriate for a two-period crossover design. The linear mixed effects model contained fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlations 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).
The hypothesis was addressed by comparing MK-1439 $AUC_{0\text{-}inf}$ and C_{max} from administration of the coated tablets to those obtained from administration of the uncoated tablets. A two-sided 90% confidence interval (CI) for the true mean difference (MK-1439 coated tablets – uncoated tablets) for MK-1439 $AUC_{0\text{-}inf}$ and C_{max} on the log scale were computed from the above linear-mixed effects model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (MK-1439 100 mg Coated Tablets/MK-1439 100 mg Uncoated Tablets) for MK-1439 $AUC_{0\text{-}inf}$ and C_{max}. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439 $AUC_{0\text{-}inf}$ and C_{max}.
MK-1439 $AUC_{0\text{-}last}$ and C_{24} were analyzed in similar fashion as above. Plots with individual ratios, GMRs and 90% CIs are provided for MK-1439 C_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{24}.

Criteria for Evaluation:
The GMRs and their 90% CIs of the MK-1439 $AUC_{0\text{-}inf}$ and C_{max} were used to assess the bioequivalence of MK-1439 coated and uncoated tablets.

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[redacted] [redacted] –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Pharmacokinetic Results:

Summary Statistics for Plasma MK-1439 Following Single Oral Dose Administration of 100 mg MK-1439 as Coated and Uncoated Tablets in Healthy Male and Female Subjects

	MK-1439 100 mg Coated Tablets			*MK-1439 100 mg Uncoated Tablets*			*MK-1439 100 mg Coated Tablets / MK-1439 100 mg Uncoated Tablets*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	24	41.0	(35.2 , 47.7)	24	39.7	(34.1 , 46.1)	1.03	(0.99 , 1.08)	7.9
$AUC_{0\text{-}last}$ (hr·µM)†	24	39.0	(33.8 , 45.0)	24	37.2	(32.3 , 42.8)	1.05	(1.01 , 1.09)	8.0
C_{max} (nM)†	24	2080	(1840 , 2350)	24	1890	(1710 , 2080)	1.10	(1.01 , 1.20)	17.0
C_{24} (nM)†	24	569	(462 , 700)	24	540	(436 , 668)	1.05	(1.00 , 1.11)	10.5
T_{max} (hr)	24	2.00	(0.50 , 6.00)	24	2.00	(1.00 , 6.00)			
$t_{½}$ (hr)	24	15.03	(31.4)	24	16.38	(35.9)			
CL/F (L/hr)	24	5.73	(36.5)	24	5.92	(37.3)			
V_d/F (L)	24	124	(31.1)	24	140	(30.7)			

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
‡ Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
Statistics for T_{max}: Median and Range (Minimum , Maximum)
Statistics for $t_{½}$, CL/F and V_d/F: GM and CV% = $100*sqrt(exp(s^2)-1)$, where s^2 is the observed between-subjects variance on the natural log-scale.

Confidential Information
The information in this report is legally privileged and confidential. Any disclosure, copying or distribution of the information contained within is strictly prohibited without written consent from the sponsor.

[redacted] [redacted] –Study Report
MK-1439 100 mg Uncoated Versus Coated Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3786
Protocol Number: MK-1439-PN039-00

Conclusions:
The coated formulation of MK-1439 100 mg tablets is bioequivalent to uncoated MK-1439 100 mg tablets (Merck Sharp & Dohme Corp., USA) after a single-dose in healthy subjects under fasted conditions.

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

Confidential Information
The information in this report is legally privileged and confidential. Any disclosure, copying or distribution of the information contained within is strictly prohibited without written consent from the sponsor.

Sponsor:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100 United States of America (USA)
Investigational Products:	MK-1439 Adult Formulation Tablets, 100 mg MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose]
Active Ingredients:	MK-1439
Study Title:	A Study to Evaluate the Comparative Bioavailability of the Investigational Oral Pediatric Minitablet Formulation of MK-1439 Compared to the Adult Formulation of MK-1439 in Healthy Adult Subjects
Investigators: Principal Investigator: Sub-Investigator(s):	[redacted], M.D., CPI [redacted], D.O. [redacted], M.D. [redacted], M.D.
Study Site:	[redacted] USA
Publication(s):	None currently planned
Studied Period: **Period I:** **Period II:** **Date First Subject Dosed:**	[redacted] 20[redacted] – [redacted] 20[redacted] [redacted] 20[redacted] – [redacted] 20[redacted] [redacted] 20[redacted]
Date of Last Pharmacokinetic (PK) Sample:	[redacted] 20[redacted]

Objective

To evaluate the comparative bioavailability of a single-dose of the investigational oral pediatric minitablet formulation of MK-1439, 0.8 mg [100 mg total dose] compared to the adult formulation of MK-1439 tablets, 100 mg in healthy adult male and female subjects under fasted conditions.

Hypothesis (Estimation):

To estimate the $AUC_{0\text{-}inf}$ and C_{max} geometric mean ratio (GMR) of the MK-1439 pediatric minitablet formulation and MK-1439 adult formulation following single-dose administration under fasted conditions.

Methodology: This was an open-label, single-dose, randomized, two-treatment, two-period, two-sequence, crossover study in 24 non-tobacco using, healthy adult male and female subjects.

In each study period, 100 mg of MK-1439 (adult tablet formulation or pediatric minitablet formulation) was administered to subjects with 6 oz. of yogurt, following an overnight fast of at least 10 hours. Reference Treatment A was MK-1439 Adult Formulation Tablet, 100 mg and Test Treatment B was MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose]. The subjects received the test product in one of the study periods and the reference product in the other study period according to a two-sequence randomization schedule. Subjects were confined at the clinical facility from at least 10 hours prior to dosing until after the 24-hour blood collection in each study period and returned to the clinical facility for blood sample collections at 48 and 72 hours after dosing. The interval between doses was 7 days. This study was conducted under Investigational New Drug application number 112,796.

Blood samples were collected at pre-dose and at intervals over 72 hours after dosing each period for subsequent analysis of plasma concentrations of MK-1439. The plasma samples were shipped to the analytical laboratory ([redacted]) for the measurement of MK-1439 concentrations using validated analytical procedures.

Statistical analysis was performed to evaluate the bioavailability of a single-dose of the investigational oral pediatric minitablet formulation of MK-1439, 0.8 mg [100 mg total dose] compared to that of the adult formulation of MK-1439 tablets, 100 mg in healthy adult male and female subjects under fasted conditions.

Safety was assessed by evaluating laboratory test results, physical examination findings, electrocardiogram (ECG) findings, vital sign assessments, and adverse events (AEs).

Number of Subjects (Planned and Analyzed): A total of 24 healthy adult subjects were enrolled in this study and all 24 subjects completed Periods I and II. Summary of

demographics are provided in Section 11.2.2. All analyses were performed and all tables, figures, and data listings were prepared by Novum using SAS, Version 9.4.

Main Criteria for Inclusion: All subjects were non-tobacco using, healthy males and females, 18-55 years of age who met all inclusion criteria and did not violate the exclusion criteria for this study.

REFERENCE TREATMENT A: MK-1439 100 mg Tablets MK-1439-043
Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Inc.
Control No.: [redacted]
Current R.E.D.: [redacted]-20[redacted]

Following dosing with one 100 mg tablet, the subjects were required to consume (within 10 minutes) the entire contents of a 6 oz. container of yogurt (provided in a clear glass bowl).

TEST TREATMENT B: MK-1439 0.8 mg 125 Mini Tablets MK-1439-043
Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Inc.
Control No.: [redacted]
Current R.E.D.: [redacted]-20[redacted]

At the specified dosing time, subjects were required to consume the entire contents of a clear glass bowl that contained 6 oz. of yogurt with the minitablets (within 10 minutes).

Route of Administration: Oral

Duration of Treatment: The study began dosing on [redacted] 20[redacted] and the last subject completed on [redacted] 20[redacted].

Criteria for Evaluation:

Efficacy**:** Not applicable

Safety**:** Safety was assessed by evaluating laboratory test results, physical examination findings, electrocardiogram (ECG) findings, vital sign assessments, and AEs. AEs were collected through both solicited and unsolicited means.

PK Analysis**:** For analysis of plasma MK-1439 concentrations, thirteen (13) blood samples were collected from each subject within 60 minutes before dosing (0 hr) and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24, 48*, and 72*hours post-dose (*return sample). The plasma concentration-time data were used to calculate the PK parameters: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, C_{24}, T_{max}, K_{el}, $t_{½}$, CL/F, and Vd/F by non-compartmental analysis. The Statistical Analysis System (SAS, Version 9.4) was used for all pharmacokinetic and statistical calculations.

Statistical Methods:

The plasma PK parameters (C_{max} and $AUC_{0\text{-inf}}$) for MK-1439 after administration of MK-1439 adult formulation tablets and investigational oral pediatric minitablet formulation were estimated using a linear mixed-effect model appropriate for a two-period crossover design. To address the primary objective, the values of C_{max} and $AUC_{0\text{-inf}}$ were natural log-transformed before analysis and analyzed with a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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).

A two-sided 90% confidence interval (CI) for the true mean difference (investigational oral pediatric minitablet formulation – adult formulation tablets) for MK-1439 $AUC_{0\text{-inf}}$ and C_{max} on the log scale was computed from the above linear-mixed effect model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (investigational oral pediatric minitablet formulation / adult formulation tablets) for MK-1439 $AUC_{0\text{-inf}}$ and C_{max}. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439 $AUC_{0\text{-inf}}$ and C_{max}. C_{24} and $AUC_{0\text{-last}}$ were analyzed in a similar manner. Plots with the individual ratios, GMRs and 90% CIs are provided for MK-1439 C_{max} and $AUC_{0\text{-inf}}$. In addition, T_{max}, apparent terminal $t_{½}$, CL/F, and Vd/F were also calculated.

Summary of Results: A table summarizing PK parameters, geometric means and 95% CIs , ratio of geometric means, and their associated 90% CIs based on linear mixed effects models and statistical comparisons for MK-1439 is provided below.

Table 2.1 **Summary of Plasma Pharmacokinetics of MK-1439 Following Dosing of Either 100 mg Adult Tablet or 0.8 mg Pediatric Minitablets [100 mg Total Dose] with Yogurt to Healthy Subjects in the Fasted State (n=24)**

	MK-1439 Adult Tablet[1]			MK-1439 Pediatric Minitablets[2]			MK-1439 Pediatric Minitablets / MK-1439 Adult Tablet		
Pharmacokinetic Parameter	N	GM[3]	95% CI[3]	N	GM[3]	95% CI[3]	GMR	90% CI	Pseudo Intra-Subject %CV[4]
$AUC_{0\text{-last}}$ (μM·hr)	23*	36.6	(31.0, 43.1)	24	25.7	(21.5, 30.8)	0.70	(0.64, 0.77)	17.7
$AUC_{0\text{-}\infty}$ (μM·hr)	24	38.3	(32.3, 45.3)	24	28.1	(23.4, 33.9)	0.73	(0.68, 0.80)	16.8
C_{24} (nM)	24	591	(491, 712)	24	434	(349, 539)	0.73	(0.64, 0.85)	29.1
C_{max} (nM)	24	2170	(1820, 2580)	23*	1150	(992, 1320)	0.53	(0.47, 0.59)	23.2
T_{max}[3] (hr)	24	2.00	(0.50, 4.00)	23*	3.02	(0.50, 6.00)	-	-	-
$t_{½}$[3] (hr)	24	14.21	27.1	24	19.06	34.1	-	-	-
CL/F[3] (L/hr)	24	6.13	(5.19, 7.25)	24	8.34	(6.93, 10.1)	-	-	-
Vd/F[3] (L)	24	126	(107, 147)	24	229	(186, 284)	-	-	-

[1] **MK-1439 Adult Tablet:** 1 x MK-1439 Adult Formulation Tablet, 100 mg (Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc.)

[2] **MK-1439 Pediatric Minitablets:** MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose] (Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc.)

[3] Least-squares Geometric Mean reported for AUC, C_{24}, and C_{max} parameters. Descriptive Geometric Mean reported for $t_{½}$, CL/F and Vd/F parameters. Median (Min-Max) reported for T_{max} in place of Geometric Mean (95% CI). Geometric CV% reported for $t_{1/2}$ in place of 95% CI. 95% CI for Vd/F and CL/F based on log-normal t-distribution.

[4] Pseudo Intra-Subject CV% estimated based on the elements of the variance-covariance matrix: $CV(\%) = 100*\text{sqrt}[(s^2_A + s^2_B - 2*s_{AB})/2]$.

*$AUC_{0\text{-last}}$ for Treatment A (Period II) was not reported for Subject 19 due to missing concentration value at 72 hrs

C_{max} and T_{max} for Treatment B (Period II) were not reported for Subject 8 due to missing concentration value at 3 hrs

Data Source: Statistical (SAS®) Geometric Means, 90% Confidence Interval Calculations at Alpha=0.05 and Intra-Subject CV% Data provided in Appendix 16.1.9.1

Safety: Seven (7) adverse events were reported by 6 of the 24 subjects who participated in this study. Of these events, 5 occurred after administration of Treatment A (MK-1439 Adult Formulation Tablet, 100 mg), and 2 occurred after administration of Treatment B (MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose]). Four (4) of the reported adverse events were considered "mild". Of these, 3 resolved and one (1) did not resolved by study completion. Three (3) adverse events were considered "moderate" severity and all 3 did not resolve by study completion. Two (2) adverse events (2 Treatment A) were considered to have reasonable possibility of being related to the study drug. The adverse events most frequently reported were blood glucose increased (Treatment A: 2 subjects, Treatment B: 1 subject), and white blood cell count increased (Treatment A: 1 subject, Treatment B: 1 subject).

Safety parameters were also evaluated via a summary of adverse events by treatment, severity, relationship to drug, as well as clinical laboratory evaluations, vital signs and ECGs. See Sections 12.2, 12.4 and 12.5.

Results:

The relative bioavailability of MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose] versus MK-1439 Adult Formulation Tablet, 100 mg was approximately 73% as measured by $AUC_{0\text{-inf}}$, 70% as measured by $AUC_{0\text{-last}}$ and 53% as measured by C_{max} for MK-1439. Both treatments were administered with yogurt following an overnight fast.

The median T_{max} of the Adult Tablet was 2.00 hours and the median T_{max} of the Pediatric Minitablets was 3.02 hours.

The apparent total plasma clearance of drug after oral administration was 6.13 L/hr for the Adult Tablet and 8.34 L/hr for the Pediatric Minitablets.

The apparent volume of distribution after oral drug administration was 126 L for the Adult Tablet and 229 L for the Pediatric Minitablets.

Conclusions:

1. Following a single dose of MK-1439 Investigational Oral Pediatric Formulation Minitablets, 0.8 mg [100 mg total dose]) administered with yogurt after an overnight fast, the total plasma exposure of MK-1439, as characterized by AUC and C_{max} are decreased 27% and 47%, respectively, compared to an equal dose of the 100 mg MK-1439 Adult Formulation Tablet, administered under the same conditions.
2. Single-dose administration of either formulation at a dose of 100 mg of MK-1439 was generally well tolerated by the healthy adult subjects in this study.

Report Date: [redacted] 20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439 (Doravirine)	
INDICATION:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection	
PROTOCOL TITLE:	A study of the Comparative Bioavailability of the Investigational Pediatric Oral Granules Formulation of MK-1439 Compared to the Adult Formulation under Fed and Fasted Conditions	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-049-00
	Clinical Phase:	1
TRIAL CENTERS:	[redacted], MD, PhD, FRCP(C): [redacted], Canada	

DESIGN:	This was an open-label, partially randomized, three-period, four-treatment, four-sequence cross-over study to determine the comparative bioavailability of two formulations of MK-1439, administered as single oral dose to healthy male and female subjects. In Period 1 and Period 2, each subject received either Treatment A or Treatment B, in a cross-over fashion, according to the randomly assigned treatment sequence. In Period 3, half of the subjects received Treatment C and the other half received Treatment D. Treatment assignment to Groups C and D was done randomly. Treatment A consisted of a single oral dose of one adult 100 mg tablet of MK-1439 administered after an overnight fast. Treatment B consisted of a single oral dose of 100 mg pediatric granules (125 oral granules x 0.8 mg) of MK-1439 administered after an overnight fast. Treatment C consisted of a single oral dose of 125 mg pediatric granules (156 oral granules x 0.8 mg) of MK-1439 administered with vanilla yogurt after an overnight fast. Treatment D consisted of a single oral dose of 100 mg pediatric granules (125 oral granules x 0.8 mg) of MK-1439 administered with vanilla pudding after an overnight fast. The washout time between drug administrations in each treatment period was 7 days (±3 hours). Safety was closely monitored throughout the study. Plasma was collected pre-dose and at specified time points up to 72 hours post-dose for measurement of MK-1439 concentrations. Twenty-four (24) healthy, non-smoking male and female subjects between the ages of 18 and 55 (inclusive) with a body mass index (BMI) ≥ 19.0 to ≤ 30 kg/m^2, participated in the study.	
	Planned duration of main phase:	Approximately 54 days
Objectives	The primary objective of this study was to evaluate the comparative bioavailability between: • MK-1439 100 mg adult tablet under fasted conditions; and • MK-1439 100 mg pediatric granules (125 oral granules x 0.8 mg) under fasted conditions; and • MK-1439 125 mg pediatric granules (156 oral granules x 0.8 mg) under fasted conditions when given with vanilla yogurt; and • MK-1439 100 mg pediatric granules (125 oral granules x 0.8 mg) under fasted conditions when given with vanilla pudding; after a single-dose in healthy subjects.	

Treatment groups	Treatment A	100 mg MK-1439 (1 adult tablet), administered under fasted conditions. [24 Subjects]
	Treatment B	100 mg MK-1439 (125 x 0.8 mg oral pediatric granules), administered under fasted conditions. [24 Subjects]
	Treatment C	125 mg MK-1439 (156 x 0.8 mg oral pediatric granules), administered with vanilla yogurt after an overnight fast. [12 Subjects]
	Treatment D	100 mg MK-1439 (125 x 0.8 mg oral pediatric granules), administered with vanilla pudding after an overnight fast. [12 Subjects]

Bulk product description and manufacturing lot numbers are provided in the table here:

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
MK-1439 100 mg Adult Tablet	[redacted]
MK-1439 0.8 mg Pediatric Oral Granules (125 count)	
MK-1439 0.8 mg Pediatric Oral Granules (156 count)	[redacted]

ENDPOINTS AND DEFINITIONS	**Primary Endpoint:**	PK	AUC0-inf, C24, and Cmax
	Secondary Endpoints:	Safety	An assessment of safety was based primarily on the frequency and severity of adverse events (AEs)
DATABASE LOCK	[redacted]-20[redacted]	**TRIAL STATUS:**	[redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All analyses for safety, tolerability, and pharmacokinetics (PK) were performed according to the protocol. The Statistical Analysis Plan (SAP) is provided in [16.1.1.1]. The PK parameters (AUC0-inf, C24, and Cmax) for MK-1439 after administration of MK-1439 adult formulation tablet and each investigational pediatric oral granule formulation and dosing conditions were analyzed using a linear mixed-effect model based on all available PK data in three periods. The PK values of AUC0-inf, C24, and Cmax were natural log-transformed prior to analysis and analyzed with a linear mixed effect model with a fixed effect term for treatment only, since the period was partially confounded with the treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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). A two-sided 90% confidence interval (CI) for the true mean difference (each investigational pediatric oral granule formulation dosed without yogurt or pudding, dosed with yogurt or dosed with pudding, respectively – adult formulation tablet) for MK-1439 AUC0-inf, C24, and Cmax on the log scale were computed from the above linear-mixed effect model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (each investigational pediatric oral granule formulation / adult formulation tablet, including B vs. A; C vs. A and D vs. A) for MK-1439 AUC0-inf, C24, and Cmax. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439 AUC0-inf, C24, and Cmax.		

	For comparisons between any two treatments with investigational pediatric oral granule formulations (including C vs. B, D vs. B and C vs. D), the aforementioned linear mixed model was used based on all available PK data in the three periods. The two-sided 90% CIs for the true GMRs for comparisons between any two treatments with investigational pediatric oral granule formulations (including C vs. B, D vs. B and C vs. D) for MK-1439 AUC0-inf, C24, and Cmax were also generated. Plots with the individual ratios, GMRs and 90% CIs for the aforementioned comparisons are presented for MK-1439 AUC0-inf, C24, and Cmax. Individual values were calculated for each pharmacokinetic parameter by treatment, additionally, individual ratios from the aforementioned comparisons were calculated for each PK parameter, and the following (non-model based) descriptive statistics are presented: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) – 1), where s2 was the observed variance on the natural log-scale).
SUBJECT DISPOSITION:	RANDOMIZED: 24 Male (age range) 6 (26 to 51) Female (age range) 18 (22 to 53) COMPLETED: 24 DISCONTINUED: 0 Other 0	
	Twenty-four (24) subjects were initially enrolled per the protocol and all subjects completed the study.	
ANALYSIS DESCRIPTION:	**Analyses** **MK-1439 Pharmacokinetics**	
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	PK analysis was performed on available data from all subjects in the per-protocol (PP) dataset. All subjects were compliant with the inclusion and exclusion criteria.	
SUMMARY:	In the fasted state, following administration of a 100 mg single oral dose of MK-1439 pediatric oral granules (125 x 0.8mg), MK-1439 AUC0-inf and C24 were decreased by 23%, while Cmax was decreased by 53% relative to administration of the adult tablet under similar conditions. Following administration of a 100 mg single oral dose of MK-1439 pediatric oral granules in pudding, MK-1439 AUC0-inf and C24 were decreased by 29% and 21%, respectively, compared to values	

	obtained after administration of the 100 mg adult tablet without food, while Cmax was decreased by 63%. Following administration of a 125 mg single oral dose of MK-1439 pediatric oral granules (156 x 0.8mg) in yogurt, MK-1439 AUC0-inf and C24 were generally similar (8-12% increase) to values obtained after administration of the 100 mg adult tablet in the fasted condition, while Cmax was decreased by 14%.

Table 2–1 Summary Statistics for Plasma Pharmacokinetics of MK-1439 Following Single Oral Dose Administration of MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) Fasted and MK-1439 100 mg (1 adult tablet) Fasted in Healthy Male and Female Subjects (B vs A)

	MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) Fasted			*MK-1439 100 mg (1 adult tablet) Fasted*			*MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) Fasted / MK-1439 100 mg (1 adult tablet) Fasted*		
PK Parameter	***N§***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	23	31.7	(27.5 , 36.5)	24	41.0	(36.7 , 45.8)	0.77	(0.71 , 0.84)	16.1
C_{max} (nM)†	24	926	(787 , 1090)	24	1990	(1740 , 2270)	0.47	(0.40 , 0.54)	29.3
C_{24} (nM)†	24	497	(441 , 561)	24	648	(571 , 734)	0.77	(0.71 , 0.83)	15.0
T_{max} (hr)#	24	3.00	(1.50 , 24.00)	24	1.81	(0.50 , 6.00)			
$t_{½}$ (hr)*	23	20.19	(39.5)	24	15.82	(24.7)			
CL/F (L/hr)*	23	7.37	(34.3)	24	5.73	(26.7)			
V_z/F (L)*	23	215	(35.6)	24	131	(31.7)			

CI = Confidence interval; CL/F = Apparent total plasma clearance of drug after oral administration (Dose/AUC0-inf); CV = Coefficient Variation; GM = Geometric mean; GMR = Least-squares Geometric Mean Ratio between treatments; N = Number of Subjects; PK = Pharmacokinetic; V_z/F = Apparent volume of distribution during the terminal phase after oral drug administration (Dose/[AUC0-inf λz])*

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_A^2 + σ_B^2 - 2*σ_{AB})/2]*

, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the two treatment groups

, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model

#Statistics for Tmax: Median and Range (Minimum , Maximum)

**Statistics for $t_{½}$, CL/F and V_z/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

§The maximum concentration value for one subject was reached at 24 hours post-dose. This did not allow sufficient data on the terminal linear phase of the semilog profile for the regression analysis.

Table 2–2 Summary Statistics for Plasma Pharmacokinetics of MK-1439 Following Single Oral Dose Administration of MK-1439 125 mg (156 x 0.8 mg pediatric oral granules) in Vanilla Yogurt and MK-1439 100 mg (1 adult tablet) Fasted in Healthy Male and Female Subjects (C vs A)

	MK-1439 125 mg (156 x 0.8 mg pediatric oral granules) in Vanilla Yogurt			*MK-1439 100 mg (1 adult tablet) Fasted*			*MK-1439 125 mg (156 x 0.8 mg pediatric oral granules) in Vanilla Yogurt / MK-1439 100 mg (1 adult tablet) Fasted*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	12	44.4	(38.3 , 51.6)	24	41.0	(36.7 , 45.8)	1.08	(1.00 , 1.18)	10.3
C_{max} (nM)†	12	1720	(1460 , 2010)	24	1990	(1740 , 2270)	0.86	(0.76 , 0.99)	19.0
C_{24} (nM)†	12	726	(635 , 829)	24	648	(571 , 734)	1.12	(1.07 , 1.18)	6.1
T_{max} (hr)#	12	3.00	(1.00 , 4.00)	24	1.81	(0.50 , 6.00)			
$t_{½}$ (hr)*	12	17.07	(24.9)	24	15.82	(24.7)			
CL/F (L/hr)*	12	6.37	(27.7)	24	5.73	(26.7)			
V_z/F (L)*	12	157	(18.5)	24	131	(31.7)			

CI = Confidence interval; CL/F = Apparent total plasma clearance of drug after oral administration (Dose/AUC0-inf); CV = Coefficient Variation; GM = Geometric mean; GMR = Least-squares Geometric Mean Ratio between treatments; N = Number of Subjects; PK = Pharmacokinetic; V_z/F = Apparent volume of distribution during the terminal phase after oral drug administration (Dose/[AUC0-inf λz])*

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_A^2 + σ_C^2 - 2*σ_{AC})/2]*

, where σ_A^2 and σ_C^2 are the estimated variances on the log scale for the two treatment groups

, and σ_{AC} is the corresponding estimated covariance, each obtained from the linear mixed effects model

#Statistics for Tmax: Median and Range (Minimum , Maximum)

**Statistics for $t_{½}$, CL/F and V_z/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

Table 2–3 Summary Statistics for Plasma Pharmacokinetics of MK-1439 Following Single Oral Dose Administration of MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) in Vanilla Pudding and MK-1439 100 mg (1 adult tablet) Fasted in Healthy Male and Female Subjects (D vs A)

	MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) in Vanilla Pudding			*MK-1439 100 mg (1 adult tablet) Fasted*			*MK-1439 100 mg (125 x 0.8 mg pediatric oral granules) in Vanilla Pudding / MK-1439 100 mg (1 adult tablet) Fasted*		
PK Parameter	***N§***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	10	29.0	(25.3 , 33.3)	24	41.0	(36.7 , 45.8)	0.71	(0.64 , 0.79)	13.8
C_{max} (nM)†	12	743	(640 , 863)	24	1990	(1740 , 2270)	0.37	(0.32 , 0.44)	29.5
C_{24} (nM)†	12	512	(452 , 580)	24	648	(571 , 734)	0.79	(0.72 , 0.87)	15.1
T_{max} (hr)#	12	6.00	(2.50 , 24.00)	24	1.81	(0.50 , 6.00)			
$t_{½}$ (hr)*	10	19.76	(32.2)	24	15.82	(24.7)			
CL/F (L/hr)*	10	8.53	(21.6)	24	5.73	(26.7)			
V_z/F (L)*	10	243	(38.4)	24	131	(31.7)			

CI = Confidence interval; CL/F = Apparent total plasma clearance of drug after oral administration (Dose/AUC0-inf); CV = Coefficient Variation; GM = Geometric mean; GMR = Least-squares Geometric Mean Ratio between treatments; N = Number of Subjects; PK = Pharmacokinetic; V_z/F = Apparent volume of distribution during the terminal phase after oral drug administration (Dose/[AUC0-inf λz])*

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_A^2 + σ_D^2 - 2*σ_{AD})/2]*

, where σ_A^2 and σ_D^2 are the estimated variances on the log scale for the two treatment groups

, and σ_{AD} is the corresponding estimated covariance, each obtained from the linear mixed effects model

#Statistics for Tmax: Median and Range (Minimum , Maximum)

**Statistics for $t_{½}$, CL/F and V_z/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

§The maximum concentration values for two subjects were reached at 24 hours post-dose. This did not allow sufficient data on the terminal linear phase of the semilog profiles for the regression analysis.

ANALYSIS DESCRIPTION:	**Safety Analysis**
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	Safety and tolerability were determined from the subjects in the All Subjects As Treated (AST) dataset as defined in the protocol. All 24 subjects were included in the assessment of safety and tolerability. The safety and tolerability was closely monitored throughout the study via physical examinations, vital signs measurements, 12-lead ECGs, and laboratory safety evaluations. All subjects were assessed for adverse events (AEs) throughout the study. Clinical and laboratory AEs were tabulated by treatment.
SUMMARY:	Single doses of MK-1439 administered alone, in vanilla yogurt, or in vanilla pudding as adult tablet or pediatric oral granules were generally well tolerated by the healthy volunteers who participated in this study. No SAE or deaths were reported. No subjects discontinued from the study due to an AE. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results. A total of 16 AEs were reported by 11 subjects. All AEs were mild in severity, transient, and had resolved by the end of the study. Overall, 11 subjects (68.75%) reported at least one AE; 2 (12.5%) subjects reported an AE in Treatment A, 4 (25.0%) subjects reported an AE in Treatment B, 3 (18.75%) subjects reported an AE in Treatment C, and 4 (25.0%) subjects reported an AE in Treatment D. The most commonly reported AE for Treatment C and Treatment D was somnolence. There were no AEs reported more than once for Treatment A and Treatment B. There were no clinically meaningful trends in clinical safety laboratory values, vital signs, or ECGs.

CONCLUSIONS:	1. The bioavailability of the pediatric oral granules is reduced approximately 25% as measured by AUC0-inf relative to the adult tablet at the same dose level of 100 mg under fasted conditions. 2. Regardless of administration without food or in pudding, the bioavailability of the pediatric oral granules (100 mg) are similarly reduced (~25% reduction in AUC0-inf) relative to the adult tablet at the same dose. 3. Similar overall total exposure (AUC0-inf) to the adult tablet (100 mg) was achieved by a pediatric oral granules formulation dose of 125 mg administered with yogurt. 4. MK-1439 is generally well tolerated following a single-dose administration of adult tablet 100 mg and pediatric oral granules 100 mg alone, or 125 mg with vanilla yogurt, or 100 mg with vanilla pudding after overnight fast.
VERSION 2 REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439	
INDICATION:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection	
PROTOCOL TITLE:	A Study of the Comparative Bioavailability of Two Second-Generation Investigational Pediatric Oral Granule Formulations of MK-1439 Compared to the Adult Formulation	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-052
	Clinical Phase:	1
TRIAL CENTER:	[redacted], MD, PhD, FRCP(C): [redacted], Canada	

DESIGN:	This was an open-label, randomized, five-period, seven-treatment, six-sequence partial cross-over study to evaluate the comparative bioavailability of two second-generation investigational pediatric oral granule formulations (uncoated and coated) of MK-1439 compared to the adult formulation tablet (henceforth referred to as 'adult tablet') of MK-1439, administered as single oral doses under fasted conditions to healthy male and female subjects. In the first 3 periods, subjects received Treatments A, B, and C, in a randomized, cross-over manner. In the last 2 periods, subjects received Treatments W and X or Treatments Y and Z, in a cross-over fashion, according to the randomly assigned treatment sequence. Treatment A consisted of a single oral dose of one 100 mg adult tablet of MK-1439 administered after an overnight fast. Treatments B, W, and X consisted of a single oral dose of 100 mg pediatric uncoated oral granules (125 oral granules x 0.8 mg) of MK-1439 administered alone (Treatment B), with vanilla pudding (Treatment W), or with apple sauce (Treatment X), after an overnight fast. Treatments C, Y, and Z consisted of a single oral dose of 100 mg pediatric coated oral granules (125 oral granules x 0.8 mg) of MK-1439 administered alone (Treatment C), with vanilla pudding (Treatment Y), or with apple sauce (Treatment Z), after an overnight fast. A washout of 7 days between drug administrations in each treatment period was observed. Plasma was collected pre-dose and at specified time points up to 72 hours post-dose for measurement of MK-1439 concentrations. Subjects rated the taste and aftertaste of the drug products through a palatability questionnaire administered immediately after and 10 minutes after receiving Treatments B, C, W, X, Y and Z. In all periods, safety and tolerability were closely monitored. Twenty-four (24) healthy, male and female subjects between the ages of 18 to 55 (inclusive) with a body mass index (BMI) ≥ 19.0 to ≤ 30 kg/m^2, participated in the study.	
	Planned duration of main phase:	Approximately 42 days

Objectives:	The 3 primary objectives of this study were: 1. To evaluate the comparative bioavailability of the MK-1439 100 mg adult tablet under fasted conditions relative to: a. MK-1439 100 mg investigational oral pediatric uncoated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions; and b. MK-1439 100 mg investigational oral pediatric coated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions. 2. To evaluate the comparative bioavailability of the MK-1439 100 mg investigational oral pediatric uncoated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions relative to: a. MK-1439 100 mg investigational oral pediatric uncoated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions when given with vanilla pudding; and b. MK-1439 100 mg investigational oral pediatric uncoated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions when given with apple sauce. 3. To evaluate the comparative bioavailability of the MK-1439 100 mg investigational oral pediatric coated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions to: a. MK-1439 100 mg investigational oral pediatric coated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions when given with vanilla pudding; and b. MK-1439 100 mg investigational oral pediatric coated granule formulation, 0.8 mg per granule (100 mg total dose), under fasted conditions when given with apple sauce.

Hypotheses:	1. The AUC0-inf, C24, and Cmax geometric mean ratio (GMR) of MK-1439 100 mg investigational oral pediatric coated and uncoated granule formulations compared to the 100 mg adult tablet was estimated under fasted conditions. 2. The AUC0-inf, C24, and Cmax GMR of MK-1439 100 mg investigational oral pediatric uncoated granule formulation when taken with vanilla pudding or apple sauce compared to the investigational oral pediatric uncoated granule formulation when taken without any food was estimated. 3. The AUC0-inf, C24, and Cmax GMR of MK-1439 100 mg investigational oral pediatric coated granule formulation when taken with vanilla pudding or apple sauce compared to the investigational oral pediatric coated granule formulation when taken without any food was estimated.	
Treatment groups	Treatment A	100 mg MK-1439 (1 adult tablet), administered under fasted conditions. [23 Subjects]
	Treatment B	100 mg MK-1439 (125 x 0.8 mg pediatric uncoated oral granules), administered under fasted conditions. [24 Subjects]
	Treatment C	100 mg MK-1439 (125 x 0.8 mg pediatric coated oral granules), administered under fasted conditions. [24 Subjects]
	Treatment W	100 mg MK-1439 (125 x 0.8 mg pediatric uncoated oral granules), administered with vanilla pudding. [12 Subjects]
	Treatment X	100 mg MK-1439 (125 x 0.8 mg pediatric uncoated oral granules), administered with apple sauce. [12 Subjects]
	Treatment Y	100 mg MK-1439 (125 x 0.8 mg pediatric coated oral granules), administered with vanilla pudding. [10 Subjects]
	Treatment Z	100 mg MK-1439 (125 x 0.8 mg pediatric coated oral granules), administered with apple sauce. [11 Subjects]

Bulk product description and manufacturing lot numbers are provided below:

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number(s)
MK-1439 100 mg adult formulation tablet	[redacted]
MK-1439 100 mg (0.8 mg/granule) pediatric uncoated oral granules formulation	[redacted] & [redacted]
MK-1439 100 mg (0.8 mg/granule) pediatric coated oral granules formulation	[redacted] & [redacted]

ENDPOINTS AND DEFINITIONS	**Primary Endpoint:**	PK	MK-1439 AUC0-inf, C24, and Cmax
	Secondary Endpoint:	Safety	Adverse events (AEs) in addition to physical examinations, vital signs measurements, and laboratory safety evaluations.
DATABASE LOCK	[redacted]-20[redacted]	**TRIAL STATUS:**	[redacted]-20[redacted] TO [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All analyses for safety and PK were performed according to the protocol and Statistical Analysis Plan (SAP).		
SUBJECT DISPOSITION:	RANDOMIZED: Male (age range) Female (age range) COMPLETED: DISCONTINUED: AE(s) Other		24 13 (21 to 52) 11 (21 to 52) 22 02 01 01
	Twenty-four (24) subjects were initially enrolled in this study as per the protocol. Two (2) subjects discontinued from the study and 22 subjects completed the study. The discontinued subjects were not replaced.		

ANALYSIS DESCRIPTION:	**Primary Analyses:** MK-1439 Pharmacokinetics The values of the pharmacokinetic (PK) parameters (AUC0-inf, C24, and Cmax) for MK-1439 after administration of the MK-1439 adult tablet and investigational oral pediatric granule (coated or uncoated formulations) without pudding and apple sauce were natural log-transformed prior to analysis and were analyzed with a linear mixed effect model with fixed effect terms for treatment. A heterogeneous compound symmetry covariance structure was used in Statistical Analysis System (SAS) PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). A two-sided 90% confidence interval (CI) for the true mean difference (each investigational pediatric oral granule coated or uncoated formulation dosed without pudding and apple sauce / adult tablet) for MK-1439 AUC0-inf, C24, and Cmax on the log scale was computed from the above linear-mixed effect model. These confidence limits were then exponentiated to obtain the 90% CIs for the true GMRs (each investigational pediatric oral granule formulation coated or uncoated without pudding and apple sauce / adult tablet) for MK-1439 AUC0-inf, C24, and Cmax. Ninety-five percent (95%) CIs were generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439 AUC0-inf, C24, and Cmax. Plots with the individual ratios, GMRs and 90% CIs were provided for MK-1439 AUC0-inf, C24, and Cmax. To evaluate the impact of administration with pudding or apple sauce for the pediatric granules (both coated and uncoated formulations), respectively, the aforementioned linear mixed model was also used. The two-sided 90% CIs for the true GMRs for comparisons between any two treatments with investigational pediatric oral granule formulations (including W versus B and, X versus B for the uncoated formulation; Y versus C and, Z versus C for the coated formulation) for MK-1439 AUC0-inf, C24, and Cmax were also provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	PK analysis was performed on available data from subjects in the Per-Protocol (PP) dataset. All subjects in this dataset were compliant with the inclusion and exclusion criteria, except for one subject who was dismissed from the study upon discovery of non-compliance to these criteria (one subject was dismissed due to suspected multiple study participation at Period 3 check-in). Additionally, one subject withdrew participation prior to Period 5 check-in. Both subjects completed at least one study treatment with available data prior to discontinuation from the study, thus, as per the protocol, were included in the PP dataset and the PK and statistical analyses.

SUMMARY:	In the fasted state, following administration of a 100 mg single oral dose of MK-1439 pediatric uncoated oral granules (125 x 0.8mg), MK-1439 AUC0-inf, Cmax and C24 were relatively similar to administration of the adult tablet (observed GMR point estimates ranged between 0.92-0.96). In the fasted state, following administration of a 100 mg single oral dose of MK-1439 pediatric coated oral granules (125 x 0.8mg), MK-1439 AUC0-inf and Cmax decreased by 11% and 23%, respectively, while C24 was similar (observed GMR=0.95) relative to administration of the adult tablet. Following administration of a 100 mg single oral dose of MK-1439 pediatric uncoated oral granules in vanilla pudding, MK-1439 AUC0-inf, Cmax, and C24 were similar compared to values obtained after a 100 mg single oral dose of MK-1439 pediatric uncoated oral granules administered alone (observed GMRs = 1.10, 1.04, and 1.04, respectively). Following administration of a 100 mg single oral dose of MK-1439 pediatric uncoated oral granules in apple sauce, MK-1439 AUC0-inf, Cmax, and C24 increased by 29%, 56%, and 20%, respectively, compared to values obtained after a 100 mg single oral dose of MK-1439 pediatric uncoated oral granules administered alone. After administration of a 100 mg single oral dose of MK-1439 pediatric coated oral granules in vanilla pudding, MK-1439 AUC0-inf, Cmax, and C24 were relatively similar compared to values obtained after a 100 mg single oral dose of MK-1439 pediatric coated oral granules administered alone (observed GMRs = 0.99, 0.90, and 0.96, respectively) After administration of a 100 mg single oral dose of MK-1439 pediatric coated oral granules in apple sauce, MK-1439 AUC0-inf, Cmax, and C24 increased by 26%, 59%, and 21%, respectively, compared to values obtained after a 100 mg single oral dose of MK-1439 pediatric coated oral granules administered alone.

Summary Statistics for MK-1439 Plasma Pharmacokinetics Following Single Oral Dose Administration of MK-1439 100 mg Adult Tablet, MK-1439 100 mg Pediatric Uncoated Granules (125x0.8 mg) and MK-1439 100 mg Pediatric Coated Granules (125x0.8 mg) Under Fasted Conditions in Healthy Adult Subjects

	MK-1439 100 mg adult tablet			***MK-1439 100 mg pediatric uncoated granules (125 x 0.8 mg)***			***MK-1439 100 mg pediatric coated granules (125 x 0.8 mg)***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***
AUC0-inf (hr·µM)†	23	43.1	(37.7 , 49.3)	24	39.6	(34.3 , 45.7)	24	38.5	(33.9 , 43.7)
Cmax (nM)†	23	2100	(1880 , 2340)	24	1950	(1780 , 2140)	24	1610	(1440 , 1790)
C24 (nM)†	23	650	(556 , 759)	24	622	(527 , 735)	24	615	(541 , 700)
Tmax (hr)#	23	2.00	(0.50 , 5.00)	24	2.50	(1.00 , 4.00)	24	2.50	(1.00 , 5.00)
t½ (hr)*	23	15.22	(35.3)	24	14.64	(22.8)	24	16.16	(31.9)
CL/F (L/hr)*	23	5.50	(32.1)	24	5.93	(35.2)	24	6.10	(31.0)
Vz/F (L)*	23	121	(29.5)	24	125	(22.7)	24	142	(25.5)

	MK-1439 100 mg pediatric uncoated granules (125 x 0.8 mg) / MK-1439 100 mg adult tablet			***MK-1439 100 mg pediatric coated granules (125 x 0.8 mg) / MK-1439 100 mg adult tablet***		
PK Parameter	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
AUC0-inf†	0.92	(0.87 , 0.97)	11.1	0.89	(0.85 , 0.94)	10.4
Cmax†	0.93	(0.86 , 1.01)	16.4	0.77	(0.70 , 0.84)	17.6
C24†	0.96	(0.90 , 1.02)	13.5	0.95	(0.89 , 1.01)	12.5

GM = Geometric mean; CI = Confidence interval; GMR = Least-squares Geometric Mean Ratio between treatments
† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_1^2 + σ_2^2 - 2*$\rho\sigma_1\sigma_2$)/2], where σ_1^2 and σ_2^2 are the estimated variances on the log scale for the two treatment groups, and ρ is the correlation parameter, each obtained from the linear mixed effects model*
 # Statistics for Tmax: Median and Range (Minimum , Maximum)
** Statistics for t½, CL/F and Vz/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

Summary Statistics for MK-1439 Plasma Pharmacokinetics Following Single Oral Dose Administration of MK-1439 100 mg Pediatric Uncoated Granules (125 x 0.8 mg) Alone, with Vanilla Pudding or with Apple Sauce in Healthy Adult Subjects

	MK-1439 100 mg pediatric uncoated granules (125 x 0.8 mg)			***MK-1439 100 mg pediatric uncoated granules with vanilla pudding (125 x 0.8 mg)***			***MK-1439 100 mg pediatric uncoated granules with apple sauce (125 x 0.8 mg)***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***
AUC0-inf (hr·µM)†	24	39.6	(34.3 , 45.7)	12	43.7	(37.1 , 51.5)	12	51.2	(43.9 , 59.7)
Cmax (nM)†	24	1950	(1780 , 2140)	12	2030	(1750 , 2360)	12	3040	(2750 , 3370)
C24 (nM)†	24	622	(527 , 735)	12	645	(539 , 773)	12	743	(615 , 899)
Tmax (hr)#	24	2.50	(1.00 , 4.00)	12	1.00	(1.00 , 4.00)	12	2.00	(0.50 , 4.00)
t½ (hr)*	24	14.64	(22.8)	12	14.86	(31.6)	12	12.06	(26.7)
CL/F (L/hr)*	24	5.93	(35.2)	12	5.58	(34.5)	12	4.76	(33.4)
Vz/F (L)*	24	125	(22.7)	12	120	(32.3)	12	82.8	(22.8)

	MK-1439 100 mg pediatric uncoated granules with vanilla pudding (125 x 0.8 mg) / MK-1439 100 mg pediatric uncoated granules (125 x 0.8 mg)			***MK-1439 100 mg pediatric uncoated granules with apple sauce (125 x 0.8 mg) / MK-1439 100 mg pediatric uncoated granules (125 x 0.8 mg)***		
PK Parameter	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
AUC0-inf†	1.10	(1.02 , 1.19)	11.7	1.29	(1.20 , 1.39)	11.3
Cmax†	1.04	(0.93 , 1.17)	16.9	1.56	(1.43 , 1.70)	13.9
C24†	1.04	(0.95 , 1.13)	13.8	1.20	(1.09 , 1.31)	14.1

GM = Geometric mean; CI = Confidence interval; GMR = Least-squares Geometric Mean Ratio between treatments

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_1^2 + σ_2^2 - 2*$\rho\sigma_1\sigma_2$)/2], where σ_1^2 and $\sigma_2^2$are the estimated variances on the log scale for the two treatment groups, and ρ is the correlation parameter, each obtained from the linear mixed effects model*

#Statistics for Tmax: Median and Range (Minimum , Maximum)

**Statistics for t½, CL/F and Vz/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

Summary Statistics for MK-1439 Plasma Pharmacokinetics Following Single Oral Dose Administration of MK-1439 100 mg Pediatric Coated Granules (125 x 0.8 mg) Alone, with Vanilla Pudding or with Apple Sauce in Healthy Adult Subjects

	MK-1439 100 mg pediatric coated granules (125 x 0.8 mg)			***MK-1439 100 mg pediatric coated granules with vanilla pudding (125 x 0.8 mg)***			***MK-1439 100 mg pediatric coated granules with apple sauce (125 x 0.8 mg)***		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***
AUC0-inf (hr·µM)†	24	38.5	(33.9 , 43.7)	10	38.1	(32.3 , 44.9)	11	48.4	(42.5 , 55.1)
Cmax (nM)†	24	1610	(1440 , 1790)	10	1460	(1230 , 1730)	11	2560	(2390 , 2760)
C24 (nM)†	24	615	(541 , 700)	10	588	(502 , 689)	11	745	(641 , 866)
Tmax (hr)#	24	2.50	(1.00 , 5.00)	10	2.50	(1.50 , 4.00)	11	2.50	(1.00 , 4.00)
t½ (hr)*	24	16.16	(31.9)	10	17.35	(34.1)	11	13.86	(23.3)
CL/F (L/hr)*	24	6.10	(31.0)	10	6.30	(37.5)	11	4.77	(32.0)
Vz/F (L)*	24	142	(25.5)	10	158	(28.6)	11	95.4	(11.2)

	MK-1439 100 mg pediatric coated granules with vanilla pudding (125 x 0.8 mg) / MK-1439 100 mg pediatric coated granules (125 x 0.8 mg)			***MK-1439 100 mg pediatric coated granules with apple sauce (125 x 0.8 mg) / MK-1439 100 mg pediatric coated granules (125 x 0.8 mg)***		
PK Parameter	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
AUC0-inf†	0.99	(0.91 , 1.07)	11.5	1.26	(1.18 , 1.34)	9.8
Cmax†	0.90	(0.79 , 1.03)	18.5	1.59	(1.47 , 1.73)	15.4
C24†	0.96	(0.88 , 1.04)	11.3	1.21	(1.12 , 1.30)	11.0

GM = Geometric mean; CI = Confidence interval; GMR = Least-squares Geometric Mean Ratio between treatments

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

*‡ Pseudo Within-Subject CV% = 100*sqrt[(σ_1^2 + σ_2^2 - 2*$\rho\sigma_1\sigma_2$)/2], where σ_1^2 and $\sigma_2^2$are the estimated variances on the log scale for the two treatment groups, and ρ is the correlation parameter, each obtained from the linear mixed effects model*

#Statistics for Tmax: Median and Range (Minimum , Maximum)

**Statistics for t½, CL/F and Vz/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

ANALYSIS DESCRIPTION:	**Safety Analysis** Incidence of the number of subjects with AEs was descriptively summarized and listed by treatment. The incidence of the number of subjects with drug-related AEs was descriptively summarized.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	Safety and tolerability were determined from the subjects in the All Subjects As Treated (AST) dataset, as defined in the protocol. All 24 subjects were included in the assessment of safety and tolerability.
SUMMARY:	Single doses of MK-1439 as an adult tablet or as pediatric oral granules (coated or uncoated), administered alone, with vanilla pudding, or with apple sauce, were generally well tolerated by the healthy volunteers who participated in this study. No Serious Adverse Events (SAEs) or deaths were reported in this study. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results. A total of 28 AEs affecting 16 subjects (66.7%) were reported in the study as follows: • Treatment B: 10 AEs were reported by 7 subjects (29.2%); • Treatment C: 9 AEs were reported by 7 subjects (29.2%); • Treatment X: 6 AEs were reported by 5 subjects (41.7%); • Treatment Y: 3 AEs were reported by 3 subjects (30.0%); and • No AEs were reported following administration of Treatment A, W, or Z. While the majority of AEs (23 of 28 AEs affecting 15 [62.5%] subjects) were deemed related to study treatment, all AEs were mild in severity and resolved. The most commonly reported AEs in this study were ‘hypoaesthesia oral’ (13 events by 9 subjects [37.5%]) and ‘somnolence’ (6 events by 6 subjects [25.0%]). All ‘hypoaesthesia oral’ and ‘somnolence’ AEs were considered related to the study drug. One subject withdrew participation from the study due to ongoing AEs (‘headache’ [treatment-related] and ‘rhinorrhoea’ [treatment-unrelated]) which later resolved. There were no clinically meaningful trends in laboratory safety measurements or vital signs reported during this study.

CONCLUSIONS:	1. Doravirine AUC0-inf, Cmax, and C24 of the pediatric uncoated oral granules were similar to the adult tablet at the same dose level of 100 mg under fasted conditions. 2. Doravirine AUC0-inf and Cmax of the pediatric coated oral granules were reduced approximately 11% and 23%, respectively, while concentrations 24 hours post-dose (C24) were similar to the adult tablet at the same dose level of 100 mg, under fasted conditions. 3. Doravirine AUC0-inf, Cmax, and C24 of the pediatric uncoated oral granules administered with vanilla pudding were similar to the uncoated granules administered alone. 4. Following administration of the pediatric uncoated oral granules given with apple sauce compared to the uncoated oral granules administered alone, AUC0-inf, Cmax and C24, increased by 29%, 56%, and 20%, respectively. 5. Similar values were observed for AUC0-inf, Cmax and C24, following administration of the coated pediatric granules with vanilla pudding compared to the coated pediatric granules administered alone. 6. Following administration of the coated pediatric granules with apple sauce compared to the coated pediatric granules administered alone, the bioavailability, as measured by AUC0-inf, Cmax and C24, increased by 26%, 59%, and 21%, respectively. 7. A higher percentage of subjects rated the pediatric uncoated granules as having an overall negative taste compared to the pediatric coated granules, regardless of administration alone, with vanilla pudding or apple sauce. Administration with vanilla pudding improved the taste score of the uncoated pediatric granules, while apple sauce improved the taste score of the coated pediatric granules. 8. Single doses of MK-1439 administered as an adult tablet, pediatric uncoated granules (alone, with vanilla pudding and with apple sauce) and pediatric coated granules (alone, with vanilla pudding and with apple sauce), were generally well tolerated by the healthy volunteers who participated in this study.
FINAL REPORT DATE:	[redacted]-20[redacted]

[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*
Title of Study: A Fasted Bioavailability Study of Two Probe MK-1439A Formulations in Healthy Subjects
Investigators: [redacted] M.D., Ph.D., FRCP(C) M.D., M.Sc., CCFP
Study Centre(s): **Clinical Facility:** [redacted] Canada, [redacted] **Clinical Laboratory:** [redacted] Canada, [redacted] **Pharmacokinetic, Statistical and Report Issuing Facility:** [redacted] Canada, [redacted] **Analytical Facility:** [redacted] The Netherlands [redacted] Canada [redacted]
Study Periods: **Period 1:** [redacted], 20[redacted] **Period 2:** [redacted], 20[redacted] **Period 3:** [redacted], 20[redacted] **Phase of Development:** Comparative Bioavailability

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Objective:
The objective of this study is to evaluate the comparative bioavailability between:
- MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets from Merck Sharp & Dohme Corp., USA,
- MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets from Merck Sharp & Dohme Corp., USA and
- MK-1439 100 mg Oral Compressed Tablets from Merck Sharp & Dohme Corp., USA, co-administered with Epivir® 300 mg Tablets from ViiV Healthcare, USA and Viread® 300 mg Tablets from Gilead Sciences, Inc., USA

after a single-dose in healthy subjects under fasting conditions.

Methodology:
- This is an open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover study comparative bioavailability study.
- Subjects were randomly assigned to one of the six dosing sequences ABC, ACB, BAC, BCA, CAB, or CBA under fasting conditions.
- Concentrations of MK-1439, lamivudine and tenofovir were measured from the samples collected over a 72-hour interval after dosing in each period.

Number of subjects (planned and analyzed):
- Twenty-four (24) subjects were dosed in Period 1.
- Twenty-three (23) subjects completed the study.
- Twenty-four (24) subjects were included in the pharmacokinetic and statistical datasets.

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 33.0 kg/m^2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, and physical examination and vital signs measurements.

Test Product 1 (Treatment A):
MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets
(Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency Value: 99.2 MK-1439; 96.2 lamivudine; 95.5 tenofovir % of label claim
Manufacturing Date: [redacted]-20[redacted]
Re-Evaluation Date: [redacted]-20[redacted]
Dose: 100 mg MK-1439/300 mg lamivudine/300 mg tenofovir
Mode of Administration: Oral under fasting conditions

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*
Test Product 2 (Treatment B): MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets (Merck Sharp & Dohme Corp., USA) Lot No.: [redacted] Potency Value: 95.2 MK-1439; 101.5 lamivudine; 98.2 tenofovir % of label claim Manufacturing Date: [redacted]-20[redacted] Re-Evaluation Date: [redacted]-20[redacted] Dose: 100 mg MK-1439/300 mg lamivudine/300 mg tenofovir Mode of Administration: Oral under fasting conditions
Reference Products 1+2+3 (Treatment C): MK-1439 100 mg Oral Compressed Tablets (Merck Sharp & Dohme Corp., USA) Lot No.: [redacted] Potency Value: 97.4 % of label claim Manufacturing Date: [redacted] 20[redacted] Re-Evaluation Date: [redacted] 20[redacted] Dose: 100 mg Mode of Administration: Oral under fasting conditions
<u>Co-administered with:</u> Epivir® 300 mg Tablets (ViiV Healthcare, USA) Lot No.: [redacted] Potency Value: Not Available Expiry Date: [redacted] 20[redacted] Dose: 300 mg Mode of Administration: Oral under fasting conditions
<u>and:</u> Viread® 300 mg Tablets (Gilead Sciences, Inc., USA) Lot No.: [redacted] Potency Value: Not Available Expiry Date: [redacted] 20[redacted] Dose: 300 mg Mode of Administration: Oral under fasting conditions
Duration of treatment: Single-dose treatment

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Criteria for Evaluation:
Pharmacokinetic:
AUC0-last, AUC0-inf, C24, Cmax, Tmax, Kel and Thalf were estimated using a non-compartmental approach based on plasma MK-1439, lamivudine, and tenofovir levels for each subject included in the pharmacokinetic dataset.
Safety:
Safety was assessed based on vital signs measurements and on the severity and causality of adverse events experienced by subjects who received drug administration.

Statistical Methods:
- The endpoints AUC0-last, AUC0-inf and Cmax were analyzed (SAS PROC MIXED) with a linear mixed effects model with fixed effects terms for treatment and period.
- A log transformation was applied to the AUC0-last, AUC0-inf and Cmax data. Back-transformed summary statistics and inferential results were reported for the AUC0-last, AUC0-inf and Cmax pharmacokinetic parameters. The 90% confidence intervals, based on the t-distribution, were generated from the mixed-effect model for the geometric mean ratios:
  - Treatment A versus Treatment C
  - Treatment B versus Treatment C

  for MK-1439, lamivudine and tenofovir AUC0-last, AUC0-inf and Cmax.
- 95% CIs were generated from the mixed-effect model for the geometric means by treatment for MK-1439, lamivudine and tenofovir, AUC0-last, AUC0-inf and Cmax.
- C24 for MK-1439 were analyzed in a similar manner.

Study Report Version 2:
Version 2 of this study report was generated to amend the contents of appendix 16.2.8 to include a listing of clinical laboratory results, as well as removing Subject ID numbers from all tables and listings per sponsor request.

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

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

Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Summary-Conclusions:
Pharmacokinetic Results:

Based on Measured Plasma MK-1439 Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC0-last	**A**	24	39.8	35.8 - 44.1	**A vs. C**	100.22	92.77 - 108.26	15.3
(µM.h)	**B**	24	33.5	30.6 - 36.6	**B vs. C**	84.37	79.06 - 90.03	12.8
	C	23	39.7	36.2 - 43.5		-	-	-
Cmax	**A**	24	1.51	1.32 - 1.71	**A vs. C**	97.67	89.30 - 106.83	17.8
(µM)	**B**	24	1.10	0.986 - 1.23	**B vs. C**	71.33	65.17 - 78.08	18.0
	C	23	1.54	1.37 - 1.73		-	-	-
AUC0-inf	**A**	24	42.7	38.5 - 47.4	**A vs. C**	100.18	93.12 - 107.78	14.4
(µM.h)	**B**	24	36.5	33.2 - 40.3	**B vs. C**	85.77	80.02 - 91.93	13.7
	C	23	42.6	38.5 - 47.2		-	-	-
C24h	**A**	24	0.687	0.608 - 0.776	**A vs. C**	101.80	92.59 - 111.92	19.0
(µM)	**B**	24	0.588	0.530 - 0.652	**B vs. C**	87.14	81.74 - 92.91	12.6
	C	23	0.675	0.609 - 0.747		-	-	-
			Median	***Range***				
Tmax	**A**	24	3.00	1.00-12.00				
(h)	**B**	24	4.00	2.00- 6.03				
	C	23	3.00	0.50- 6.00				
			GM	***CV(%)*****				
t½	**A**	24	17.35	25.5				
(h)	**B**	24	18.57	26.0				
	C	23	17.77	26.6				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma^2_1 + \sigma^2_2 - 2*\sigma_{12})/2]$*
*** GCV = 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale*

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

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

Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Based on Measured Plasma Lamivudine Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC0-last	**A**	24	10900	9800 - 12200	**A vs. C**	102.51	98.56 - 106.61	7.8
(ng.h/mL)	**B**	24	11600	10400 - 13000	**B vs. C**	108.93	105.54 - 112.42	6.2
	C	23	10700	9540 - 12000		-	-	-
Cmax	**A**	24	2170	1900 - 2480	**A vs. C**	92.64	85.95 - 99.85	14.9
(ng/mL)	**B**	24	2540	2260 - 2850	**B vs. C**	108.29	101.57 - 115.45	12.6
	C	23	2340	2050 - 2680		-	-	-
AUC0-inf	**A**	21	11100	10000 - 12300	**A vs. C**	102.00	97.52 - 106.68	8.3
(ng.h/mL)	**B**	22	11900	10600 - 13200	**B vs. C**	108.69	105.22 - 112.28	6.0
	C	21	10900	9760 - 12200		-	-	-
			Median	***Range***				
Tmax	**A**	24	2.00	1.00- 3.00				
(h)	**B**	24	1.00	1.00- 2.00				
	C	23	1.00	0.50- 3.00				
			GM	***CV(%)*****				
t½	**A**	21	12.59	62.3				
(h)	**B**	22	12.51	77.3				
	C	21	11.56	66.2				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma^2_1 + \sigma^2_2 - 2*\sigma_{12})/2]$*
*** $GCV = 100 \times sqrt(exp(s^2) - 1)$, where s^2 is the observed variance on the natural log-scale*

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

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

Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Based on Measured Plasma Tenofovir Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC0-last	**A**	24	1880	1630 - 2180	**A vs. C**	99.49	94.58 - 104.65	10.0
(ng.h/mL)	**B**	24	1850	1600 - 2140	**B vs. C**	97.65	92.48 - 103.12	10.8
	C	23	1890	1640 - 2180		-	-	-
Cmax	**A**	24	202	174 - 235	**A vs. C**	91.22	80.76 - 103.03	24.3
(ng/mL)	**B**	24	192	167 - 222	**B vs. C**	86.79	78.55 - 95.90	19.7
	C	23	221	183 - 268		-	-	-
AUC0-inf	**A**	24	1980	1710 - 2300	**A vs. C**	99.39	94.55 - 104.48	9.9
(ng.h/mL)	**B**	24	1950	1680 - 2260	**B vs. C**	97.53	92.27 - 103.08	11.0
	C	23	2000	1720 - 2310		-	-	-
			Median	***Range***				
Tmax	**A**	24	1.00	1.00- 2.08				
(h)	**B**	24	1.01	0.50- 3.00				
	C	23	1.00	0.50- 3.00				
			GM	***CV(%)*****				
t½	**A**	24	18.03	12.2				
(h)	**B**	24	17.82	13.3				
	C	23	18.14	14.1				

** Estimated based on the elements of the variance-covariance matrix as: CV(%) = 100*sqrt[(σ^2_1 + σ^2_2 -2*σ_{12})/2]*
*** GCV = 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale*

Safety Results:

No serious AEs 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.

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3137
Protocol Number: 014-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 50 mg/150 mg/150 mg Bilayer Tablets and MK-1439A 100 mg/300 mg/300 mg Monolithic Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Conclusions:

The pharmacokinetics of MK-1439, lamivudine, and tenofovir were similar following a single dose of the MK-1439A 50 mg/150 mg/150 mg Bilayer Tablet and following a single dose of the MK-1439 100 mg Oral Compressed Tablet co-administered with the Epivir® 300 mg and Viread® 300 mg Tablets.

The AUC0-inf, AUC0-last and Cmax of MK-1439 following a single dose of the MK-1439A 100 mg/300 mg/300 mg Monolithic Tablet are ~14%, ~16% and ~29% lower than the corresponding values obtained following a single dose of the MK-1439 100 mg Oral Compressed Tablet co-administered with the Epivir® 300 mg and Viread® 300 mg Tablets.

The pharmacokinetics of lamivudine were similar following a single dose of the MK-1439A 100 mg/300 mg/300 mg Monolithic Tablet and a single dose of MK-1439 100 mg Oral Compressed Tablet co-administered with the Epivir® 300 mg and Viread® 300 mg Tablets.

The AUC0-inf and AUC0-last of tenofovir following a single dose of the MK-1439A 100 mg/300 mg/300 mg Monolithic Tablet are similar to the AUC0-inf and AUC0-last obtained following a single dose of MK-1439 100 mg Oral Compressed Tablets co-administered with Epivir® 300 mg Tablets and Viread® 300 mg Tablets. The Cmax of tenofovir following a single dose of the MK-1439A 100 mg/300 mg/300 mg Monolithic Tablet is ~13% lower than Cmax obtained following single doses of MK-1439 100 mg Oral Compressed Tablets co-administered with Epivir® 300 mg Tablets and Viread® 300 mg Tablets.

Both test products exhibited similar total and peak exposure for lamivudine as compared to the reference products. While both test formulations displayed similar total exposure for tenofovir compared to the reference, the bi-layer tablets (Treatment A) showed a relatively higher peak exposure compared to the monolithic tablets (Treatment B), resulting in Cmax values closer to those achieved by the reference. Of the two test formulations, the bi-layer tablets (Treatment A) displayed a comparable total and peak exposure for MK-1439A relative to the reference, while the monolithic tablet (Treatment B) exhibited a lower peak and total exposure for MK-1439A relative to the reference.

Date of Version 2 Report: Final Report: [redacted] 20[redacted]

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Title of Study:
A Fasted Bioavailability Study of a Probe MK-1439A Formulation in Healthy Subjects

Investigators:
[redacted] MD, PhD, FRCP(C)
[redacted] MD, MSc, CCFP

Study Centre(s):

Clinical Facility: [redacted] Canada, [redacted]

Clinical Laboratory: [redacted] Canada, [redacted]

Bioanalytical Facilities: [redacted] The Netherlands

[redacted] Canada [redacted]

Pharmacokinetic and Statistical Facility: [redacted] Canada, [redacted]

Report Issuing Facility: [redacted] Canada, [redacted]

Phase of Development: Comparative Bioavailability

Study Periods:
Period 1: [redacted], 20[redacted]
Period 2: [redacted], 20[redacted]

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Objective:
To evaluate the comparative bioavailability between:

- MK-1439A 100 mg/300 mg/300 mg Tablets (Merck Sharp & Dohme Corp., USA) and
- MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA), co-administered with Epivir® 300 mg Tablets (ViiV Healthcare, USA) and Viread® 300 mg Tablets (Gilead Sciences, Inc., USA)

after a single-dose in healthy subjects under fasting conditions.

Methodology:

- This is an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.
- This study is designed to evaluate the comparative bioavailability in healthy male and female subjects under fasting conditions.
- Concentrations of MK-1439, lamivudine and tenofovir were measured from the samples collected over a 72-hour interval after dosing in each period.
- The following pharmacokinetic parameters were estimated using a non-compartmental approach for MK-1439:

  AUC0-last, AUC0-inf, C24, Cmax, Tmax, Kel and Thalf.

- The following pharmacokinetic parameters were estimated using a non-compartmental approach for lamivudine and tenofovir:

  AUC0-last, AUC0-inf, Cmax, Tmax, Kel and Thalf.

Number of subjects (planned and analyzed):

- Planned for inclusion: 24 subjects
- Total number of subjects that completed all periods of the study: 24 subjects
- Included in the safety data analyses: 24 subjects
- Included in the pharmacokinetic data analyses: 24 subjects
- Included in the statistical data analyses: 24 subjects

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 33.0 kg/m^2, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements.

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*
Test Product (Treatment A): MK-1439A 100 mg/300 mg/300 mg Tablets (Merck Sharp & Dohme Corp., USA) Lot No.: [redacted] Potency: MK-1439 - 98.6% of label claim Lamivudine – 96.3% of label claim Tenofovir – 92.3% of label claim Use by End Date: [redacted]/20[redacted] Dose: 100 mg MK-1439/300 mg lamivudine/300 mg tenofovir Mode of Administration: Oral under fasting conditions
(Treatment B) Co-administration of: **Reference Product 1:** MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA) Lot No.: [redacted] Potency: 97.4% of label claim Use by End Date: [redacted]/20[redacted] Dose: 100 mg of MK-1439 Mode of Administration: Oral under fasting conditions
Reference Product 2: Epivir® 300 mg Tablets (ViiV Healthcare, USA) Lot No.: [redacted] Potency: Not Available Expiry Date: [redacted] 20[redacted] Dose: 300 mg of lamivudine Mode of Administration: Oral under fasting conditions
Reference Product 3: Viread® 300 mg Tablets (Gilead Sciences, Inc., USA) Lot No.: [redacted] Potency Value: Not Available Expiry Date: [redacted] 20[redacted] Dose: 300 mg of tenofovir Mode of Administration: Oral under fasting conditions
Duration of treatment: Single-Dose treatment

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*
Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Statistical Methods:

- The endpoints AUC0-last, AUC0-inf and Cmax were analyzed (SAS PROC MIXED) with a linear mixed effects model with fixed effects terms for treatment and period.
- A log transformation was applied to the AUC0-last, AUC0-inf and Cmax data. Back-transformed summary statistics and inferential results were reported for the AUC0-last, AUC0-inf and Cmax pharmacokinetic parameters. The 90% confidence intervals, based on the t-distribution, were generated from the above mixed-effect model for the geometric mean ratios:
    - Treatment A versus Treatment B

  for MK-1439, lamivudine and tenofovir, AUC0-last, AUC0-inf and Cmax.
- 95% CIs were also generated from the above mixed-effect model for the geometric means by treatment for MK-1439, lamivudine and tenofovir, AUC0-last, AUC0-inf and Cmax.
- C24 was also analyzed in a similar manner for MK-1439.

Study Report Version 2:
Version 2 of this study report was generated to amend the contents of appendix 16.2.8 to include a listing of clinical laboratory results, as well as removing Subject ID numbers from all tables and listings per sponsor request.

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

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

Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Results:
Pharmacokinetic Results:

Based on Measured Plasma MK-1439 Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
$AUC_{0\text{-last}}$	**A**	24	40.1	35.3 - 45.5	**A vs B**	106.85	99.31 - 114.97	14.8
(hr·µM)	**B**	24	37.5	34.1 - 41.2		-	-	-
$AUC_{0\text{-inf}}$	**A**	22	43.3	38.5 - 48.7	**A vs B**	109.51	101.84 - 117.76	13.9
(hr·µM)	**B**	24	39.5	35.8 - 43.6		-	-	-
C_{max}	**A**	24	1.84	1.59 - 2.14	**A vs B**	112.89	101.37 - 125.72	21.7
(µM)	**B**	24	1.63	1.48 - 1.80		-	-	-
C_{24hr}	**A**	24	0.628	0.538 - 0.733	**A vs B**	105.44	98.60 - 112.75	13.5
(µM)	**B**	24	0.596	0.517 - 0.687		-	-	-
			Median	***Range***				
T_{max}	**A**	24	3.00	0.50- 6.03				
(h)	**B**	24	3.00	1.00- 4.00				
			GM	***CV(%)*****				
t½	**A**	22	15.5	30.9				
(h)	**B**	24	15.7	25.1				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$*

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

Treatment A: MK-1439A 100mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp., USA)*
Treatment B: MK-1439/Epivir®/Viread® 100 mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp./ViiV Healthcare/Gilead Sciences, Inc., USA)*

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

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

Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Based on Measured Plasma Lamivudine Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
$AUC_{0\text{-last}}$	**A**	24	12600	11700 - 13600	**A vs B**	98.86	93.83 - 104.15	10.5
(hr·ng/mL)	**B**	24	12800	11700 - 13900		-	-	-
$AUC_{0\text{-inf}}$	**A**	24	12900	12000 - 13900	**A vs B**	98.49	93.65 - 103.57	10.2
(hr·ng/mL)	**B**	24	13100	12100 - 14200		-	-	-
C_{max}	**A**	24	2620	2330 - 2940	**A vs B**	92.23	83.18 - 102.26	20.8
(ng/mL)	**B**	24	2840	2490 - 3240		-	-	-
			Median	***Range***				
T_{max}	**A**	24	1.01	1.00- 4.00				
(h)	**B**	24	1.00	0.50- 3.00				
			GM	***CV(%)*****				
t½	**A**	24	18.8	56.7				
(h)	**B**	24	18.5	58.7				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$*

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

Treatment A: MK-1439A 100mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp., USA)*
Treatment B: MK-1439/Epivir®/Viread® 100 mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp./ViiV Healthcare/Gilead Sciences, Inc., USA)*

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

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

Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Based on Measured Plasma Tenofovir Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
$AUC_{0\text{-last}}$	**A**	24	2280	2040 - 2560	**A vs B**	98.09	92.02 - 104.56	12.9
(hr·ng/mL)	**B**	24	2330	2080 - 2610		-	-	-
$AUC_{0\text{-inf}}$	**A**	24	2440	2170 - 2750	**A vs B**	98.56	92.46 - 105.07	12.9
(hr·ng/mL)	**B**	24	2480	2200 - 2790		-	-	-
C_{max}	**A**	24	242	205 - 286	**A vs B**	83.67	75.40 - 92.85	21.0
(ng/mL)	**B**	24	289	259 - 323		-	-	-
			Median	***Range***				
T_{max}	**A**	24	1.00	1.00- 3.02				
(h)	**B**	24	0.76	0.50- 2.08				
			GM	***CV(%)*****				
t½	**A**	24	19.2	17.7				
(h)	**B**	24	18.7	12.3				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$*

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

Treatment A: MK-1439A 100mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp., USA)*
Treatment B: MK-1439/Epivir®/Viread® 100 mg/300 mg/300 mg Tablets, Lot No.: [redacted] *(MSD Corp./ViiV Healthcare/Gilead Sciences, Inc., USA)*

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[redacted] [redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

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

Name of Finished Product: *MK-1439A 100 mg/300 mg/300 mg Tablets*

Name of Active Ingredient: *MK-1439, lamivudine and tenofovir*

Safety Results:

	Severity			Relation to the Drug					Intervention	
TRT	Mild	Moderate	Severe	Definitely Related	Probably Related	Possibly Related	Probably Not Related	Definitely Not Related	DT	NDT
A	6	0	0	0	0	3	0	3	0	0
B	10	0	0	0	0	7	0	3	0	0
Total	16	0	0	0	0	10	0	6	0	0

There were 16 adverse events (AEs) involving 11 subjects in the study. All adverse events were judged to be mild in severity.

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.

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

Conclusions:

Following single dose administration of the fixed dose combination MK-1439A 100 mg/300 mg/300 mg Tablets or MK-1439 100 mg co-administered with Epivir® 300 mg Tablets and Viread® 300 mg Tablets:

1. MK-1439 total exposure was similar, but peak exposure was ~13% higher, for the FDC relative to co-administration.
2. Lamivudine total and peak exposure were similar for the FDC compared to co-administration.
3. Tenofovir total exposure was similar, but the peak exposure was ~17% lower, for the FDC, relative to co-adminstration.
4. Single dose administration of MK-1439A 100 mg/300 mg/300 mg Tablets or co-administration of MK-1439 100 mg with Epivir® 300 mg Tablets and Viread® 300 mg Tablets was generally well-tolerated.

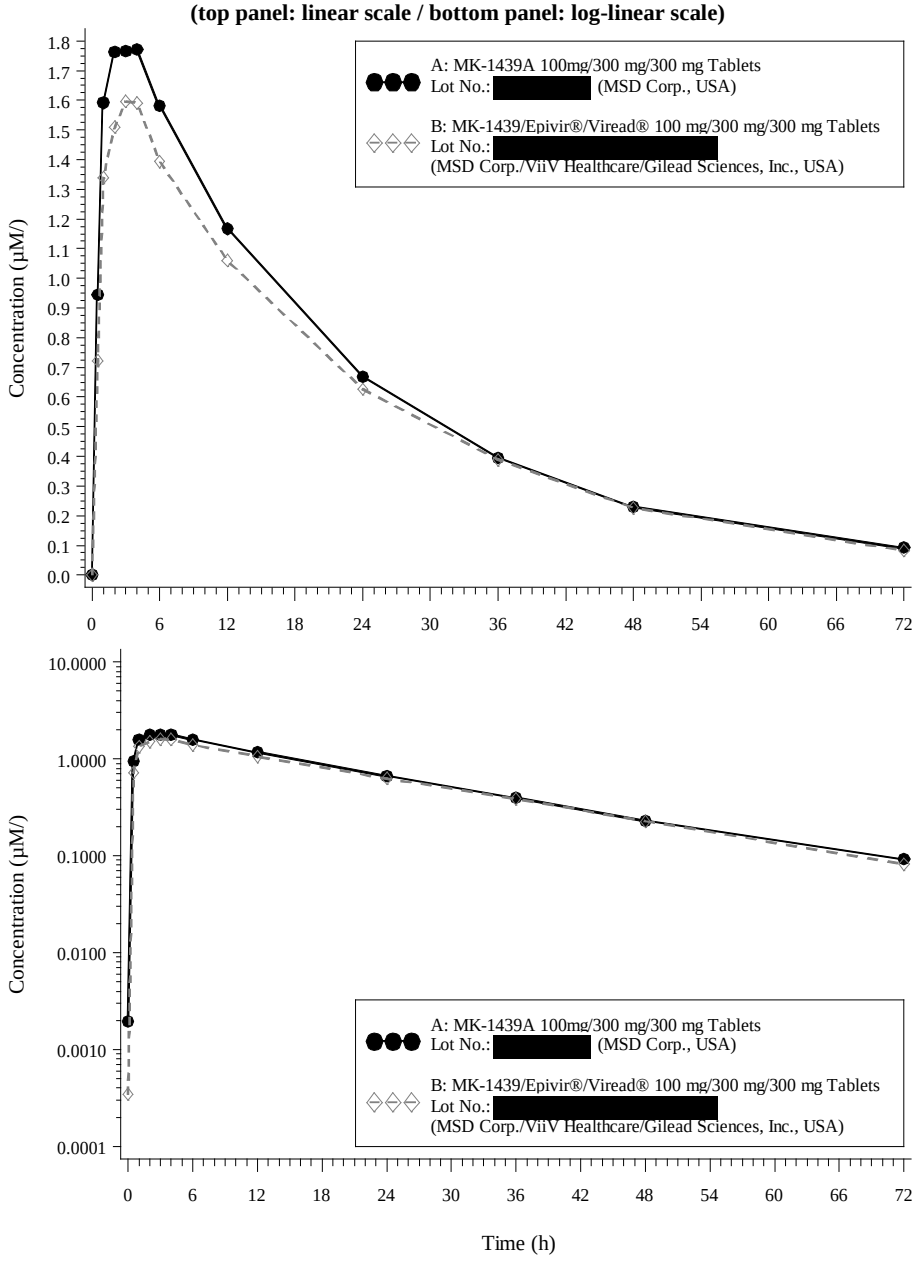
Date of Version 2 Report: Final Report: [redacted] 20[redacted]

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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

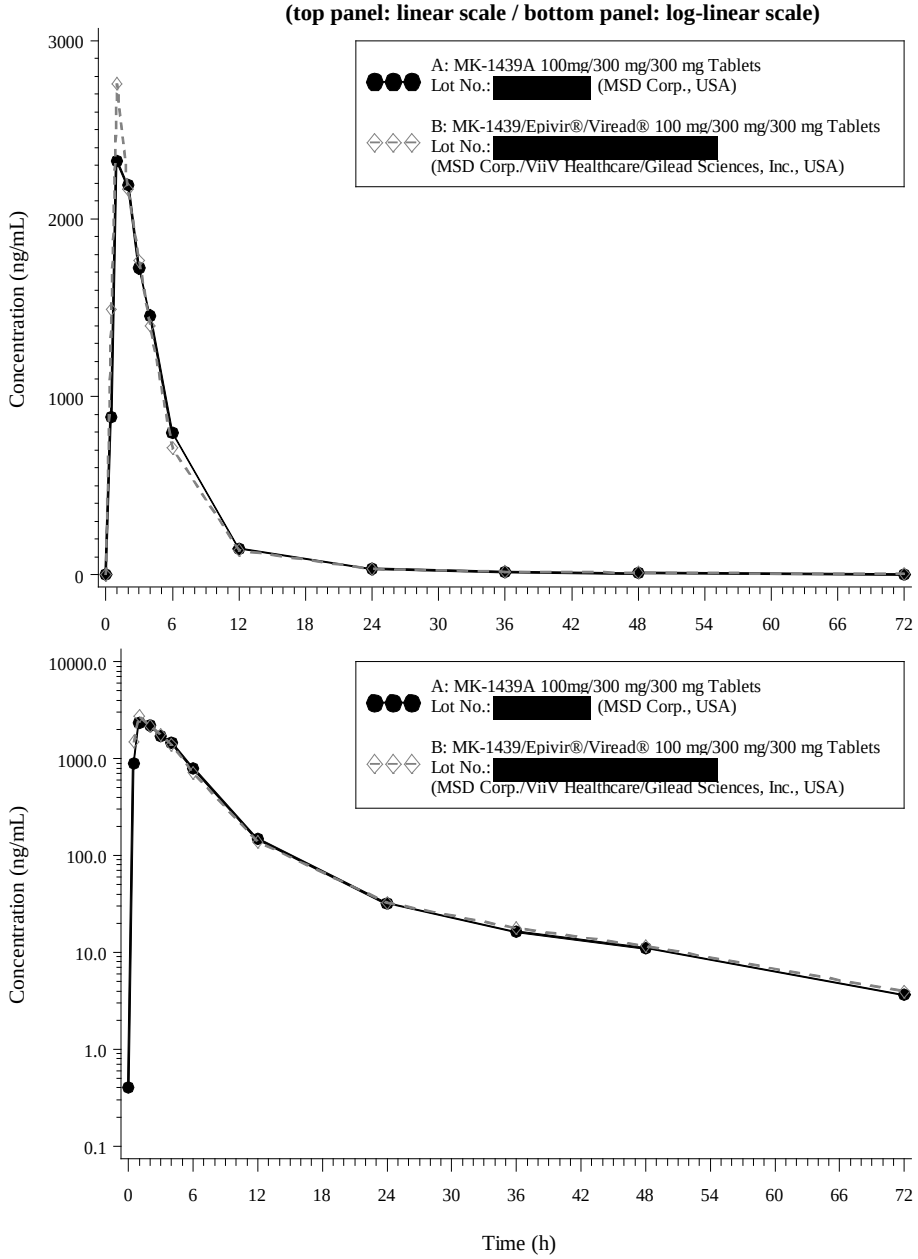
Mean MK-1439 Plasma Concentration-Time Profiles
A: n = 24 / B: n = 24
(top panel: linear scale / bottom panel: log-linear scale)



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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

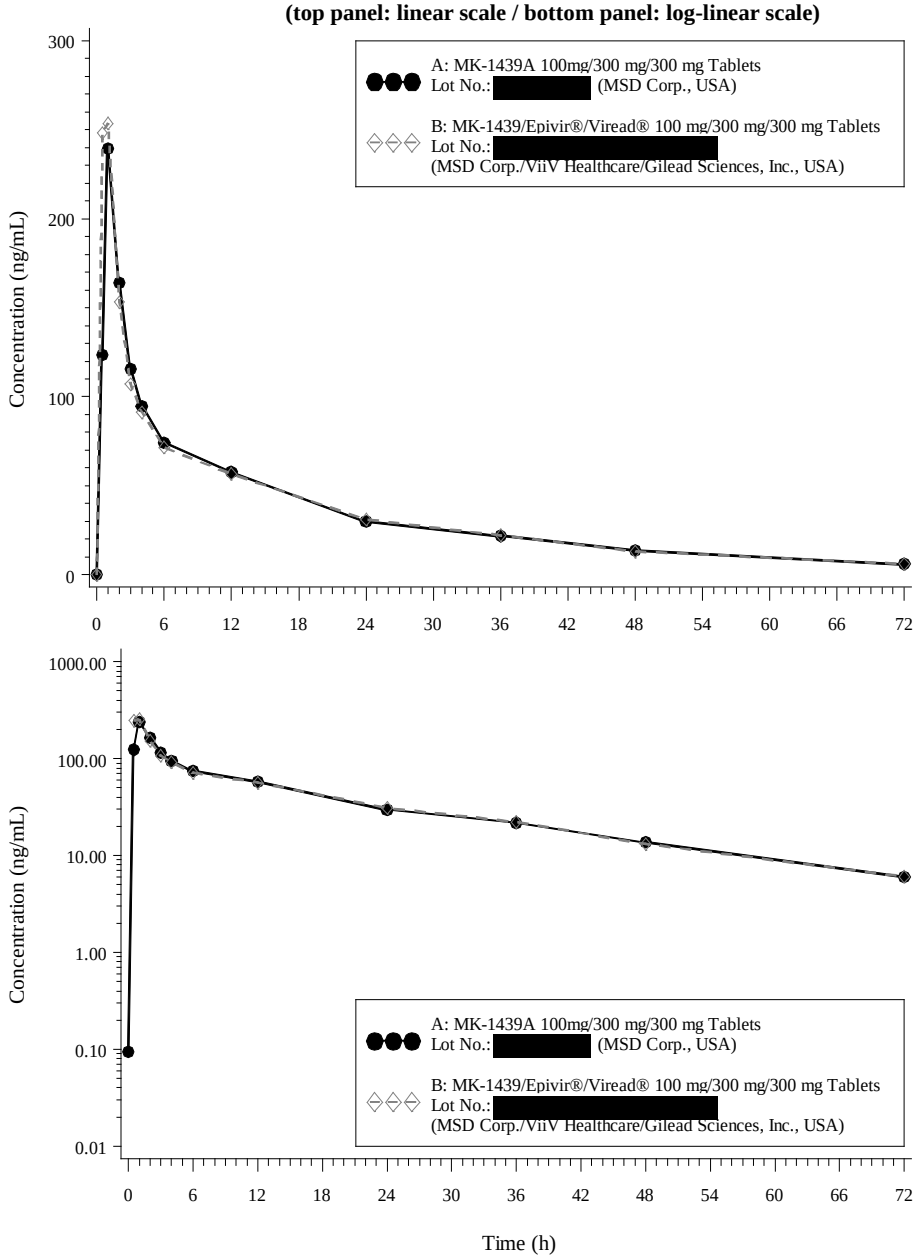
Mean Lamivudine Plasma Concentration-Time Profiles
A: n = 24 / B: n = 24
(top panel: linear scale / bottom panel: log-linear scale)



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[redacted] – Version 2 Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasting Study
[redacted] Study Number: 20[redacted]-3303
Protocol Number: 015-00

Mean Tenofovir Plasma Concentration-Time Profiles
A: n = 24 / B: n = 24
(top panel: linear scale / bottom panel: log-linear scale)



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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Title of Study:
A Comparative Bioavailability Study of MK-1439A in Healthy Subjects under Fasted Conditions

Investigators:
[redacted] MD, PhD, FRCP(C)
MD, MSc, CCFP

Study Centre(s):

Clinical Facility: [redacted] Canada, [redacted]

Clinical Laboratory Facility: [redacted] Canada, [redacted]

Bioanalytical Facility:
Lamivudine and Tenofovir
[redacted] Canada, [redacted]

MK-1439
[redacted]
The Netherlands

Pharmacokinetic and Statistical Facility: [redacted] Canada, [redacted]

Report Issuing Facility: [redacted] Canada, [redacted]

Phase of Development: Phase I

Study Periods:
Period 1: [redacted], 20[redacted]
Period 2: [redacted], 20[redacted]

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Objective:
The objective of this study was to evaluate the comparative bioavailability between:

- MK-1439A 100 mg/300 mg/300 mg Tablets (Merck Sharp & Dohme Corp., USA); and
- Co-administration of:
  - MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA);
  - Epivir® 300 mg Film-Coated Tablets (ViiV Healthcare UK Limited, United Kingdom); and
  - Viread® 245 mg Film-Coated Tablets (Gilead Sciences Intl Ltd, United Kingdom);

after a single-dose in healthy subjects under fasted conditions.

Hypothesis:
The $AUC_{0\text{-}inf}$ and C_{max} GMR (geometric mean ratio) of MK-1439A when taken as a single tablet compared to the individual component tablets taken concomitantly will be estimated.

Methodology:

- This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.
- This study was designed to evaluate the comparative bioavailability in healthy male and female subjects under fasted conditions.
- Concentrations of MK-1439, lamivudine, and tenofovir were measured from the samples collected over a 72-hour interval after dosing in each period.
- The following pharmacokinetic (PK) parameters were estimated using a non-compartmental approach for MK-1439:
  - C_{max}, C_{24}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, T_{max}, K_{el}, CL/F, V_d/F and $t_{1/2}$
- The following PK parameters were estimated using a non-compartmental approach for lamivudine and tenofovir:
  - C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, T_{max}, K_{el}, CL/F, V_d/F and $t_{1/2}$

Number of subjects:

- Planned for inclusion: 24 subjects
- Total number of subjects that completed the study: 24 subjects
- Included in the safety data analyses: 24 subjects
- Included in the PK data analyses: 24 subjects
- Included in the statistical data analyses: 24 subjects

Main criteria for inclusion:
The study population included non-smoking, male and female volunteers from 18 to 65 years of age, with a BMI from 19.0 to 33.0 kg/m^2, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements.

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Test Product (Treatment A):
MK-1439A 100 mg/300 mg/300 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: 98.8% of label claim
Expiry Date: [redacted]/20[redacted]
Dose: 100 mg MK-1439/300 mg lamivudine/300 mg tenofovir (as disoproxil fumarate)
Mode of Administration: Oral under fasted conditions

Reference Product 1 (Treatment B):
MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Expiry Date: [redacted]/20[redacted]
Dose: 100 mg
Mode of Administration: Oral under fasted conditions

Reference Product 2 (Treatment B):
Epivir® 300 mg Film-Coated Tablets (ViiV Healthcare UK Limited, United Kingdom)
Lot No.: [redacted]
Expiry Date: [redacted] 20[redacted]
Dose: 300 mg
Mode of Administration: Oral under fasted conditions

Reference Product 3 (Treatment B):
Drug Name Viread® 245 mg Film-Coated Tablets (Gilead Sciences Intl Ltd, United Kingdom)
Lot No.: [redacted]
Expiry Date: [redacted] 20[redacted]
Dose: 245 mg
Viread® 245 mg Tablets, containing 245 mg of tenofovir disoproxil as fumarate, are equivalent to 300 mg tenofovir disoproxil fumarate or 136 mg of tenofovir.
Mode of Administration: Oral under fasted conditions

Duration of treatment:
Single-Dose treatment

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Safety Results:

		Pre-dose	Trt A	Trt B	Total
Severity	Mild	6	10	6	22
	Moderate	0	1	0	1
	Severe	0	0	0	0
Overall Relationship to Study Drug	Related	0	4	4	8
	Not Related	6	7	2	15

There were 6 non-treatment emergent adverse events (NTEAEs) involving 6 subjects that occurred prior to administration of any drug product. All of these events were judged to be mild in severity.

There were 17 adverse events (AEs) involving 10 subjects in the study. The most common AE was somnolence. One AE was judged to be moderate in severity, while all other AEs were judged to be mild in severity.

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.

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

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Statistical Methods:

The PK parameters of MK-1439 ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and C_{24}), lamivudine ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}), and tenofovir ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}), after administration of MK-1439A and co-administration of 100 mg MK-1439, 300 mg Epivir®, and 245 mg Viread® as individual tablets, were each analyzed separately using a linear mixed-effect model appropriate for a 2-period crossover design. The model included fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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). A log transformation was applied to the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, C_{24} (MK-1439 only) data. The 90% confidence intervals (CIs), based on the t-distribution, was generated from the above mixed-effect model for the geometric mean ratios (GMRs, MK-1439A /co-administration [MK-1439+lamivudine+tenofovir disoproxil fumarate]) for MK-1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and C_{24}, lamivudine and tenofovir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. Ninety-five percent CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for the above PK parameters.

Individual values were listed for each PK parameter by treatment and analyte, and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

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MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Results:

Pharmacokinetic Results:

MK-1439 Pharmacokinetic Results

	MK-1439A: 100 mg/300 mg/300 mg FDC tablets			*MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets*			*MK-1439A: 100 mg/300 mg/300 mg FDC tablets / MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM) †	23	38.1	(33.1 , 43.7)	24	37.7	(32.4 , 43.7)	1.01	0.94 , 1.08	13.9
$AUC_{0\text{-}last}$ (hr·µM) †	23	36.0	(31.5 , 41.0)	24	35.2	(30.8 , 40.2)	1.02	0.95 , 1.09	13.6
C_{max} (nM) †	24	1780	(1540 , 2050)	24	1790	(1580 , 2030)	0.99	0.91 , 1.09	18.2
C_{24} (nM) †	24	546	(461 , 646)	24	533	(447 , 634)	1.02	0.94 , 1.12	17.7
T_{max} (hr)	24	3.00	(0.50 , 12.00)	24	3.51	(1.00 , 6.00)			
$t_{½}$ (hr)	23	15.26	(35.1)	24	15.89	(37.1)			
CL/F (L/hr)	23	6.10	(33.7)	24	6.24	(36.2)			
V_d/F (L)	23	134	(35.0)	24	143	(38.0)			

The last two samples (48 and 72-hour) were not collected for Subject 0023 in Period 2 (Treatment A: MK-1439A: 100 mg/300mg/300mg); $AUC_{0\text{-}inf}$, $t_{½}$, CL/F and V_d/F were not estimated for this subject in Period 2 and $AUC_{0\text{-}last}$ (24 hours post-dose) of Subject 0023 in Period 2 was excluded from the statistical analysis.

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
‡ Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
Statistics for Tmax: Median and Range (Minimum, Maximum)
*Statistics for $t_{½}$, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Lamivudine Pharmacokinetic Results

	MK-1439A: 100 mg/300 mg/300 mg FDC tablets			***MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets***			***MK-1439A: 100 mg/300 mg/300 mg FDC tablets / MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets***		
PK Parameter†	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·ng/mL) †	23	13600	(12400 , 14800)	24	13000	(11800 , 14300)	1.04	1.00 , 1.09	8.1
$AUC_{0\text{-}last}$ (hr·ng/mL) †	23	13300	(12100 , 14600)	24	12800	(11600 , 14000)	1.04	1.00 , 1.08	8.1
C_{max} (ng/mL) †	24	2730	(2420 , 3090)	24	2750	(2410 , 3130)	1.00	0.91 , 1.09	18.0
T_{max} (hr)	24	2.00	(1.00 , 3.00)	24	1.00	(1.00 , 4.00)			
$t_{½}$ (hr)	23	17.29	(53.3)	24	17.36	(45.9)			
CL/F (L/hr)	23	22.1	(22.3)	24	23.1	(23.0)			
V_d/F (L)	23	550	(54.5)	24	578	(41.1)			

The last two samples (48 and 72-hour) were not collected for Subject 0023 in Period 2 (Treatment A: MK-1439A: 100 mg/300mg/300mg); $AUC_{0\text{-}inf}$, $t_{½}$, CL/F and V_d/F were not estimated for this subject in Period 2 and $AUC_{0\text{-}last}$ (24 hours post-dose) of Subject 0023 in Period 2 was excluded from the statistical analysis.

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
‡ Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
Statistics for Tmax: Median and Range (Minimum, Maximum)
Statistics for t½, CL/F and V_d/F: GM and CV% = $100*sqrt(exp(s^2)-1)$, where s^2 is the observed between-subjects variance on the natural log-scale.

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C Confidential

[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Tenofovir Pharmacokinetic Results

PK Parameter	*MK-1439A: 100 mg/300 mg/300 mg FDC tablets*			*MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets*			*MK-1439A: 100 mg/300 mg/300 mg FDC tablets / MK-1439 100 mg Tablets + Epivir® 300 mg Tablets + Viread® 245 mg Tablets*		
	N	*GM*	*95% CI*	*N*	*GM*	*95% CI*	*GMR*	*90% CI for GMR*	*Intra-Sbj % CV‡*
$AUC_{0\text{-inf}}$ (hr·ng/mL) †	23	2400	(2180 , 2640)	24	2450	(2180 , 2750)	0.98	0.93 , 1.03	10.1
$AUC_{0\text{-last}}$ (hr·ng/mL) †	23	2230	(2030 , 2440)	24	2260	(2010 , 2540)	0.99	0.94 , 1.04	10.4
C_{max} (ng/mL) †	24	244	(214 , 279)	24	282	(239 , 331)	0.87	0.78 , 0.97	21.6
T_{max} (hr)	24	1.00	(0.50 , 3.00)	24	1.00	(0.50 , 2.00)			
$t_{½}$ (hr)	23	20.81	(15.8)	24	20.31	(17.4)			
CL/F (L/hr)	23	57.0	(23.7)	24	55.6	(27.7)			
V_d/F (L)	23	1710	(23.1)	24	1630	(28.5)			

The last two samples (48 and 72-hour) were not collected for Subject 0023 in Period 2 (Treatment A: MK-1439A: 100 mg/300mg/300mg); $AUC_{0\text{-inf}}$, $t_{½}$, CL/F and V_d/F were not estimated for this subject in Period 2 and$AUC_{0\text{-last}}$ (24 hours post-dose) of Subject 0023 in Period 2 was excluded from the statistical analysis.

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
‡ Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
Statistics for Tmax: Median and Range (Minimum, Maximum)
*Statistics for t½, CL/F and V_d/F: GM and CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.*

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[redacted] – Study Report
MK-1439/lamivudine/tenofovir 100 mg/300 mg/300 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3716
Protocol Number: MK-1439A-026-00

Conclusions:
1. The plasma AUC and C_{max} of MK-1439 are similar when administered as an MK-1439A FDC Tablet or co-administered with lamivudine 300 mg tablets and tenofovir disoproxil 245 mg tablets.

2. The plasma AUC and C_{max} of lamivudine are similar when administered as an MK-1439A FDC Tablet or co-administered with MK-1439 100 mg Tablets and tenofovir disoproxil 245 mg tablets.

3. The plasma AUC and C_{max} of tenofovir are generally similar when administered as an MK-1439A FDC Tablet or co-administered with MK-1439 100 mg tablets and lamivudine 300 mg tablets.

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

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SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439, Tablet and Nanoparticle suspension	
INDICATION:	Antiviral treatment for HIV-1 infection	
PROTOCOL TITLE:	An Open-Label, Single-Dose, Fixed-Sequence Study to Evaluate the Comparative Bioavailability of Two Nanoparticle Formulations of MK-1439 to the Current Market Image Tablet	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-034
	Clinical Phase:	1
	EudraCT Number:	Not Applicable
TRIAL CENTER:	[redacted], MD [redacted], MD [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, 3-period, fixed-sequence study in healthy subjects under fasting conditions to evaluate the comparative bioavailability of 2 nanoparticle formulations of MK-1439 to the current market image tablet (MIT). Eighteen (18) healthy, adult, non-tobacco using, male and female subjects were enrolled. On Day 1 of Period 1, subjects received a single oral dose of 100 mg MK-1439 as large nanoparticles (LN) in an on-site formulation suspension (4 mL of 25 mg/mL), following an overnight fast. On Day 1 of Period 2, subjects received a single oral dose of 100 mg MK-1439 as small nanoparticles (SN) in an on-site formulation suspension (4 mL of 25 mg/mL), following an overnight fast. On Day 1 of Period 3, subjects received a single oral dose of 100 mg MK-1439 as market image tablet (MIT) (1 x 100 mg tablet), following an overnight fast. The washout period was at least 7 days between each dose of MK-1439. **DIAGNOSIS/INCLUSION CRITERIA:** Adult healthy non-smoking 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 screening visit were eligible to enter the study.	
	Planned duration of main phase:	6.5 weeks from screening to Day 4 of Period 3 8.5 weeks from screening to follow-up

OBJECTIVES:	(1): To evaluate the comparative bioavailability between the MK-1439 tablet and the MK-1439 large nanoparticle on-site formulation from Merck Sharp & Dohme Corp., USA under fasting conditions. (2): To evaluate the comparative bioavailability between the MK-1439 tablet and the MK-1439 small nanoparticle on-site formulation from Merck Sharp & Dohme Corp., USA under fasting conditions	
ESTIMATIONS:	(1): The pharmacokinetic parameters AUC0-∞ and Cmax of MK-1439 after a single oral dose of MK-1439 large nanoparticle on-site formulation will be estimated and compared with the pharmacokinetic parameters of MK-1439 after a single oral dose of MK-1439 tablet. (2): The pharmacokinetic parameters AUC0-∞ and Cmax of MK-1439 after a single oral dose of MK-1439 small nanoparticle on-site formulation will be estimated and compared with the pharmacokinetic parameters of MK-1439 after a single oral dose of MK-1439 tablet.	
TREATMENT GROUPS:	MK-1439 LN	A single oral dose of 100 mg MK-1439 as large nanoparticles in an on-site formulation suspension on Day 1 of Period 1, 18 subjects
	MK-1439 SN	A single oral dose of 100 mg MK-1439 as small nanoparticles in an on-site formulation suspension on Day 1 of Period 2, 18 subjects
	MK-1439 Tablet	A single oral dose of 100 mg MK-1439 as a market image tablet on Day 1 of Period 3 18 subjects enrolled, 17 subjects completed

Clinical Supplies Dispensed to Subjects

Product Name	How Supplied	Batch Number	Site of Manufacture
MK-1439 API†	30 g pre-weighed bulk powder	[redacted]	Merck & Co., Inc. 126 East Lincoln Avenue, Rahway, NJ 07065
MK-1439	100 mg strength MIT	[redacted]	Merck Sharp & Dohme Limited, Ballydine, Kilsheelan, Clonmel Co. Tipperary, Ireland

†Supplied as API = Active Pharmaceutical Ingredient
MIT supplied as OCT = Oral Compressed Tablets. At the time of the trial PN034, OCT tablets were considered to be the MIT

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Plasma MK-1439 pharmacokinetics were summarized using the following pharmacokinetic parameters: AUC0-∞, AUC0-last, Cmax, C24, CL/F, Vz/F, Tmax, and apparent terminal t½. The primary pharmacokinetic endpoints included MK-1439 AUC0-∞ and Cmax. **Safety** The safety and tolerability of MK-1439 were assessed by clinical evaluation, including physical examinations, vital signs (heart rate and blood pressure), 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry, and urinalysis) obtained at pre-specified time points. Subjects were also monitored for adverse events throughout the study.
DATABASE LOCK:	[redacted]-20[redacted]	**TRIAL STATUS:** [redacted]-20[redacted] first subject first visit to [redacted]-20[redacted] last subject last visit

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

Disposition of Subjects

	MK-1439 LN	MK-1439 SN	MK-1439 Tablet
	N (%)	N (%)	N (%)
Subjects in Population	18	18	18
Completed	18 (100.0%)	18 (100.0%)	17 (94.4%)
Discontinued	0 (0.0%)	0 (0.0%)	1 (5.6%)
Withdrawal by Subject	0 (0.0%)	0 (0.0%)	1 (5.6%)

ANALYSIS DESCRIPTION:	**Primary Analysis – Pharmacokinetics of MK-1439** The pharmacokinetics of MK-1439 (AUC0-∞ and Cmax) after administration of "MK-1439 LN", "MK-1439 SN", and "MK-1439 Tablet", were natural log (ln)-transformed and analyzed using a linear mixed-effects model appropriate for a 3-period fixed-sequence design 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 different treatment measurements within the same subject via the REPEATED statement in SAS PROC MIXED. The Kenward-Roger method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). Least-squares means and 95% confidence intervals (CIs), based on the t-distribution were generated from the above mixed-effects model and back transformed to provide estimates for the geometric means (GMs) by treatment for MK-1439 AUC0-∞ and Cmax. Difference in least-squares means and 90% CIs, based on the t-distribution were generated from the above mixed-effects model and back transformed to provide estimates for the geometric mean ratios (GMRs) (MK-1439 LN/MK-1439 Tablet, MK-1439 SN/ MK-1439 Tablet) for MK-1439 AUC0-∞ and Cmax. C24 and AUC0-last were analyzed in a similar fashion to AUC0-∞ and Cmax.

ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	Per Protocol: The population used for the pharmacokinetic analysis included the subset of subjects who complied with the protocol sufficiently to ensure that generated data would likely exhibit the effects of treatment, according to the underlying scientific model. Eighteen (18) healthy adult male and female subjects were enrolled in the study and 17 subjects completed the study per protocol. One (1) subject was discontinued on Day -1 of Period 3, due to a scheduling conflict; therefore, this subject had no available data for the MK-1439 tablet treatment.
SUMMARY:	**Pharmacokinetics:** Results of the analyses of the single-dose plasma pharmacokinetics of MK-1439 following single oral doses of 100 mg MK-1439 as LN in suspension, SN in suspension, and as the MIT in healthy adult subjects are summarized in the table below. The administration of a single oral 100 mg dose of MK-1439 LN suspension resulted in a 31%, 34%, 43%, and 34% reduction in AUC0-∞, AUC0-last, Cmax, and C24, respectively, compared to that following administration of a single oral 100 mg dose of MK-1439 MIT. The GM CL/F and Vz/F following administration of the MK-1439 LN suspension were increased 45% and 79%, respectively, compared to that following administration of the MK-1439 Tablet. The median Tmax was unchanged at 3 hours postdose, while the observed mean apparent terminal t½ following the MK-1439 LN suspension (19.64 hours) was similar than that following the MK-1439 Tablet (15.90 hours). The administration of a single oral 100 mg dose of MK-1439 SN suspension resulted in a 20%, 23%, 33%, and 23% reduction in AUC0-∞, AUC0-last, Cmax, and C24, respectively, compared to that following administration of a single oral 100 mg dose of MK-1439 MIT. The GM CL/F and Vz/F following administration of the MK-1439 SN suspension were increased 26% and 50%, respectively, compared to that following administration of the MK-1439 Tablet. The median Tmax was comparable between both the MK-1439 SN suspension and tablet formulations at 3.5 hours and 3 hours postdose, respectively, while the observed mean apparent terminal t½ following the MK-1439 SN suspension (18.86 hours) was similar than that following the MK-1439 Tablet (15.90 hours).

Statistical Comparisons and Summary Statistics of MK-1439 Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 100 mg MK-1439 as Large Nanoparticles in Suspension, Small Nanoparticles in Suspension, and Market Image Tablet (Reference) in Healthy Adult Subjects

MK-1439 Pharmacokinetic Parameter	MK-1439 LN			MK-1439 SN			MK-1439 Tablet		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
AUC0-∞[†] (uM•hr)	18	27.9	(24.2, 32.1)	18	32.0	(28.1, 36.4)	17	40.2	(35.1, 46.0)
AUC0-last[†] (uM•hr)	18	24.9	(21.8, 28.4)	18	29.2	(25.8, 33.0)	17	37.8	(32.9, 43.5)
Cmax[†] (nM)	18	1000	(865, 1170)	18	1190	(1070, 1330)	17	1780	(1540, 2050)
C24[†] (nM)	18	398	(338, 468)	18	463	(394, 543)	17	599	(508, 706)
CL/F[‡] (L/hr)	18	8.44	28.8	18	7.34	26.4	17	5.81	28.2
Vz/F[‡] (L)	18	239	44.8	18	200	37.8	17	133	29.1
Tmax[§] (hr)	18	3.00	(1.00, 6.04)	18	3.50	(1.00, 6.01)	17	3.00	(1.00, 6.00)
Apparent terminal t½[‡] (hr)	18	19.64	44.61	18	18.86	35.79	17	15.90	17.45

MK-1439 Pharmacokinetic Parameter	MK-1439 LN/MK-1439 Tablet			MK-1439 SN/MK-1439 Tablet		
	GMR	90% CI	Pseudo Within Subject %CV[‖]	GMR	90% CI	Pseudo Within Subject %CV[‖]
AUC0-∞[†] (uM•hr)	0.69	(0.64, 0.75)	12.825	0.80	(0.75, 0.85)	10.391
AUC0-last[†] (uM•hr)	0.66	(0.61, 0.71)	13.548	0.77	(0.73, 0.82)	10.382
Cmax[†] (nM)	0.57	(0.49, 0.65)	23.414	0.67	(0.60, 0.75)	18.893
C24[†] (nM)	0.66	(0.61, 0.72)	14.621	0.77	(0.73, 0.82)	9.775

MK-1439 LN: A single oral dose of 100 mg MK-1439 as large nanoparticle in an on-site formulation suspension on Day 1 of Period 1.
MK-1439 SN: A single oral dose of 100 mg MK-1439 as small nanoparticle in an on-site formulation suspension on Day 1 of Period 2.
MK-1439 Tablet: A single oral dose of 100 mg MK-1439 as market image tablet on Day 1 of Period 3 (reference)
[†]Back-transformed least-squares means and confidence intervals from linear-mixed effects model performed on natural log-transformed values.
[‡]Geometric Mean (Percent Geometric Coefficient of Variation) reported for CL/F, Vz/F and apparent terminal t½.
[§]Median (min, max) reported for T_{max}.
[‖]Pseudo within-subject %CV = 100*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 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
Note: One subject dropped on Day -1 of Period 3 (MK-1439 market image tablet).
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval

ANALYSIS DESCRIPTION:	**Secondary Analysis - Safety** The safety and tolerability of MK-1439 was evaluated by clinical assessment of adverse events and other safety measurements. Incidence of the number of subjects with adverse events was descriptively summarized and listed by treatment. The incidence of the number of subjects with drug-related adverse events was descriptively summarized by treatment. Because no meaningful changes in individual values for laboratory safety tests, ECGs, and vital signs were observed, summary statistics for these safety assessments were not provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	All Subjects as Treated Population – The population used for the assessment of safety and tolerability consisted of all subjects who received at least 1 dose of the investigational drugs. All 18 subjects were included in the evaluation of safety.

SUMMARY:	**Safety:** Administrations of single oral doses of MK-1439 LN, MK-1439 SN, and MK-1439 Tablet were generally well tolerated in healthy male and female subjects. Eight (8, 44%) subjects reported a total of 15 mild adverse events, 10 of which were considered drug-related (2 following MK-1439 LN, 1 following MK-1439 SN, and 7 following MK-1439 Tablet) by the Investigator. The most common adverse events reported in this study were headache and sinus congestion. All adverse events were transient in nature and resolved by end of study. There were no serious adverse events, laboratory adverse events, ECIs, adverse events of special interest, or deaths reported during the study. No clinically meaningful relationships were observed for differences between clinical laboratory values, vital signs, or ECG safety parameters as a function of treatment.
CONCLUSIONS:	1. A single oral 100 mg dose of the MK-1439 large nanoparticles suspension resulted in a 31% lower AUC0-∞ and 43% lower Cmax relative to that following a single oral 100 mg dose of the current MIT formulation. 2. A single oral 100 mg dose of the MK-1439 small nanoparticles suspension resulted in a 20% lower AUC0-∞ and 33% lower Cmax relative to that following a single oral 100 mg dose of the current MIT formulation.
REPORT DATE:	Amendement 1: [redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439	
INDICATION:	Treatment of Human Immunodeficiency Virus-1 (HIV-1) Infection	
PROTOCOL TITLE:	A Rapid Pharmacokinetic Trial of the Bioavailability of Four MK-1439 Nano Formulations in Healthy Adults	
TRIAL IDENTIFIERS:	Protocol Number:	046
	Clinical Phase:	1
	EudraCT Number:	20[redacted]-002702-36
	IND Number:	112,796
TRIAL CENTERS:	[redacted], United Kingdom	
DESIGN:	This was an open-label, 5-period, fixed sequence trial comparing 4 formulations of MK-1439 nanoparticle formulation with the MK 1439 100 mg film coated tablet in healthy subjects. Sixteen subjects participated in 5 treatment periods.	
	Planned duration of the trial:	Approximately 4 months
	Planned duration of run-in phase:	not applicable
	Planned duration of extension phase:	not applicable
Objectives	**Primary:** 1) To evaluate and compare the relative bioavailability of four MK-1439 experimental nanoparticle formulations with the MK-1439 100 mg film coated tablet. 2) To assess the safety and tolerability of the four MK-1439 experimental nanoparticle formulations and the MK-1439 100 mg film coated tablet. **Exploratory:** 1) To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this trial.	

Hypotheses (Estimation)	**Primary:** 1) The geometric mean ratio (GMR) of the experimental nanoparticle formulation in each period to the MK-1439 100 mg film coated tablet will be estimated for area under the concentration versus time curve from time zero to infinity (AUC0-inf), area under the concentration versus time curve from time zero to last (AUC0-last), maximum observed plasma concentration (Cmax) and the concentration at 24 hours post-dose (C24).
Treatment Periods	**Treatment (N = 16)**
Period 1	Treatment B: Single MK-1439 nanoparticle formulation Type 1 dose (150 mg tablet [% drug loaded])
Period 2	Treatment A: Single MK-1439 100 mg film coated tablet
Period 3	Treatment C: Single MK-1439 nanoparticle formulation Type 2 dose (150 mg tablet [% drug loaded])
Period 4	Treatment D: Single MK-1439 nanoparticle formulation Type 3 dose (150 mg tablet [% drug loaded])
Period 5	Treatment E: Single MK-1439 nanoparticle formulation Type 4 dose (100 mg tablet [% drug loaded])

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

Product Description	Product Potency	Lot-Number
MK-1439 Film Coated Tablet	100 mg	
MK-1439 Nanoparticle Formulation Type 1 Tablet	150 mg	
MK-1439 Nanoparticle formulation Type 2 Tablet	150 mg	
MK-1439 Nanoparticle formulation Type 3 Tablet	150 mg	
MK-1439 Nanoparticle formulation Type 4 Tablet	100 mg	

Endpoints and definitions	Pharmacokinetic: Primary pharmacokinetic (PK) endpoints include AUC0-inf, AUC0-last, Cmax and C24 for MK-1439. Secondary PK endpoints include area under the concentration versus time curve from time zero to 48 hours (AUC0-48), time corresponding to occurrence of Cmax (Tmax) and apparent terminal elimination half-life (t½). Note: Subjects excluded from certain PK analyses are identified in the footnote of the relevant table. Safety: Primary safety endpoints include all types of adverse events (AEs), in addition to electrocardiograms (ECGs), vital signs and physical examination findings.
Database lock	[redacted]-20[redacted] Trial status [redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All analyses for safety and PK were performed according to the trial protocol.

Table 1: Subject Disposition (Randomized Subjects)

	Overall N = 16
Enrolled	16 (100%)
Completed the Study	16 (100%)
Discontinued from the Study	0 (0.0%)

N = number of subjects

Analysis description	**Primary Analysis** Pharmacokinetics: The individual PK value of MK-1439 (AUC0-inf, AUC0-last, AUC0-48, Cmax, and C24) was natural log-transformed and then analyzed using a linear mixed-effect model with a fixed effect term for treatment. A heterogeneous-compound symmetry covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same 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). Back-transformed summary statistics and inferential results were reported for PK parameters. The 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) (MK-1439 experimental nanoparticle formulation/MK-1439 100 mg film coated tablet) were provided for MK-1439 AUC0-inf, AUC0-last, AUC0-48, Cmax and C24. The 95% CIs for the GMs by each experimental nanoparticle formulation and film coated tablet for MK-1439 AUC0-inf, AUC0-last, AUC0-48, Cmax and C24 were also provided. Individual values are listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation (SD), arithmetic percent coefficient of variation (CV) (calculated as 100 x SD/arithmetic mean), median, minimum, maximum, geometric mean (GM) and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 was the observed variance on the natural log-scale). Safety: For safety, all AEs and vital signs are listed for each subject and tabulated. All AEs are tabulated by treatment. Summary statistics were generated for the change from baseline values in the vital signs.
Analysis population and time point description	The PK analyses were performed on the Per-Protocol population defined as the subset of subjects who complied with the protocol sufficiently to ensure that the data exhibited the effects of treatment, according to the underlying scientific model. The analyses for safety and tolerability were conducted on the All Subjects As Treated population, consisting of all subjects who received at least 1 administration of the trial drug. Data were available for all subjects who received each treatment and no data were excluded from the analyses for the PK and safety.

Summary	Pharmacokinetic Summary Summary AUC0-inf, AUC0-last, AUC0-48, Cmax, C24, Tmax and apparent terminal t½ values for MK-1439 after a single dose of each formulation and the subsequent statistical analyses can be found in the tables that follow. The AUC0-inf GMRs (90%CI) for Treatment B (150 mg tablet [% drug loaded]), Treatment C (150 mg tablet [% drug loaded]), Treatment D (150 mg tablet [% drug loaded]) and Treatment E (100 mg tablet [% drug loaded]) compared to Treatment A (100 mg film coated tablet) were 0.96 (0.85 to 1.09), 1.13 (1.02 to 1.26), 0.99 (0.88 to 1.11) and 0.89 (0.80 to 0.99), respectively.

Table 2: Summary MK-1439 Plasma Pharmacokinetic Parameters Following in Healthy Adult Subjects Following Administration of a Single Oral Dose of Nanoparticle Formulation or 100 mg Film Coated Tablet (Per Protocol Population)

	Treatment				
Parameter Statistic	**Treatment B Period 1**	**Treatment A Period 2**	**Treatment C Period 3**	**Treatment D Period 4**	**Treatment E Period 5**
AUC0-inf (µM·h)					
n	13	16	15	12	15
Geo. Mean	28.6	31.9	35.5	29.1	28.0
Geo.CV%	34.6	33.9	29.6	30.3	27.5
AUC0-last (µM·h)					
n	16	16	16	16	16
Geo. Mean	26.3	29.9	32.7	27.0	26.3
Geo.CV%	29.3	31.1	26.3	28.4	27.0
AUC0-48 (µM·h)					
n	16	16	16	16	16
Geo. Mean	22.8	27.2	28.8	23.2	23.3
Geo.CV%	27.5	29.2	24.8	27.3	25.9
Cmax (nM)					
n	16	16	16	16	16
Geo. Mean	1070	1520	1320	1060	1160
Geo.CV%	26.5	32.5	27.8	27.0	24.2
C24 (µM)					
n	16	16	16	16	16
Geo. Mean	395	483	508	412	402
Geo.CV%	31.9	33.3	23.3	28.0	32.0
Tmax (h)					
n	16	16	16	16	16
Minimum	1.50	0.500	1.50	1.48	1.02
Median	2.51	2.00	3.01	3.00	2.00
Maximum	6.02	4.00	6.00	6.00	4.02
t½					
n	13	16	15	12	15
Geo. mean	20.23	16.82	19.65	20.35	18.85
Geo. CV%	34.49	28.58	30.72	29.96	32.76

AUC = Area under the concentration versus time curve; AUC0-inf = AUC from time zero to infinity; AUC0-last = AUC from time zero to last; AUC0-48 = AUC from time zero to 48 hours; Cmax = maximum observed plasma concentration; C24 = the concentration at 24 hours post-dose
Treatment B (150 mg tablet MK-1439 nanoparticle formulation Type 1 [[redacted]% drug loaded [redacted]]) (Period 1), Treatment A (MK-1439 100 mg film coated tablet) (Period 2), Treatment C (150 mg tablet MK-1439 nanoparticle formulation Type 2 [[redacted]% drug loaded [redacted]]) (Period 3), Treatment D (150 mg tablet MK-1439 nanoparticle formulation Type 3 [[redacted]% drug loaded [redacted]]) (Period 4), Treatment E (100 mg tablet MK-1439 nanoparticle formulation Type 4 [[redacted]% drug loaded [redacted]]) (Period 5)
The following subjects were excluded from descriptive statistics for AUC0-∞ and t½ as [(lambda z upper - lambda z lower)/t½] < 1.5: subjects 102, 112, 116 in Treatment B: subject 116 in Treatment C: subjects 102, 104, 108, 116 in Treatment D: subject 116 in Treatment E

Table 3: Statistical Comparison of MK-1439 Experimental Nanoparticle formulations / MK-1439 100 mg Film Coated Tablet Plasma Pharmacokinetics in Healthy Adult Subjects

	B (150 mg tablet [% drug loaded]) / A (100 mg film coated tablet)		
Parameter	**GMR**	**90% CI**	**CV (%)**
AUC0-inf (µM.h)	0.96	(0.85, 1.09)	18.8
AUC0-last (µM.h)	0.88	(0.79, 0.98)	18.1
AUC0-48 (µM.h)	0.84	(0.75, 0.94)	18.7
Cmax (nM)	0.70	(0.61, 0.82)	25.2
C24 (nM)	0.82	(0.72, 0.93)	20.9
	C (150 mg tablet [% drug loaded]) / A (100 mg film coated tablet)		
Parameter	**GMR**	**90% CI**	**CV (%)**
AUC0-inf (µM.h)	1.13	(1.02, 1.26)	18.3
AUC0-last (µM.h)	1.09	(0.98, 1.21)	17.2
AUC0-48 (µM.h)	1.06	(0.95, 1.18)	17.8
Cmax (nM)	0.87	(0.75, 1.01)	22.5
C24 (nM)	1.05	(0.94, 1.18)	19.3
	D (150 mg tablet [% drug loaded]) / A (100 mg film coated tablet)		
Parameter	**GMR**	**90% CI**	**CV (%)**
AUC0-inf (µM.h)	0.99	(0.88, 1.11)	18.6
AUC0-last (µM.h)	0.90	(0.81, 1.00)	17.6
AUC0-48 (µM.h)	0.85	(0.76, 0.95)	18.6
Cmax (nM)	0.70	(0.60, 0.81)	22.5
C24 (nM)	0.85	(0.76, 0.96)	20.2
	E (100 mg tablet [% drug loaded]) / A (100 mg film coated tablet)		
Parameter	**GMR**	**90% CI**	**CV (%)**
AUC0-inf (µM.h)	0.89	(0.80, 0.99)	18.2
AUC0-last (µM.h)	0.88	(0.79, 0.97)	17.2
AUC0-48 (µM.h)	0.86	(0.77, 0.96)	17.9
Cmax (nM)	0.76	(0.66, 0.88)	21.2
C24 (nM)	0.83	(0.74, 0.94)	20.8

AUC = Area under the concentration versus time curve; AUC0-inf = AUC from time zero to infinity; AUC0-last = AUC from time zero to last; AUC0-48 = AUC from time zero to 48 hours; Cmax = maximum observed plasma concentration; C24 = the concentration at 24 hours post-dose; CV (Pseudo Within-Subject) was calculated as 100*sqrt[(sT2 + sR2 - 2sTR)/2], where sT2 and sR2 are the estimated variances on the log scale for the Treatment and Reference, and sTR is the corresponding estimated covariance.

	Safety Summary: All 16 enrolled subjects received trial drug administration and successfully completed the trial as per protocol. Single dose administrations of Treatment A (100 mg MK-1439 film coated tablet), Treatment B (150 mg tablet [[redacted]% drug loaded [redacted]]), Treatment C (150 mg tablet [[redacted]% drug loaded [redacted]]), Treatment D (150 mg tablet [[redacted]% drug loaded [redacted]]) and Treatment E (100 mg tablet [[redacted]% drug loaded [redacted]]) doses were generally well tolerated. No deaths, SAEs, events of clinical interest, or AEs leading to discontinuation were reported. Ten treatment-emergent adverse events (TEAEs) were reported for 6 (37.5%) subjects following Treatment D administration, 7 TEAEs were reported for 5 subjects (31.3%) following Treatment A administration, 5 TEAEs were reported for 4 (25.0%) subjects following Treatment C administration, 2 TEAEs were reported for 2 (12.5%) subjects following Treatment B administration, 1 TEAE was reported for 1 (6.3%) subject following Treatment E administration. The majority of the TEAEs were mild in intensity, with 4 moderate TEAEs reported following administration of Treatment C and Treatment D and 3 moderate TEAEs were reported following Treatment A administration. Three TEAEs reported for 3 subjects (vision blurred and 2 events of headache) following Treatment A administration, 3 TEAEs reported for 2 subjects (3 events of headache) following Treatment D administration and 2 TEAEs reported for 2 subjects (diarrhea and headache) following Treatment C administration, were considered related to the trial drug. Treatment-emergent adverse events reported for 2 subjects or more included headache reported for 3 subjects following Treatment D, 2 subjects each following Treatment A and Treatment C administration and 1 subject following Treatment B; nasopharyngitis reported for 2 subjects following Treatment A; laceration reported for 2 subjects following Treatment C and cough reported for 2 subjects following Treatment D administration. All other TEAEs were isolated events reported for individual subjects. All AEs were limited in duration. There were no clinically significant abnormal clinical laboratory test results, vital signs, ECG findings or physical examination findings.

CONCLUSIONS:	1. MK-1439 AUC0-inf of 150 mg nanoparticle formulation ([redacted]% drug loaded [redacted]) was similar to the 100 mg film coated tablet, while Cmax, AUC0-last, and C24 decreased by 30%, 12% and 18%, respectively. 2. MK-1439 AUC0-inf of the 150 mg nanoparticle formulation ([redacted]% drug loaded [redacted]) increased by 13% relative to the 100 mg film coated tablet, while Cmax decreased by 13%. MK-1439 AUC0-last and C24 of the 150 mg nanoparticle formulation ([redacted]% drug loaded [redacted]) were similar to the 100 mg film coated tablet. 3. MK-1439 AUC0-inf and AUC0-last of the 150 mg nanoparticle formulation ([redacted]% drug loaded [redacted]) was similar to the 100 mg film coated tablet, while Cmax and C24decreased by 30% and 15%, respectively. 4. MK-1439 AUC0-inf, AUC0-last, C24, and Cmax of the 100 mg nanoparticle formulation ([redacted]% drug loaded [redacted]) decreased by 11%, 12%, 17%, and 24%, respectively, relative to the 100 mg film coated tablet. 5. Single dose administrations of all five treatments administered were generally well tolerated.
REPORT DATE:	[redacted]-20[redacted] (Final 1.0)

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	HIV-1 Infection	
PROTOCOL TITLE:	A Single and Multiple Dose Study to Evaluate the Safety and Pharmacokinetics of Doravirine (MK-1439) and to Evaluate the Effect of Multiple Doses of Doravirine on Midazolam	
TRIAL IDENTIFIERS:	Protocol Number:	001
	Clinical Phase:	1
	EudraCT Number:	2010-024245-70
TRIAL CENTERS:	[redacted], BELGIUM	
DESIGN:	This was a three-part, double-blind, randomized, placebo-controlled study in fifty eight (58) healthy young male subjects 18 to 50 years of age. **Part I** explored rising single-doses up to 450 mg of doravirine or matching placebo in 16 healthy young male subjects. Two alternating panels, Panels A and B, of eight (8) subjects each were randomized to receive doravirine (n=6) or matching placebo (n=2) in up to 5 (Panel A) and 4 (Panel B) treatment periods. The doses for Panel A were, 6-, 25-, 100-, 300-, and 450-mg dosed in the fasted state. The doses for Panel B were 12-, 50-, and 150-mg dosed in the fasted state and 50 mg dosed with food. At least 3 days elapsed between administrations at each dose level. Within each panel, the washout between study drug administration in Periods 1 and 2 was at least 7 days, and at least 14 days between subsequent doses. **Part II** explored rising multiple-doses of doravirine or matching placebo in four serial rising-dose panels (Panels C, D, E, and F). Panels C, D, and F each consisted of 8 subjects who were randomized to receive doravirine (n=6) or matching placebo (n=2) once-daily (QD) for 10 days. The doses for Panel C, D, and F were 30-, 60-, and 240-mg, respectively. Subjects in Panel E received 120 mg doravirine QD for 14 days, and in addition, the effect of doravirine on midazolam pharmacokinetics (PK) was assessed. Ten (10) subjects received a single oral dose of 2.0 mg midazolam hydrochloride (HCL) syrup (2 mg/mL) on Days -1 and 13, and 120 mg doravirine (n=8) or matching placebo (n=2) once-daily for 14 days. At least 3-days elapsed between panels.	

	Part III was a fixed- sequence, 4-period study to compare the tablet (probe enabled) formulation of doravirine used in Parts I and II of this study with a capsule (probe conventional) formulation. Food effect and dose response of the capsule formulation were also explored. One panel of 8 subjects received single oral doses of doravirine (n=6) or matching placebo (n=2) in 4 periods (Periods 1 to 4). Subjects randomized to receive matching placebo received placebo in all 4 periods. In Period 1, subjects received a single 50 mg dose of the tablet formulation in the fasted state. In Periods 2 and 3, subjects received single 50 mg doses of the capsule formulation in the fasted and fed states, respectively. In Period 4, subjects received a single dose of 300 mg of doravirine as the capsule formulation in the fasted state. For each subject, there was at least a 2-week washout period between study drug administrations in each period.	
	Planned duration of main phase:	Part I: approximately 14 weeks Part II: approximately 8 weeks Part III: approximately 14 weeks

Objectives	**Primary (Part I, II, and III)**: 1. To evaluate the safety of doravirine in healthy adult male subjects after single dose administration and multiple dose administration for up to 14 days at approximately steady state concentration. 2. To obtain preliminary information on plasma pharmacokinetics (e.g., C_{24hr}, $AUC_{0-\infty}$, AUC_{0-24hr}, C_{max}, T_{max}, accumulation ratio, and apparent $t_{1/2}$) of doravirine after single and multiple oral dose administration in healthy adult male subjects. **Secondary**: Part I 1. To compare the effects of a high-fat breakfast on the plasma pharmacokinetics (plasma $AUC_{0-\infty}$ and C_{max}) of doravirine to those in the fasted state after administration of a single oral dose of doravirine in healthy young adult males. Part II 2. To compare the pharmacokinetic profile (e.g., $AUC_{0-\infty}$, C_{max}, T_{max}, and apparent $t_{½}$) of midazolam following a single oral 2 mg dose of midazolam given alone or after multiple doses of doravirine. Part III 3. To compare the plasma pharmacokinetics of doravirine after administration as a probe enabled formulation and after administration as a probe conventional formulation to inform formulation selection. 4. To compare the effects of a high-fat breakfast on the plasma pharmacokinetics (plasma $AUC_{0-\infty}$ and C_{max}) of a conventional formulation of doravirine to those in the fasted state after administration of a single oral dose of doravirine in healthy young adult males. **Exploratory:** Part I 1. To evaluate urinary excretion of intact drug following single oral dose administration of doravirine.

<table>
<tr><td>Hypotheses</td><td colspan="2"><u>Primary</u>:
<u>Part I & III</u>
1. Administration of single doses of doravirine is sufficiently safe and well tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation.
2. At a dose that is generally well tolerated, the true geometric mean plasma concentration at 24 hours postdose exceeds 54 nM after single dose administration. That is, the geometric mean C_{24hr} is greater than 54 nM.
<u>Part II</u>
1. Administration of multiple doses of doravirine for up to 14 days at approximately steady state concentration is sufficiently safe and well tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation.
2. At a dose that is generally well tolerated, the true geometric mean plasma concentration at 24 hours at approximately steady state exceeds 54 nM after multiple dose administration. That is, the geometric mean C_{24hr} is greater than 54 nM.
<u>Secondary</u>
<u>Part I</u>
1. Estimation: Plasma $AUC_{0-\infty}$ and C_{max} following a single oral dose of doravirine administered following a standard high-fat breakfast will be estimated and compared to that observed with the identical dose administered in the fasted state.
<u>Part II</u>
2. The $AUC_{0-\infty}$ of midazolam following multiple-dose administration of doravirine at approximately steady state is similar to the $AUC_{0-\infty}$ of midazolam when administered alone. That is, the true $AUC_{0-\infty}$ geometric mean ratio (midazolam + doravirine/midazolam alone) is contained within the interval (0.50, 2.00).
<u>Part III</u>
3. Estimation: The pharmacokinetics ($AUC_{0-\infty}$ and C_{max}) of doravirine after administration of the probe enabled formulation and administration of the probe conventional formulation will be estimated and compared.
4. Estimation: Plasma $AUC_{0-\infty}$ and C_{max} following a single oral dose of doravirine administered as a conventional formulation following a standard high-fat breakfast will be estimated and compared to that observed with the identical dose administered in the fasted state.</td></tr>
<tr><td rowspan="2">TREATMENT GROUPS:</td><td colspan="2">Part I</td></tr>
<tr><td>Panel A</td><td>Single oral doses of 6-, 25-, 100-, 300-, and 450-mg doravirine or placebo (n=8 [6 active; 2 placebo]) in Periods 1 through 5, respectively.</td></tr>
</table>

	Panel B	Single oral doses of 12-, 50- (fasted), 150-, and 50-mg (fed) doravirine or placebo (n=8 [6 active; 2 placebo]) in Periods 1 through 4, respectively.
	Part II	
	Panel C	30 mg doravirine or placebo QD Days 1-10, n=8 (6 active; 2 placebo)
	Panel D	60 mg doravirine or placebo QD Days 1-10, n=8 (6 active; 2 placebo)
	Panel E	120 mg doravirine or placebo QD Days 1-14, n=10 (8 active; 2 placebo)
		2 mg midazolam HCL syrup QD Days 1 and 13, n=10 (open-label)
	Panel F	240 mg doravirine or placebo QD Days 1-10, n=8 (6 active; 2 placebo)
	Part III	
	Panel G	Single oral doses of 50 mg tablet, 50 mg capsule fasted, 50 mg capsule fed, and 300 mg capsule doravirine or placebo (n=8 [6 active; 2 placebo]) in Periods 1 through 4, respectively.

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

CLINICAL SUPPLIES DISPENSED TO SUBJECTS

Bulk Product Description	Manufacturing Lot Number
DFC MK-1439 (005F) 100mg	[redacted]
DFC MK-1439 (005F) 10mg	[redacted]
DFC MK-1439 (005F) 1mg	[redacted]
DFC Standard Image Placebo (Size 0, 400 mg fill weight)	[redacted]
DFC Standard Image Placebo (Size 3, 150 mg fill weight)	[redacted]
OCT MK-1439 (000V) 100mg	[redacted]
OCT MK-1439 (000V) 10mg	[redacted]
OCT MK-1439 (000V) 1mg	[redacted]
OCT Standard Image Placebo (1000mg Compression Weight)	[redacted]
OCT Standard Image Placebo (100 mg Compression Weight)	[redacted]
Midazolam, 2mg/ml (Manufacturer: Ratiopharm, Lot Number # [redacted], Expiry Date: 31/05/2014) was supplied by the sponsor locally.	
OCT = oral compressed tablet, DFC = dry filled capsules	

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Safety** Adverse experiences (AEs), vital signs (VS), 12-lead electrocardiograms (ECG), and laboratory safety tests (hematology, blood chemistry, and urinalysis).	
		Pharmacokinetics The plasma PK of doravirine (C_{24hr}, $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, T_{max}, accumulation ratio and apparent $t_{1/2}$) after single and multiple oral dose administration.	
	Secondary Endpoints	**Pharmacokinetics** 1. The plasma PK of doravirine ($AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, and apparent $t_{1/2}$) after a single oral dose administration following a standard high-fat breakfast. 2. The plasma PK of midazolam ($AUC_{0-\infty,}$ C_{max}, T_{max}, and apparent $t_{1/2}$) prior to and after oral administration of multiple doses of doravirine. 3. The PK of doravirine ($AUC_{0-\infty,}$ C_{max}, C_{24hr}, T_{max}, and apparent $t_{1/2}$) after oral administration of an enabled formulation and a conventional formulation. 4. The PK of doravirine ($AUC_{0-\infty,}$ C_{max}, C_{24hr}, T_{max}, and apparent $t_{1/2}$) after oral administration of a single dose of doravirine administered as a probe conventional formulation following a standard high-fat breakfast.	
	Exploratory Endpoints	Urinary excretion of intact drug following administration of single oral doses of doravirine.	
DATABASE LOCK:	15-Dec-2011	**TRIAL STATUS:**	17-Mar-2011 to 30-Aug-2011
RESULTS AND ANALYSIS:	All analyses for safety were performed according to protocol. All available data from 48 subjects dosed with doravirine were included in the PK analysis. One subject in Part II Panel E (120 mg doravirine QD x 14 days) discontinued on Day 7 and received 6 doses of doravirine; available PK data for this subject was included in the PK analysis. The protocol stated that harmonic mean and jack-knife standard deviations would be provided for half-life. Instead, geometric mean (GM) and percent geometric coefficient of variation (CV) were provided, in order to be consistent with reporting done in other studies. All other analyses for PK were performed according to protocol.		

Subject Characteristics
Part 1

	Panel A		Panel B	
	n	(%)	n	(%)
Subjects in population	8		8	
Gender				
Male	8	(100.0)	8	(100.0)
Age (Years)				
0 to 17	0	(0.0)	0	(0.0)
18 to 50	8	(100.0)	8	(100.0)
>50	0	(0.0)	0	(0.0)
Mean	31.0		34.6	
SD	10.1		11.5	
Median	27.5		35.0	
Range	21 to 44		20 to 49	
Race				
Black Or African American	1	(12.5)	0	(0.0)
White	7	(87.5)	8	(100.0)
Ethnicity				
Not Hispanic Or Latino	8	(100.0)	8	(100.0)

Panel A = Doses of 6, 25, 100, 300, 450 mg or placebo
Panel B = Doses of 12, 50, 150, 50mg (fed), placebo (fed) or placebo

C Confidential

Subject Characteristics
Part 2

	Panel C		Panel D		Panel E		Panel F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		10		8	
Gender								
Male	8	(100.0)	8	(100.0)	10	(100.0)	8	(100.0)
Age (Years)								
0 to 17	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
18 to 50	8	(100.0)	8	(100.0)	10	(100.0)	8	(100.0)
>50	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	27.1		27.9		30.8		28.4	
SD	5.6		5.9		11.3		7.5	
Median	25.5		27.5		26.0		26.0	
Range	22 to 39		20 to 38		20 to 48		21 to 43	
Race								
Asian	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)
Black Or African American	0	(0.0)	1	(12.5)	1	(10.0)	0	(0.0)
White	8	(100.0)	7	(87.5)	8	(80.0)	8	(100.0)
Ethnicity								
Not Hispanic Or Latino	8	(100.0)	8	(100.0)	10	(100.0)	8	(100.0)

Panel C = 30 mg MK-1439 once-daily x 10-days or Placebo
Panel D = 60 mg MK-1439 once-daily x 10-days or Placebo
Panel E =120 mg MK-1439 once-daily x 14-days (Days 1-14) or Placebo and 2.0 mg Midazolam HCL syrup (single doses Days -1 and 13)
Panel F = 240 mg MK-1439 once-daily x 10-days or Placebo

Subject Characteristics
Part 3

	Panel G	
	n	(%)
Subjects in population	8	
Gender		
Male	8	(100.0)
Age (Years)		
0 to 17	0	(0.0)
18 to 50	8	(100.0)
>50	0	(0.0)
Mean	33.5	
SD	10.3	
Median	30.5	
Range	24 to 50	
Race		
White	8	(100.0)
Ethnicity		
Not Hispanic Or Latino	8	(100.0)

Panel G = Doses of MK-1439 50 mg Enabled, 50 mg Conventional(Fasted), 50mg Conventional (Fed), 300 mg Conventional (Fasted), Placebo (Fasted), or Placebo (Fed).

Disposition of Subjects
Part 1

	Panel A		Panel B		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		16	
Trial Disposition						
Completed	8	(100.0)	8	(100.0)	16	(100.0)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Panel A = Doses of MK-1439 6, 25, 100, 300, 450 mg or Placebo.
Panel B = Doses of MK-1439 12, 50, 150, 50 (fed) mg or Placebo (fasted or fed).

Disposition of Subjects
Part 2

	Panel C		Panel D		Panel E		Panel F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		10		8	
Trial Disposition								
Completed	7	(87.5)	8	(100.0)	9	(90.0)	8	(100.0)
Discontinued	1	(12.5)	0	(0.0)	1	(10.0)	0	(0.0)
Adverse Event	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)
Withdrawal By Subject	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)

Disposition of Subjects
Part 2

	Total	
	n	(%)
Subjects in population	34	
Trial Disposition		
Completed	32	(94.1)
Discontinued	2	(5.9)
Adverse Event	1	(2.9)
Withdrawal By Subject	1	(2.9)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Panel C = 30 mg MK-1439 once-daily x 10-days or Placebo
Panel D = 60 mg MK-1439 once-daily x 10-days or Placebo
Panel E =120 mg MK-1439 once-daily x 14-days (Days 1-14) or Placebo and 2.0 mg Midazolam HCL syrup (single doses Days -1 and 13)
Panel F = 240 mg MK-1439 once-daily x 10-days or Placebo

Disposition of Subjects
Part 3

	Panel G	
	n	(%)
Subjects in population	8	
Trial Disposition		
Completed	8	(100.0)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Panel G = Doses of MK-1439 50 mg enabled, 50 mg conventional (fasted), 50 mg conventional (fed), 300 mg conventional (fasted), Placebo (fasted or fed).

ANALYSIS DESCRIPTION	**Primary Analysis - Safety** Incidence of the number of subjects with AEs were descriptively summarized and listed by study part and treatment. The incidence of the number of subjects with drug related AEs was descriptively summarized. Summary statistics and plots were generated for the change from baseline values in the VSs, ECGs, and selected laboratory safety values. Depending on the safety parameters, the difference from baseline was either computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or VSs were also computed.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION	All subjects who received at least one dose of the investigational drugs or placebo were included in the assessment of safety and tolerability. All 58 subjects were included in the evaluation of safety and tolerability.
SUMMARY	**Part I** Single oral doses of doravirine (from 6- to 450-mg) were generally well tolerated in healthy adult male subjects. Across all doses, 13 of the 16 subjects (81.3%) reported a total of 46 treatment-emergent AEs, 6 of which were considered by the investigator to be drug related (4 after receiving active treatment and 2 after receiving placebo treatment). The majority of AEs were mild to moderate in intensity, transient in nature, and all resolved by the end of the study. One subject (allocation number [AN] 0001) experienced syncope that was considered severe in intensity, but was not considered related to treatment. No other severe AE's were reported. The most common AEs reported following treatment with doravirine or placebo were abdominal pain and fatigue reported by 3 subjects (18.8%) each. Diarrhoea, headache, urine output decreased, urine output increased, gingivitis, and vessel puncture site haematoma were reported by 2 subjects (12.5%) each. No other AE was reported by more than 1 subject. There were no serious AEs (SAEs), events of clinical interest (ECIs), deaths, or discontinuations due to an AE reported during Part I. No trends were observed between AE incidence and increasing dose levels. No clinically meaningful trends were observed for changes in clinical laboratory values, VSs, or ECGs as a function of dose or treatment. **Part II** Multiple oral doses of doravirine (30- to 240-mg) administered QD alone or in combination with a single dose of midazolam were

	generally well tolerated in healthy adult male subjects. Two subjects discontinued from the study; 1 subject withdrew consent due to personal reasons and 1 was discontinued due to laboratory AEs that were severe in intensity but not considered to be related to treatment. Across treatments, 21 of 34 (61%) subjects reported a total of 59 treatment-emergent AEs, 31 of which were considered by the investigator to be drug related (22 in the active treatment groups and 9 in the placebo treatment group). The majority of AEs were mild to moderate in intensity and transient in nature. All AEs resolved by the end of the study. One subject (AN 0040) experienced 3 laboratory AEs which were mild to severe in intensity and not considered related to study drug (significantly elevated aspartate aminotransferase [AST] from Days 6 through 9; creatine phosphokinase [CPK] from Day 1 until Day 2 and Days 5 through 13; and myoglobin on Day 7). No other severe AE's were reported. The most common AEs reported following treatment with doravirine or placebo were headache and back pain which were reported by 11 (32.4%) and 3 (8.8%) subjects, respectively. Diarrhoea, dizziness, and pain in extremity were each reported by 2 subjects (5.9 % each). No other AE was reported by more than 1 subject. There were no SAEs, ECIs, or deaths reported during Part II. No trends were observed between AE incidence and increasing dose levels. No clinically meaningful trends were observed for changes in clinical laboratory values, VS, or ECGs as a function of dose or treatment. **Part III** Single oral doses of the conventional (capsule) formulation (50 mg [fasted, fed] and 300 mg [fasted]) and the enabled (tablet) formulation (50 mg, fasted) were generally well tolerated in healthy adult male subjects. Across treatments, 5 of 8 (62%) subjects reported a total of 10 treatment-emergent AEs, 7 of which were considered by the investigator to be drug related (6 in the active treatment group and 1 in the placebo treatment group). All AEs were mild in intensity, transient in nature, and all resolved by the end of the study. The most common AE reported following treatment with doravirine or placebo was nausea reported by 2 (25%) subjects. No other AE was reported by more than 1 subject. There were no SAEs, ECIs, deaths, or discontinuations due to an AE reported during Part III. No clinically meaningful trends were observed for changes in clinical laboratory values, VSs, or ECGs as a function of treatment.

ANALYSIS DESCRIPTION	**Second Primary Analysis:** PK of doravirine **Parts I and III**: Individual values of PK parameters ($AUC_{0-\infty}$, AUC_{0-24hr}, C_{max}, and C_{24hr}) of doravirine were natural log transformed prior to analysis and analyzed by a linear mixed-effects model containing treatment as a fixed effect and subject as a random effect. The hypothesis that the true GM C_{24hr} of doravirine after single dose administration would exceed 54 nM at a generally safe and well-tolerated fasted dose was tested using the following procedure: At the highest safe and well-tolerated fasted dose, a two-sided 90% confidence interval (CI) for the GM of C_{24hr} was constructed. The secondary primary hypothesis was supported if the lower limit of the 90% CI for C_{24hr} exceeds 54 nM. If the hypothesis was supported in the previous step, then the same procedure was applied to the next lower safe and well tolerated fasted dose. The procedure continued in this stepwise fashion until the lower limit of the 90% CI at a particular dose failed to exceed 54 nM. For estimation purposes, 90% CIs were also constructed for all doses at which the true GM C_{24hr} failed to exceed 54 nM. **First Secondary Hypothesis (Estimation) – Food Effect:** To assess the effect of food on the enabled formulation, 90% CIs were constructed for the $AUC_{0-\infty}$, C_{max} and C_{24hr} geometric mean ratios (GMRs) (enabled formulation fed/fasted) of doravirine. Additionally, 95% CIs were constructed for the GMs of doravirine $AUC_{0-\infty}$, C_{max}, and C_{24hr} for both the fed and fasted states.
ANALYSIS DESCRIPTION (Continued):	**Part II:** Individual values of PK parameters (AUC_{0-24hr}, C_{24hr} and C_{max}) of doravirine were natural log transformed and analyzed based on a linear mixed-effects model containing fixed effects for treatment, day (Day 1 and the last day of dosing) and treatment-by-day interaction as well as a random effect for subject within treatment. The above stated model was used to address the hypothesis that the true GM plasma concentration C_{24hr} of doravirine after multiple dose administration exceeds 54 nM. This hypothesis was tested using the same stepwise procedure as that used for single dose administration. **Second Secondary Hypothesis -- Midazolam Interaction:** Individual midazolam $AUC_{0-\infty}$ was natural log transformed and analyzed using a linear mixed-effects model with a fixed effect term of treatment and a random subject effect. A 90% CI was generated

	from the model for the $AUC_{0-\infty}$ GMR (midazolam + doravirine/midazolam alone). If the 90% CI fell within the pre-specified bound (0.50, 2.00), it was claimed that the $AUC_{0-\infty}$ of midazolam following multiple dose administration of doravirine at approximately steady state was similar to the $AUC_{0-\infty}$ of midazolam when administered alone. **Third Secondary Hypothesis (Estimation) -- Formulation effect**: To assess the effect of formulation, 90% CIs were constructed for the $AUC_{0-\infty}$ and C_{max} GMR (conventional fasted / enabled fasted) of doravirine from the above model. Additionally, 95% CIs were constructed for the GMs of doravirine $AUC_{0-\infty}$ and C_{max} for both the enabled formulation and conventional formulation.
ANALYSIS DESCRIPTION (Continued):	**Fourth Secondary Hypothesis (Estimation) -- Food effect**: To assess the effect of food on the conventional formulation, 90% CIs were constructed for the GMR (fed/fasted) of doravirine $AUC_{0-\infty}$ and C_{max}. Additionally, 95% CIs were constructed for the GMs of doravirine $AUC_{0-\infty}$ and C_{max}, in the fed and fasted states.
Analysis population and time point description	All subjects who were compliant with the protocol sufficiently to ensure that data were likely to exhibit the effects of treatment, according to the underlying scientific model, and had available data from at least one treatment, were included in the primary analysis data set. Forty eight (48) subjects received at least one dose of doravirine. However, one subject (AN 0040 in Part II Panel E: 120 mg doravirine QD x 14 days) was discontinued after 6 dosing days. Available PK data before the discontinuation for this subject and all data from the other 47 subjects were included in the PK analysis.
SUMMARY	**Pharmacokinetics:** **<u>Part I:</u>** Following single dose administration, doravirine (enabled formulation; tablet) was rapidly absorbed with median T_{max} ranging from 1 to 5 hours and apparent terminal half-life ranging from 11.67 to 15.67 hours over the 6 mg to 450 mg dose range (see table below). An exploratory analysis of dose proportionality suggests that doravirine $AUC_{0-\infty}$, AUC_{0-24hr} and C_{max} increased in a less than dose proportional fashion over the dose range studied. The target doravirine C_{24hr} of 54 nM was attained at doses of 12 mg and higher. The effect of a standard high-fat breakfast on the PK of doravirine was assessed at the 50 mg dose. For a single dose of 50 mg, the GMRs (fed/fasted) and 90% CIs were 1.33 (1.07, 1.65) and 0.95 (0.74, 1.23) for doravirine $AUC_{0-\infty}$ and C_{max}, respectively. Based on a single 50 mg oral fasted dose of doravirine, ~6% of the doravirine dose was recovered unchanged in urine.

Summary Statistics of Plasma MK-1439 Pharmacokinetics Following Single Oral Fasted Doses of 6- to 450-mg MK-1439 in Healthy Young Male Subjects (Part I)

Pharmacokinetic Parameters	Panel A 6 mg			Panel B 12 mg			Panel A 25 mg			Panel B 50 mg		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ (µM*hr) †	6	2.88	(2.35, 3.52)	6	4.88	(3.98, 5.98)	6	11.2	(9.17, 13.7)	6	17.6	(14.4, 21.6)
AUC_{0-24hr} (µM*hr) †	6	2.02	(1.70, 2.41)	6	3.66	(3.07, 4.35)	6	7.03	(5.91, 8.36)	6	12.7	(10.6, 15.1)
C_{max} (nM) †	6	156	(126, 193)	6	297	(240, 367)	6	460	(372, 569)	6	1070	(860, 1320)
C_{24hr} (nM) †	6	43.9	(35.1, 54.8)	6	73.0	(58.2, 91.4)	6	194	(155, 243)	6	269	(215, 338)
T_{max} (hr) ‡	6	1.00	(1.00, 4.00)	6	1.00	(1.00, 3.00)	6	5.00	(1.00, 6.00)	6	1.00	(1.00, 4.00)
Apparent $t_{1/2}$ (hr) §	6	11.68	9.95	6	11.67	15.70	6	15.67	20.42	6	13.29	10.59
Pharmacokinetic Parameters	Panel A 100 mg			Panel B 150 mg			Panel A 300 mg			Panel A 450 mg		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ (µM*hr) †	6	38.3	(31.3, 46.8)	6	49.9	(40.7, 61.2)	6	92.6	(75.7, 113)	6	127	(104, 155)
AUC_{0-24hr} (µM*hr) †	6	22.8	(19.2, 27.1)	6	34.0	(28.6, 40.5)	6	58.9	(49.5, 70.1)	6	82.4	(69.3, 98.0)
C_{max} (nM) †	6	1720	(1390, 2120)	6	2680	(2170, 3320)	6	3810	(3090, 4710)	6	6010	(4870, 7430)
$_{24hr}$ (nM) †	6	593	(475, 741)	6	750	(599, 940)	6	1490	(1190, 1870)	6	2070	(1660, 2580)
T_{max} (hr) ‡	6	1.50	(1.00, 5.00)	6	1.50	(1.00, 4.00)	6	3.50	(2.00, 5.00)	6	2.00	(1.00, 5.00)
Apparent $t_{1/2}$ (hr) §	6	15.26	43.98	6	13.84	27.65	6	15.62	27.08	6	14.80	34.52

† Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed fasted values.
‡ Median (min, max) reported for T_{max}.
§ Geometric mean and percent geometric CV reported for apparent $t_{1/2}$.
Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.178 for $AUC_{0-\infty}$, 0.181 for AUC_{0-24hr}, 0.195 for C_{max}, and 0.207 for C_{24hr}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
GM = Geometric least-squares mean; CI = Confidence interval.

SUMMARY (Continued):	Pharmacokinetics: Part II: Following multiple dose administration for 10 days for 30-, 60-, and 240-mg and for 14 days for 120 mg, doravirine (enabled tablet formulation) had a median T_{max} ranging from 2 to 4 hours and apparent terminal half-life ranging from 12.59 to 14.99 hours over the 30- to 240-mg dose range (see table below). Exploratory analysis of dose proportionality on Day 10 (Day 14 for 120 mg) suggests that doravirine AUC_{0-24hr} and C_{max} increased in a slightly less than proportional fashion over the 30- to 240-mg range. The target Day 10 (Day 14 day for 120 mg) C_{24hr} of 54 nM was attained at doses of 30 mg and higher. Median time to 90% of steady state was after 2 days for all dose levels. The accumulation ratios for doses of 30- to 240-mg ranged from 1.23 to 1.38 for AUC_{0-24hr}. Similarly, the accumulation ratios for doses 30- to 240-mg ranged from 1.15 to 1.39 for C_{24hr}, and 1.18 to 1.38 for C_{max}, respectively. An assessment of the effect of doravirine on midazolam PK was conducted for the 120 mg dose of doravirine. The GMR (midazolam + doravirine / midazolam alone) for midazolam $AUC_{0-\infty}$ and corresponding 90% CI were 0.82 and (0.70, 0.97), which falls within pre-specified bound of (0.50, 2.00), thus the claim that the midazolam $AUC_{0-\infty}$ following co-administration with doravirine at steady state is similar to that when administered alone is supported. The GMR (midazolam + doravirine / midazolam alone) for midazolam C_{max} and corresponding 90% CI were 1.02 and (0.81, 1.28).

Summary of MK-1439 Pharmacokinetics Following Once Daily Multiple Dose Administration for 10 or 14 Days of 30- to 240-mg in Healthy Male Subjects (Part II)

Pharmacokinetic Parameters	30 mg N = 6	60 mg N = 6	120 mg N = 8 [††]	240 mg N = 6
Day 1 (First Dose)				
$AUC_{0\text{-}24hr}$ (µM*hr) [†]	8.42 (6.49, 10.9)	14.1 (10.9, 18.3)	27.3 (21.8, 34.2)	43.8 (33.7, 56.7)
C_{24hr} (nM) [†]	177 (125, 250)	336 (237, 475)	671 (497, 906)	1060 (751, 1500)
C_{max} (nM) [†]	672 (515, 875)	1020 (785, 1330)	1920 (1530, 2420)	3240 (2490, 4230)
T_{max} (hr) [‡]	1.00 (1.00,5.00)	3.00 (1.00,4.02)	2.00 (1.00,4.00)	1.50 (1.00,5.00)
Day 10 (Last Dose)[#]				
$AUC_{0\text{-}24hr}$ (µM*hr) [†]	11.5 (8.84, 14.9)	17.3 (13.4, 22.5)	36.8 (29.2, 46.3)	60.6 (46.7, 78.6)
C_{24hr} (nM) [†]	246 (174, 348)	385 (272, 544)	875 (644, 1190)	1340 (948, 1900)
C_{max} (nM) [†]	796 (611, 1040)	1300 (1000, 1700)	2520 (1990, 3190)	4470 (3430, 5830)
Apparent $t_{1/2}$ (hr) [§]	13.63 (11.27)	12.59 (18.28)	14.99 (22.90)	13.35 (15.94)
T_{max} (hr) [‡]	3.50 (1.00,5.00)	2.00 (1.00,4.00)	4.00 (1.00,5.00)	3.00 (1.00,5.00)
Accumulation Ratio: Day 10[#] / Day 1				
$AUC_{0\text{-}24hr}$ (µM*hr) [¶]	1.36 (1.19, 1.56)	1.23 (1.07, 1.41)	1.35 (1.19, 1.53)	1.38 (1.21, 1.59)
C_{24hr} (nM) [¶]	1.39 (1.17, 1.64)	1.15 (0.97, 1.36)	1.30 (1.12, 1.52)	1.26 (1.07, 1.49)
C_{max} (nM) [¶]	1.18 (0.99, 1.42)	1.27 (1.07, 1.52)	1.31 (1.11, 1.54)	1.38 (1.16, 1.65)

[†] Back-transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log-transformed values.
[‡] Median (min, max) reported for T_{max}.
[§] Geometric mean and percent geometric CV reported for apparent $t_{1/2}$.
[#] Day 14 for 120 mg.
[¶] Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.
Square root of conditional mean squared error (residual error) from the linear mixed effect model = 0.140 for $AUC_{0\text{-}24hr}$, 0.179 for C_{max} and 0.168 for C_{24hr}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
[††] Panel E 120 mg, n = 7 for Day 14.

SUMMARY (Continued):	**Pharmacokinetics:** **Part III:** The target doravirine C_{24hr} of 54 nM was attained at doses of 50 mg and higher in both conventional (capsule) and enabled (tablet) formulations. The comparison for the single dose plasma PK of a probe conventional formulation of doravirine to the enabled formulation, which was used in Parts I and II of this study, is shown in the following table. The GMRs (50 mg conventional fasted /50 mg enabled fasted) and 90% CIs were 0.51 (0.43, 0.61), 0.42 (0.36, 0.50), 0.34 (0.27, 0.41), and 0.57 (0.47, 0.69) for $AUC_{0-\infty}$, AUC_{0-24hr}, C_{max}, and C_{24hr}, respectively. The conventional formulation was evaluated at two dose levels and after high-fat fed and fasted administration. The GMRs (50 mg conventional fed /50 mg conventional fasted) and 90% CIs were 2.07 (1.75, 2.45), 2.35 (1.99, 2.78), 2.52 (2.05, 3.10), and 2.19 (1.81, 2.65) for $AUC_{0-\infty}$, AUC_{0-24hr}, C_{max} and C_{24hr} respectively. The GMRs (300 mg conventional fasted /50 mg conventional fasted) and 90% CIs were 1.74 (1.47, 2.06), 1.51 (1.28, 1.79), 1.64 (1.33, 2.01), and 1.39 (1.15, 1.68) for $AUC_{0-\infty}$, AUC_{0-24hr}, C_{max}, and C_{24hr}, respectively.

Statistical Comparison of Plasma MK-1439 Pharmacokinetics following Administration of Single Doses of MK-1439 as an Enabled (Tablet) Formulation (Fasted) and after Administration as a Conventional (Capsule) Formulation (Fed and Fasted) in Healthy Young Male Subjects (Part III)

Pharmacokinetic Parameters	50-mg Enabled Fasted			50-mg Conventional Fasted			50-mg Conventional Fed			300-mg Conventional Fasted		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ (µM*hr) †	6	23.2	(17.9, 29.9)	6	11.9	(9.21, 15.4)	6	24.7	(19.1, 31.8)	6	20.7	(16.0, 26.7)
AUC_{0-24hr} (µM*hr) †	6	16.2	(13.7, 19.2)	6	6.84	(5.76, 8.12)	6	16.1	(13.6, 19.1)	6	10.3	(8.70, 12.3)
C_{max} (nM) †	6	1220	(1000, 1500)	6	412	(337, 504)	6	1040	(848, 1270)	6	675	(552, 826)
C_{24hr} (nM) †	6	356	(277, 458)	6	203	(158, 262)	6	446	(346, 573)	6	282	(219, 363)
T_{max} (hr) ‡	6	2.00	(1.00, 4,00)	6	3.50	(2.00, 8.00)	6	5.50	(2.00, 10.00)	6	5.00	(2.00, 5.00)
Apparent $t_{1/2}$ (hr) §	6	12.28	12.07	6	13.97	9.70	6	13.54	15.53	6	21.52	41.18

Pharmacokinetic Parameters	50 mg Conventional Fasted / 50 mg Enabled Fasted		50 mg Conventional Fed / 50 mg Conventional Fasted		300 mg Conventional Fasted / 50 mg Conventional Fasted	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM*hr) †	0.51	(0.43, 0.61)	2.07	(1.75, 2.45)	1.74	(1.47, 2.06)
AUC_{0-24hr} (µM*hr) †	0.42	(0.36, 0.50)	2.35	(1.99, 2.78)	1.51	(1.28, 1.79)
C_{max} (nM) †	0.34	(0.27, 0.41)	2.52	(2.05, 3.10)	1.64	(1.33, 2.01)
C_{24hr} (nM) †	0.57	(0.47, 0.69)	2.19	(1.81, 2.65)	1.39	(1.15, 1.68)

† Back-transformed least squares mean (ratio) and confidence interval from linear mixed effects model performed on natural log-transformed values.
‡ Median (min, max) reported for T_{max}.
§ Geometric mean and percent geometric CV reported for apparent $t_{1/2}$.
Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.166 for $AUC_{0-\infty}$, 0.165 for AUC_{0-24hr}, 0.189 for C_{max}, and 0.204 for C_{24hr}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

CONCLUSIONS:	**Safety** 1. Across Parts I-III of the study, single and multiple doses of doravirine up to 450- and 240-mg, respectively, were generally well tolerated in healthy subjects. **PK** <u>Part I:</u> 2. The true GM doravirine C_{24hr} exceeded 54 nM at single oral doses of ≥ 12 mg doravirine. 3. Administration of doravirine with a high-fat meal did not result in a meaningful change in the $AUC_{0-\infty}$ or C_{max}. 4. Increases in doravirine $AUC_{0-\infty}$ and C_{max} following single oral doses of doravirine appeared to be less than dose proportional from 6- to 450-mg. 5. Renal excretion did not have an important role in the elimination of doravirine, as ~6% of the doravirine dose was recovered unchanged in urine. <u>Part II:</u> 6. The true GM steady state doravirine C_{24hr} exceeded 54 nM at multiple QD doses of ≥ 30 mg. 7. Doravirine AUC_{0-24hr} and C_{max} following multiple doses of doravirine appeared to increase in a less than dose proportional manner from 30- to 240-mg. 8. Midazolam $AUC_{0-\infty}$ and C_{max} was similar after administration with multiple doses of 120 mg of doravirine compared to administration alone. <u>Part III:</u> 9. The true GM doravirine C_{24hr} exceeded 54 nM for 50- and 300-mg single doses of doravirine using the conventional formulation. 10. At 50 mg, doravirine $AUC_{0-\infty}$ and C_{max} for the conventional formulation were 49% and 66% lower when compared to the enabled formulation, respectively.

	11. Administration of the conventional formulation of doravirine with a high fat meal resulted in 2.1 and 2.5-fold increases in doravirine $AUC_{0-\infty}$ and C_{max}.
PUBLICATION(S)	Safety, tolerability and pharmacokinetics of doravirine, a novel HIV non-nucleoside reverse transcriptase inhibitor, after single and multiple doses in healthy subjects. ISSN 1359-6535
REPORT DATE:	25-May-2016
REVISED DATE:	01-Aug-2017

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	**Doravirine (MK-1439)**	
INDICATION:	HIV-1 Infection	
PROTOCOL TITLE:	A Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Doravirine (MK-1439)	
TRIAL IDENTIFIERS:	Protocol Number:	006
	Clinical Phase:	1
	EudraCT Number:	2011-004260-30
TRIAL CENTERS:	[redacted], BELGIUM	
DESIGN:	This was a double-blind, randomized, placebo-controlled, multiple-period, single-rising and multiple dose study to assess the safety and pharmacokinetics (PK) of MK-1439 (hereafter referred to as doravirine) in 16 healthy male subjects 18 to 50 years of age. Two panels (Panels A and B) of 8 subjects each were randomized to receive doravirine or matching placebo (in a 3:1 ratio, respectively), in up to 3 treatment periods (Periods 1 to 3). In Panel A, Periods 1 and 2, subjects received a single oral dose of doravirine 600- and 800-mg or matching placebo, respectively. In Period 3, subjects received doravirine 450 mg or matching placebo once-daily (QD) for 10 days. In Panel B, Periods 1 and 2, subjects received a single oral dose of doravirine 1000- and 1200-mg or matching placebo, respectively. In Period 3, subjects received doravirine 750-mg or matching placebo QD for 10 days. For each subject, there was at least a 7-day washout period between study drug administration in Periods 1 and 2, and between Period 2 and the first dose of study drug in Period 3.	
	Planned duration of main phase:	Approximately 10 to 15 weeks

<table>
<tr><td>Objectives</td><td colspan="2">Primary:
1. To evaluate the safety and tolerability of doravirine in healthy adult male subjects after single dose administration and multiple dose administration for up to 10 days at approximately steady state concentration.
2. To obtain preliminary information of plasma pharmacokinetics (e.g. C24hr, AUC0-inf, AUC0-24hr, Cmax, Tmax) of doravirine after single and multiple oral dose administration in healthy adult male subjects.</td></tr>
<tr><td>Hypotheses</td><td colspan="2">Primary
1. Administration of single and multiple doses of doravirine for up to 10 days is sufficiently safe and well tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation.
2. At a dose that is generally well tolerated, the true geometric mean plasma concentration at 24 hours postdose exceeds 54 nM after 10 days of administration. That is, the true geometric mean C24hr is greater than 54 nM on Day 10.</td></tr>
<tr><td rowspan="5">Treatments groups</td><td colspan="2">Panel A</td></tr>
<tr><td>Periods 1 and 2</td><td>Single oral dose of doravirine 600 mg (Period 1) and 800 mg (Period 2), n = 8 [6 active, 2 matching placebo] at each dose level</td></tr>
<tr><td>Period 3</td><td>450 mg of doravirine, n = 8 (6 active, 2 matching placebo) QD for 10 days</td></tr>
<tr><td colspan="2">Panel B</td></tr>
<tr><td>Periods 1 and 2</td><td>Single oral dose of doravirine 1000 mg (Period 1) and 1200 mg (Period 2), n = 8 (6 active, 2 matching placebo) at each dose level</td></tr>
<tr><td></td><td>Period 3</td><td>750 mg of doravirine, n = 8 (6 active, 2 matching placebo) QD for 10 days</td></tr>
</table>

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

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
OCT MK-1439 (000V) 100mg	[redacted]
OCT MK-1439 (000V) 10mg	[redacted]
OCT Standard Image Placebo (1000mg Compression Weight)	[redacted]
OCT Standard Image Placebo (100 mg Compression Weight)	[redacted]
OCT: Oral compressed tablet.	

Endpoints and definitions	**Primary endpoints**	**Safety** Adverse experiences (AEs), laboratory safety tests, electrocardiograms (ECGs), and vital signs (VS). **Pharmacokinetics** The plasma PK of doravirine (C24hr, AUC0-inf, AUC0-24hr, Cmax, Tmax, and apparent half-life [t1/2]) after single and multiple oral dose administration.	
Database lock	24-Oct-2012	Trial status	10-Nov-2011 to 01-Jun-2012
RESULTS AND ANALYSIS:	All analyses for safety were performed according to protocol. All available data from 16 subjects dosed with doravirine were included in the PK analysis.		

Subject Characteristics

	Panel A		Panel B		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		16	
Gender						
Male	8	(100.0)	8	(100.0)	16	(100.0)
Age (Years)						
0 to 17	0	(0.0)	0	(0.0)	0	(0.0)
18 to 50	8	(100.0)	7	(87.5)	15	(93.8)
>50	0	(0.0)	1	(12.5)	1	(6.3)
Mean	36.8		40.1		38.4	
SD	8.7		9.1		8.8	
Median	37.0		42.0		40.5	
Range	25 to 49		23 to 51		23 to 51	
Race						
White	8	(100.0)	8	(100.0)	16	(100.0)
Ethnicity						
Not Hispanic Or Latino	8	(100.0)	8	(100.0)	16	(100.0)

Panel A=single doses of 600 mg or Placebo, 800 mg or Placebo in Period 1 and 2 respectively, 450 mg MK-1439 once-daily for 10-days or Placebo in Period 3.
Panel B=single doses of 1000 mg or Placebo, 1200 mg or Placebo in Period 1 and 2 respectively, 750 mg MK-1439 once-daily for 10-days or Placebo in Period 3.
One subject enrolled in Panel B was 50 years of age at the time of Screening and therefore, had qualified for the trial.

Disposition of Subjects

	Panel A		Panel B		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		16	
Gender (Age Range in Years)						
Male	8	(25 to 49)	8	(23 to 51)	16	(23 to 51)
Trial Disposition						
Completed	8	(100.0)	7	(87.5)	15	(93.8)
Discontinued	0	(0.0)	1	(12.5)	1	(6.3)
Adverse Event	0	(0.0)	1	(12.5)	1	(6.3)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Panel A=single doses of 600 mg or Placebo, 800 mg or Placebo in Period 1 and 2 respectively, 450 mg MK-1439 once-daily for 10-days or Placebo in Period 3.
Panel B=single doses of 1000 mg or Placebo, 1200 mg or Placebo in Period 1 and 2 respectively, 750 mg MK-1439 once-daily for 10-days or Placebo in Period 3.
One subject enrolled in Panel B was 50 years of age at the time of Screening and therefore, had qualified for the trial.

Analysis description	**Primary Analysis -- Safety** Incidence of the number of subjects with AEs were descriptively summarized and listed by treatment. The incidence of the number of subjects with drug related AEs was descriptively summarized. Summary statistics were generated for the raw and change from baseline values for VS, ECG parameters, and laboratory safety parameters. Depending on the safety parameter, the change from baseline was either computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).
Analysis population and time point description	All subjects who received at least one dose of the investigational drugs or placebo were included in the assessment of safety and tolerability. All 16 subjects were included in the evaluation of safety, but only partial data from one subject (allocation number [AN] 0014 in Panel B Period 3: 750 mg doravirine QD from Day 1 to Day 9 predose, who discontinued after 8 dosing days due to a serious adverse event [SAE]) were included in the evaluation of safety summary statistics.

Summary	Overall, single and multiple-dose administrations of doravirine up to 1200- and 750-mg, respectively, were generally well tolerated in healthy adult male subjects. The majority of AEs were mild in severity and all resolved by the end of study. One subject experienced an SAE of sarcoidosis of moderate severity that was not considered related to treatment. This was the only subject who was discontinued due to an AE. There were no deaths or events of clinical interest (ECI). Across all single dose doravirine treatment groups pooled, 12 of 16 (75%) subjects reported 38 AEs, 11 of which were considered drug-related by the investigator. The most common AEs reported in the doravirine treatment groups were headache (n=8 subjects, 50%) and oropharyngeal pain (n=4, 25%). Following single-dose treatment with placebo, 6 of 8 (75%) subjects reported 9 AEs, 3 of which were considered drug-related. The most common AE reported was headache (n=3, 37.5%). No other AE was reported by more than one subject in the placebo group. Following single-dose administration of 600-, 800-, 1000- and 1200-mg of doravirine, 4 of 6 (66.7%), 6 of 6 (100%), 3 of 6 (50%) and 4 of 6 (66.7%) subjects reported at least one AE. There were no dose-related trends for specific AEs. Across both doravirine multiple dose treatment groups, 7 of 12 (58.3%) subjects reported 43 AEs, 19 of which were considered drug-related. The most common AEs were headache (n=5 subjects, 41.7%) and nausea (n=3, 25%). Two of 4 subjects (50%) in the multiple dose placebo group reported 9 AEs, 5 of which were considered drug-related. No AE was reported by more than one subject in the multiple dose placebo group. Following multiple dose administration of 450 mg and 750 mg of doravirine, 3 of 6 (50%) and 4 of 6 (66.7%) subjects reported at least one AE, respectively. There were no dose-related trends for specific AEs. No clinically meaningful trends were observed for changes in clinical safety laboratory values, VS, or ECGs as a function of treatment.

Analysis description	**Second Primary Analysis - PK of doravirine** **Single-Dose PK (Periods 1 and 2)** The assessment of single dose PK was conducted using Panels A and B and Period 1 and 2 data. Doravirine C24hr was log transformed and analyzed by a linear mixed-effects model containing a fixed effect for treatment and a random effect for subject. For estimation purposes, the geometric mean (GM) of doravirine C24hr was generated from the model along with its corresponding 90% confidence interval (CI) for each dose level in both panels. Doravirine AUC0-inf and Cmax were analyzed in a similar fashion. **Multiple-Dose PK (Period 3)** Individual C24hr values of doravirine after multiple dose administration were log transformed and analyzed based on a linear mixed-effects model using Panels A and B Period 3 data only. The model contains a fixed effect for treatment, day (Days 1 and 10), and treatment-by-day interaction and a random effect for subject within treatment. The covariance structure of this model was assumed to be compound symmetry (CS). Based on this model, the second primary hypothesis, the true GM C24hr of doravirine after multiple dose administration exceeds 54 nM on Day 10, was tested using the following stepwise procedure. At the highest safe and well-tolerated fasted dose, a two-sided 90% CI for the GM of C24hr on Day 10 was constructed. The hypothesis was supported if the lower limit of this 90% CI (equivalent to the lower limit of a one-sided 95% CI) was greater than 54 nM. If the hypothesis was supported in the previous step, then the same procedure was applied to the next lowest safe and well tolerated fasted dose. The procedure continued in this stepwise fashion until the lower limit of the 90% CI at a particular dose failed to exceed 54 nM. For estimation purposes, 90% CIs were also constructed for all doses at which the true GM C24hr failed to exceed 54 nM. Doravirine AUC0-24hr and Cmax were analyzed in a similar fashion. Ninety-five percent CIs were also constructed for the GMs of doravirine AUC0-24hr, C24hr, and Cmax by treatment and day. The accumulation of doravirine was assessed through the construction of a 90% CI for the geometric mean ratio (GMR, Day 10 / Day 1) of C24hr, AUC0-24hr and Cmax.

Analysis population and time point description	All subjects who were compliant with the protocol sufficiently to ensure that data were likely to exhibit the effects of treatment, according to the underlying scientific model, and had available data from at least one treatment, were included in the primary analysis data set. Sixteen (16) subjects received at least one dose of doravirine. However, one subject (AN 0014 in Panel B Period 3: 750 mg doravirine QD x 10 days) was discontinued after 8 dosing days and had PK data available until predose of Day 9, due to an SAE. Available PK data before the discontinuation for this subject and all data from the other 15 subjects were included in the PK analyses.
Summary	**Pharmacokinetics (Periods 1 and 2):** Following single dose administration, doravirine was rapidly absorbed with median Tmax ranging from 2 to 4 hours and geometric mean apparent half-life ranging from 13.58 to 18.88 hours over the 600- to 1200-mg dose range. Geometric mean and 90% CI for doravirine AUC, Cmax, and C24hr are presented in the table below. An exploratory analysis of dose proportionality suggested that AUC, Cmax, and C24hr increased in a less than dose proportional fashion over the dose range studied.

Summary Statistics of Plasma MK-1439 Pharmacokinetics Following Single Doses of 600- to 1200-mg MK-1439 in Healthy Adult Males (Period 1 and 2)

Pharmacokinetic Parameters	Panel A 600 mg			Panel A 800 mg		
	N	GM	90% CI	N	GM	90% CI
AUC0-inf (µM*hr) †	6	146	(126, 169)	6	179	(154, 208)
AUC0-24hr (µM*hr) †	6	101	(88.8, 115)	6	118	(104, 134)
Cmax (nM) †	6	7420	(6380, 8630)	6	8180	(7030, 9520)
C24hr (nM) †	6	2240	(1900, 2650)	6	2570	(2180, 3040)
Tmax (hr) ‡	6	2.50	(0.50, 4.00)	6	4.00	(2.00, 5.00)
Apparent t1/2 (hr) §	6	13.58	(14.10)	6	16.45	(26.97)
Pharmacokinetic Parameters	Panel B 1000 mg			Panel B 1200 mg		
	N	GM	90% CI	N	GM	90% CI
AUC0-inf (µM*hr) †	6	216	(186, 250)	6	246	(212, 286)
AUC0-24hr (µM*hr) †	6	138	(121, 156)	6	152	(134, 173)
Cmax (nM) †	6	10100	(8670, 11700)	6	10800	(9270, 12600)
C24hr (nM) †	6	3200	(2710, 3780)	6	3640	(3080, 4300)
Tmax (hr) ‡	6	2.00	(0.50, 5.00)	6	3.00	(1.00, 5.00)
Apparent t1/2 (hr) §	6	15.42	(10.97)	6	18.88	(34.23)

† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.

‡ Median (min, max) reported for Tmax.

§ Geometric mean and percent geometric CV reported for apparent t1/2.

Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.135 for AUC0-inf, 0.112 for AUC0-24hr, 0.130 for Cmax and 0.138 for C24hr. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.

GM = Geometric least-squares mean; CI = Confidence interval.

Summary (Continued)	**Pharmacokinetics (Period 3):** Following multiple dose administration for 10 days of 450- and 750-mg, doravirine had a median Tmax ranging from 1 to 3 hours and apparent half-life ranging from 14.67 to 20.95 hours over the 450- to 750-mg dose range (see table below). Exploratory analysis of dose proportionality on Day 10 suggests that the point estimates of AUC0-24hr, Cmax and C24hr increase in a slightly less than dose proportional manner. The targeted Day 10 C24hr of 54 nM was attained at all studied doses (450 mg and higher). Geometric mean and 90% CI of C24hr on Day 10 was 2090 (1710, 2560) nM for 450 mg and 2850 (2320, 3510) nM for 750 mg, respectively. Median time to 90% of steady state was 2 days for both dose levels. The accumulation ratios for doses of 450- to 750-mg ranged from 1.22 to 1.39 for AUC0-24hr. Similarly, the accumulation ratios for doses 450- to 750-mg ranged from 1.08 to 1.21 for C24hr, and 1.36 to 1.50 for Cmax, respectively.

Summary Statistics of Plasma MK-1439 Pharmacokinetic Following Once Daily Multiple Doses Administration for 10 Days of 450- and 750- mg MK-1439 in Healthy Adult Male Subjects (Period 3)

Pharmacokinetic Parameter	Panel A 450 mg (N=6)	Panel B 750 mg (N=6 ¶)
Day1 (First dose)		
AUC0-24hr (µM*hr) †	82.0 (70.2, 95.7)	99.1 (84.9, 116)
Cmax (nM) †	5580 (4810, 6460)	6980 (6020, 8080)
C24hr (nM) †	1940 (1520, 2470)	2370 (1850, 3020)
Tmax (hr) ‡	3.00 (1.00, 4.00)	3.00 (1.00, 5.00)
Day 10 (Last dose)		
AUC0-24hr (µM*hr) †	100 (85.7, 117)	138 (118, 161)
Cmax (nM) †	7590 (6550, 8790)	10500 (8910, 12400)
C24hr (nM) †	2090 (1640, 2670)	2850 (2220, 3670)
Tmax (hr) ‡	1.50 (1.00, 4.00)	1.00 (0.52, 5.00)
Apparent t1/2 (hr) §	14.67 (30.50)	20.95 (55.14)
Accumulation Ratio (Day 10/ Day 1)		
AUC0-24hr #	1.22 (1.13, 1.32)	1.39 (1.28, 1.51)
Cmax #	1.36 (1.15, 1.61)	1.50 (1.26, 1.79)
C24hr #	1.08 (0.95, 1.23)	1.21 (1.04, 1.39)

† Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.

‡ Median (min, max) for Tmax.

§ Geometric mean and percent geometric CV reported for apparent t1/2.

Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.

¶ N=5 for 750 mg (Panel B) on day 10.

Square root of conditional mean squared error (residual error) from the linear mixed effect model = 0.072 for AUC0-24hr, 0.154 for Cmax and 0.126 for C24hr. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.

CONCLUSIONS:	**Safety** Single and multiple- dose administration of doravirine up to 1200- and 750-mg, respectively, are generally well tolerated in healthy adult male subjects. **Pharmacokinetics** 1. The true GM C24hr exceeds 54 nM after 10 days of administration after QD oral doses of 450- and 750-mg. 2. Doravirine AUC0-inf and Cmax following single oral doses of doravirine appear to increase in a less than dose proportional manner from 600- to 1200-mg. 3. Doravirine AUC0-24hr and Cmax on Day 10 following QD oral multiple dose administration of doravirine appear to increase in a less than dose proportional manner from 450- to 750mg. 4. The time to reach steady state following QD oral multiple dose administration of doravirine is approximately 2-3 days.
PUBLICATION(S):	Anderson MS, Gilmartin J, Cilissen C, De Lepeleire I, Van Bortel L, Dockendorf MF, *et al*. "Safety, Tolerability and Pharmacokinetics of doravirine, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, After Single and Multiple doses in Healthy Subjects". *Antivir Ther*. 2015;20(4):397-405. Anderson MS, Gilmartin J, Cilissen C, De Lepeleire I, Van Bortel L, Dockendorf MF, *et al*. "Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses of MK-1439, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, in Healthy Subjects". Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3-6; Atlanta, GA.
REPORT DATE:	**04-MAY-2017**

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CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Study to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of MK-1439 #008

INVESTIGATOR/STUDY CENTER: [redacted]

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 12-Jun-2013. The frozen file date was 25-Jul-2013.

CLINICAL PHASE: I

DURATION OF TREATMENT:
Subjects received a single average oral dose of approximately 351 mg (~211 microcurie [µCi]) [^{14}C]MK-1439 (actual doses ranged from 349 mg – 353 mg [210 – 212 µCi]) on Day 1. Five (5) of 6 subjects remained confined for 168 hours and 1 subject remained confined for 192 hours. Discharge criteria were met and all subjects were released within 9 days following dosing. The total duration of the study for each subject, from screening through to the final protocol-specified contact (follow-up phone call), was 23 days.

OBJECTIVES:

Primary:

1. To investigate the route(s) of elimination and mass balance of MK-1439 after oral administration of a single 350 mg (sodium salt in hydroxypropylmethyl cellulose [HPMC] capsules) (~200 µCi) dose of [^{14}C]MK-1439 in healthy adult male subjects.
2. To quantitate total radioactivity and concentrations of MK-1439 in plasma after oral administration of a single 350 mg (~200 µCi) dose of [^{14}C]MK-1439 sodium pentahydrate salt in healthy adult male subjects.
3. To examine the metabolism of MK-1439 in humans and identify major metabolites in biological specimens.

Secondary:

To evaluate the safety and tolerability of a single 350 mg (~200 µCi) dose of [^{14}C]MK-1439 sodium pentahydrate salt in healthy adult male subjects.

HYPOTHESES:

Primary:

1. Estimation: The mean recovery of total radioactivity in urine and feces after oral administration of a single 350 mg (~200 µCi) dose of [^{14}C]MK-1439 sodium pentahydrate salt in healthy adult male subjects will be estimated.
2. Estimation: The total radioactivity and concentrations of MK-1439 in plasma after oral administration of a single 350 mg (~200 µCi) dose of [^{14}C]MK-1439 sodium pentahydrate salt in healthy adult male subjects will be estimated.

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STUDY DESIGN:

This was a single-dose, open-label, 1-period study to investigate the absorption, metabolism, excretion, and mass balance of MK-1439 in healthy adult male subjects. Six (6) healthy, adult, non-tobacco using male subjects were enrolled in this study. On Day 1, a single average oral dose of approximately 351 mg (~211 µCi) [^{14}C]MK-1439 (actual doses ranged from 349 mg – 353 mg [210 – 212 µCi]) was administered to each subject with 240 mL of water after an overnight fast. Blood, urine, and fecal samples were collected to measure total radioactivity (plasma, urine, and fecal samples), MK-1439 concentrations (plasma samples only), and metabolic profiling (plasma, urine, and fecal samples) for at least 168 hours postdose (Day 8). For each subject, if discharge criteria were not met on Day 8, collection of blood samples (for determination of total radioactivity and metabolic profiling only), urine, and fecal samples was to have continued until the majority of the administered radioactivity was recovered or up to a maximum of 28 days (672 hours [Day 29]). Beyond 168 hours postdose until discharge criteria are met (or Day 29 is reached), blood sample collection for total radioactivity analyses were to stop if 2 consecutive samples were below the total radioactivity limit of quantification. If at the end of 28 days, a subject's recovered radioactivity did not meet the discharge criteria, at the discretion of the Sponsor, the collection of urine and feces may be extended for a maximum of 7 days (through Day 36). If discharge criteria were met or early termination occurred, subjects were to have been released from the clinical research unit (CRU) within 14 days following dosing. Subjects were to receive a follow-up phone call approximately 14 days after dosing to determine if any adverse experiences had occurred since their release.

SUBJECT DISPOSITION:

ENTERED: Total	6
Male N (age range in years)	6 (23 to 42)
COMPLETED:	6
DISCONTINUED: Total	0
Clinical adverse experience	0
Laboratory adverse experience	0
Other	0

DOSAGE/FORMULATION NOS.: [^{14}C]MK-1439 was supplied as a sodium pentahydrate salt and was encapsulated in HPMC capsules at the CRU. A single oral dose of approximately 350 mg (~200 µCi) (actual average dose of 351 mg (~211 µCi) [^{14}C]MK-1439 was administered as 6 x 58.33 mg (33.33 µCi) capsules on Day 1.

Drug	Potency	Formulation No.	Dosage Form	Control No.
[^{14}C]MK-1439	99.9%	[redacted]	Powder	NA
Empty HPMC capsule[†]	NA	NA	Capsule	[redacted]

[†]Empty HPMC capsules (a product of Qualicaps) were purchased and stored by the pharmacy. The expiration date was Sep-2015.
NA – Not applicable.

DIAGNOSIS/INCLUSION CRITERIA:

Healthy adult non-smoking male subjects ≥ 19 and ≤ 55 years of age with a body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2.

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EVALUATION CRITERIA:

PHARMACOKINETICS: Blood samples for plasma total radioactivity assay, MK-1439 concentrations, and metabolic profiling were collected at predose and specified time points up to 168 hours following a single 351 mg (~211 µCi) dose of [^{14}C]MK-1439 sodium pentahydrate salt (actual doses ranged from 349 mg – 353 mg [210 – 212 µCi]). MK-1439 plasma pharmacokinetics were summarized with the following parameters: AUC0-48, AUC0-last, AUC0-∞, Cmax, C24, Tmax, apparent terminal t½, and Tlast. Total drug-derived radioactivity in plasma was summarized with AUC0-48, AUC0-last, Cmax, C24, Tmax, and Tlast.

Urine was collected in discrete intervals from predose until 168 hours for 5 of 6 subjects and until 192 hours for a single subject for the analysis of total radioactivity and metabolic profiling. Fecal samples were collected in daily intervals from 48 hours prior to drug administration until 168 hours for 5 of 6 subjects and until 192 hours for a single subject for the analysis of total radioactivity and metabolic profiling. The percent of dose (based on total radioactivity) excreted in each collection interval, as well as the cumulative percent of dose and dose-equivalent amount (Ae) recovered across all intervals combined, were determined in urine and feces. Mass balance for MK-1439 was calculated from the sum of cumulative percent of dose excreted in urine and feces.

Metabolic profiling was performed on plasma (0-24 hr), urine (0-96 hr), and fecal (0-168 hr) samples. The results were used to identify the metabolites and to quantify their relative percentages in plasma, urine, and feces.

SAFETY: Safety was monitored throughout the study for all types of adverse events through physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory safety evaluations (hematology, blood chemistry, and urinalysis). Subjects were monitored closely throughout the study for any adverse experiences.

STATISTICAL PLANNING AND ANALYSIS:

METHODS:

Pharmacokinetics: Plasma total radioactivity and MK-1439 AUC0-48, Cmax, and C24 values were natural log (ln)-transformed and evaluated using a linear mixed effects model with analyte as a fixed effect and subject as random effect. Model based means and 95% confidence intervals (CIs) were constructed on the ln-scale and referenced the t-distribution. To estimate the proportion of total radioactivity accounted for by MK-1439 in plasma, the geometric mean ratios ([GMRs] MK-1439/Total Radioactivity) of AUC0-48, Cmax, and C24 were computed, along with corresponding 95% CIs. Exponentiating the means, mean differences, and CIs yielded estimates for the population geometric means, population GMRs, and CIs about the geometric means and GMRs on the original scale.

Non-model based descriptive statistics were provided for AUC0-last and AUC0-∞ (geometric means and corresponding 95% CIs), Tmax, Tlast (median, minimum and maximum), and t½ (geometric means and percent geometric coefficient of variation). Summary statistics (number of subjects with non-missing data [N], arithmetic mean [AM], standard deviation [SD], arithmetic coefficient of variation [ACV], geometric mean [GM], coefficient of variation [GCV], median [Med], minimum [Min], and maximum [Max]) were provided for AUC0-48, AUC0-last, AUC0-∞, Cmax, C24, Tmax, t½, and Tlast.

The arithmetic mean (on the raw scale) and its corresponding 95% CI of the arithmetic mean for the total radioactivity recovered in urine, feces, and overall (as % of dose administered) following a single oral dose of [^{14}C]MK-1439 in healthy adult male subjects was also calculated. Summary statistics (N, AM, SD, ACV, GM, GCV, Med, Min, and Max) were provided for urinary and fecal data for individual and cumulative percent recoveries by interval and overall.

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STATISTICAL PLANNING AND ANALYSIS (Continued):

METHODS (Continued):

Safety: The safety and tolerability of a single average 351 mg (~211 µCi) MK-1439 dose of [^{14}C]MK-1439 sodium pentahydrate salt was evaluated by clinical assessment of adverse experiences and other safety measurements. Incidence of the number of subjects with adverse experiences was descriptively summarized. Because laboratory safety tests, ECGs, and vital signs were not deemed clinically significant, the safety parameters were not summarized.

RESULTS:

PHARMACOKINETICS:

A single average oral dose of approximately 351 mg (~211 µCi) administered to healthy adult male subjects was absorbed with a median Tmax of 4.50 hours for MK-1439 and 3.02 hours for total radioactivity. Total radioactivity in plasma was below the lower limit of quantification (LLOQ) of 94 ng equivalents/g (221 nM equivalents) in all subjects by 120 hours postdose, and plasma MK-1439 concentrations fell below the LLOQ of 1.00 ng/mL (2.35 nM) in half the subjects (3) by 168 hours postdose. Summary statistics and the comparison of exposure relative to total radioactivity in plasma are presented in the table below. MK-1439 was the major component of total radioactivity detected in plasma, accounting for approximately 76% and 78% of the plasma total radioactivity AUC0-48 and Cmax, respectively. This correlated well with the metabolic profiling results, which showed that in the 0 - 24 hour pooled plasma ~75% of the radioactivity consisted of unchanged MK-1439. The major metabolite in plasma was the oxidative product (M9, 12.9%). An N-acetylcysteine conjugate (M15) and a glucuronide conjugate of an oxidative metabolite (M7) accounted for a further 2.8% of the total radioactivity. Trace amounts of 5 other metabolic products, including 2 N-dealkylated products (M8 and M11) and oxidative or hydrolysis products M10, M18, and M19 were also detected in plasma.

Total radioactivity in urine and feces samples was present at quantifiable levels up to the last collection interval for each subject, where a sample was produced. The majority (100.9%) of the radioactive dose was excreted by 168 hours, mainly in feces. Overall, 101.22% (95% CI: 97.52% - 104.93%) of the radioactive dose was recovered, with 90.43% in feces (95% CI: 86.26% - 94.59%) and 10.80% in urine (95% CI: 7.98% - 13.62%). In feces, unchanged MK-1439 accounted for approximately 84.1% of total radioactivity, most likely from unabsorbed drug. Oxidative metabolite M9 accounted for 2.7%, with other minor metabolites detected including 2 N-dealkylated products (M8 and M11), oxidative or hydrolysis products (M5, M10, M18, and M19), and conjugates of oxidative products (M14, M15).The primary components in urine were M9 and unchanged MK-1439, accounting for approximately 6.7% and 2.2% of the administered dose, respectively. M8, M10, and M18 were also detected in urine, but combined, represented only approximately 0.5% of the administered dose. Trace amounts of other metabolites (M5, M11, M14, M15, and M19) were also detected in urine.

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RESULTS (Continued):

PHARMACOKINETICS (Continued):

Summary Statistics of Plasma Pharmacokinetic Parameters for MK-1439 Compared to Total Radioactivity Following Administration of a Single Oral Dose of 351 mg [^{14}C] MK-1439 (~211 µCi) in Healthy Adult Male Subjects

Parameter/Analyte	N	GM[†]	95% CI	GMR[‡]	95% CI[†]	rMSE[§]
AUC0-48 (µM•hr or µM equivalents•hr)						
MK-1439	6	17.02	(12.49, 23.18)	0.76	(0.67, 0.88)	0.093
Total Radioactivity	6	22.26	(16.34, 30.32)			
AUC0-last[‖] (µM•hr or µM equivalents•hr)						
MK-1439	6	26.83	(20.06, 35.89)			
Total Radioactivity	6	26.12	(18.30, 37.26)			
AUC0-∞[‖] (µM•hr)						
MK-1439	6	27.59	(20.80, 36.59)			
Cmax (nM or nM equivalents)						
MK-1439	6	501.36	(347.72, 722.90)	0.78	(0.67, 0.90)	0.096
Total Radioactivity	6	645.62	(447.77, 930.90)			
C24 (nM or nM equivalents)						
MK-1439	6	347.42	(252.72, 477.61)	0.75	(0.64, 0.88)	0.105
Total Radioactivity	6	462.60	(336.50, 635.94)			
Tmax[¶] (hr)						
MK-1439	6	4.50	(3.00, 12.00)			
Total Radioactivity	6	3.02	(3.01, 48.01)			
Apparent terminal t½[††] (hr)						
MK-1439	6	22.95	50.7			
Tlast[¶] (hr)						
MK-1439	6	144.00	(120.00, 168.16)			
Total Radioactivity	6	60.01	(48.01, 72.01)			

Proportion of the Radioactivity Dose Recovered[‡‡]

	Urine	Feces	Total
Fraction of Radioactivity Recovery (%)	10.80	90.43	101.22
95% Confidence Interval	(7.98, 13.62)	(86.26, 94.59)	(97.52, 104.93)

[†]Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values.
[‡]GMR = Ratio of geometric least-squares means with respect to total radioactivity (i.e. MK-1439 total radioactivity).
[§]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model.
rMSE*100% approximates the within-subject %CV on the raw scale.
[‖]Geometric mean and 95% confidence interval (non-model based) from the summary statistics were reported for AUC0-last and AUC0-∞.
[¶]Median (min, max) reported for Tmax and Tlast.
[††]Geometric mean and percent of geometric coefficient of variation reported for apparent terminal t½.
[‡‡]Arithmetic mean and 95% confidence interval from the summary statistics were reported for the proportion of the radioactive dose recovered in urine, feces, and overall.
AUC0-last represents the area under the concentration versus time curve from 0 to the time of the last quantifiable (above LLOQ) sample.
AUC0-48 represents the area under the concentration time curve from 0 to the nominal time of 48 hours postdose, which is the last common time point at which total radioactivity and plasma MK-1439 were quantifiable in all subjects.
AUC0-∞ and apparent terminal t½ were not determined for total radioactivity.
GMR = Geometric least-squares mean ratio; GM = Geometric least-squares mean; CI = Confidence interval.

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RESULTS (Continued):

SAFETY:

A single average 351 mg (~211 µCi) MK-1439 dose of [^{14}C]MK-1439 sodium pentahydrate salt was well tolerated in the healthy males in this study. No deaths, serious adverse experiences, laboratory adverse experiences, events of clinical interest (ECIs), drug-related adverse experiences, or deaths occurred during the study, and no subject discontinued because of an adverse experience. One (1) subject experienced a single mild adverse experience of constipation that was considered not related to study drug and resolved by study completion with magnesium hydroxide treatment. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

CONCLUSIONS:

1. Following administration of a single average oral dose of 351 mg [^{14}C] MK-1439 (~211 µCi) in healthy adult male subjects, mass balance was achieved. The mean total radioactivity recovered was 101.22% (95% CI: 97.52% - 104.93%) of the dose over the collection period (8 days), with 90.43% radioactivity recovered in feces and 10.80% recovered in urine. The majority (100.9%) of the radioactivity was recovered in the first 7 days (168 hours).
2. Based on the excretion and profiling data, MK-1439 has good recovery and is excreted mainly in feces as unchanged MK-1439, likely from unabsorbed dose, and as products of oxidative metabolism. The major route of elimination of the absorbed dose was oxidative metabolism.
    - MK-1439 was the major radioactive component in plasma, accounting for approximately 76% and 78% of the plasma total radioactivity for AUC0-48 and Cmax, respectively. This correlated well with the metabolic profiling results which indicated that approximately 75% of the radiochromatographic profile consisted of unchanged MK-1439. M9, an oxidative metabolite represented approximately 12.9% of the plasma radioactivity. The N-acetylcysteine conjugate M15 and the glucuronide conjugate of an oxidative metabolite M7 together accounted for a further 2.8% of the total radioactivity in plasma. Trace amounts of 5 other metabolic products, including 2 N-dealkylated products (M8 and M11) and oxidative or hydrolysis products (M10, M18, and M19) were also detected in plasma.
    - In feces, unchanged MK-1439 and the oxidative metabolite M9 accounted for approximately 84.1% and 2.7% of the administered dose, respectively. Trace amounts of other metabolites (M5, M8, M10, M11, M14, M15, M18, and M19) were also detected in feces.
    - The primary components in urine were M9 and unchanged MK-1439, accounting for approximately 6.7% and 2.2% of the administered dose, respectively. M8, M10, and M18 were also detected in urine, but combined represented only approximately 0.5% of the administered dose. Trace amounts of other metabolites (M5, M11, M14, M15, and M19) were also detected in urine.
3. A single average 351 mg (~211 µCi) MK-1439 dose of [^{14}C]MK-1439 sodium pentahydrate salt was well tolerated in healthy male subjects.

REPORT DATE: Final: 29-Apr-2014

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	**MK-1439**	
INDICATION:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection.	
PROTOCOL TITLE:	A Single-Dose, Parallel, Pharmacokinetic, Safety and Tolerability Study of MK-1439 Long Acting Parenteral (LAP) Intramuscular Injections	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-031
	Clinical Phase:	1
ETHICS:	This study 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.	
TRIAL CENTER:	[redacted], MD, PhD, FRCP(C) [redacted] [redacted], Canada [redacted]	
DESIGN:	This was an open-label, parallel, two-part, pharmacokinetic (PK), safety and tolerability study. Part 1 was an open-label, non-randomized, multiple oral-dose, single-period, single-treatment, safety study to evaluate the safety and tolerability of MK-1439 in the study population in order to proceed to Part 2. Subjects were dosed one oral MK-1439 100 mg tablet once daily (QD) for 14 days. Of the 42 initially enrolled in Part 1, thirty-six (36) subjects, who successfully completed Part 1 of the study, participated in Part 2. Part 2 was an open-label, randomized, single-dose, single-period, three-treatment, parallel, PK, safety and tolerability study to evaluate the single-dose PK and safety of three treatments (Treatments A, B, and C) of MK-1439 intramuscular (IM) suspension. Following completion of Part 1, eligible subjects were randomized to one of the following three treatments in Part 2 of the study: Treatment A consisted of a single 1 mL (20% suspension) IM injection of 200 mg MK-1439 administered in the deltoid muscle. Treatment B consisted of a single 0.66 mL (30% suspension) IM	

	injection of 200 mg MK-1439 administered in the deltoid muscle. Treatment C consisted of two (2) 0.5 mL (20% suspension) IM injections of 200 mg MK-1439 administered in the deltoid muscles (1 injection of approximately 100 mg per injection in each deltoid muscle). A washout period of 10 days between the last dose in Part 1 and the IM injection in Part 2 was observed for subjects in Part 1 that participated in Part 2 of the study. Blood samples for PK analyses were collected during Part 2 of the study for measurement of MK-1439 concentrations as follows: venous plasma samples by direct venipuncture (in clinic) were collected at pre-dose and at specified time points up to 183 days post IM injection; venous dried blood spot (DBS) samples (in clinic) were collected pre-dose and at specified time points up to 43 days post IM injection; and fingerstick DBS samples (in clinic and at-home) were collected by subjects pre-dose and at specified time points up to 36 and 35 days, respectively, post IM injection. Subjects were provided with and trained to use paper and/or electronic diary (e-diary) cards to record the date and time of all fingerstick DBS samples collected at home. Subjects provided feedback related to fingerstick DBS sampling and the use of e-diary through a questionnaire completed on Day 36 of receiving the IM injection, the results of which were evaluated with descriptive statistics. Safety and tolerability were closely monitored throughout the study through standard clinical safety evaluations (clinical safety laboratories, vital signs, electrocardiograms [ECGs], and physical examination) and monitoring of adverse events/experiences (AEs), and, in addition, inspection of the IM injection sites in Part 2 of the study. Forty-two (42) healthy male and female subjects from 18 to 65 years of age (inclusive) with a body mass index (BMI) $\geq$ 19.0 to $\leq$ 33.0 kg/m^2 participated in Part 1 of the study. Thirty-six (36) subjects, compliant with the aforementioned inclusion criteria, were selected from the previous group based on a safety evaluation and participated in Part 2 of the study. No subject from Part 1 was excluded from participation in Part 2 due to safety or tolerability reasons.	
	Planned duration of main phase (date first ICF was signed to date safety call was made):	The duration of the study was approximately 9 months.

<table>
<tr><td>Objectives</td><td colspan="3">The primary objective of Part 1 of this study was to evaluate the feasibility (safety) of dosing Part 2.

The objective of Part 2 of this study was to evaluate the PK, safety, and tolerability of MK-1439 IM suspensions.

Primary Objective (Part 2):

The primary objective of this study was to evaluate the PK of MK-1439 in healthy subjects following the administration of:

• MK-1439 1 mL fixed dose IM 200 mg suspension (20% suspension [median particle size distribution approximately 8 µm]);

• MK-1439 0.66 mL fixed dose IM 200 mg suspension (30% suspension [median particle size distribution approximately 8 µm]); and

• MK-1439 1 mL fixed dose IM 200 mg suspension split into two 100 mg injections (20% suspension [median particle size distribution approximately 8 µm]).

Secondary Objective (Part 2):

The secondary objective was to monitor the safety and tolerability of MK-1439 IM suspensions.</td></tr>
<tr><td>Hypotheses</td><td colspan="3">Not applicable</td></tr>
<tr><td rowspan="4">Treatment groups</td><td>Part 1</td><td>Drug Product</td><td>100 mg MK-1439 (one tablet) QD for 14 days.

[42 Subjects]</td></tr>
<tr><td rowspan="3">Part 2</td><td>Treatment A (Drug Product 1)</td><td>200 mg MK-1439 (one 1 mL [20% suspension] IM injection) administered in the deltoid muscle.

[12 Subjects]</td></tr>
<tr><td>Treatment B (Drug Product 2)</td><td>200 mg MK-1439 (one 0.66 mL [30% suspension] IM injection) administered in the deltoid muscle.

[12 Subjects]</td></tr>
<tr><td>Treatment C (Drug Product 1)</td><td>200 mg MK-1439 (two 0.5 mL [20% suspension] IM injections) administered in the deltoid muscles (one injection of 100 mg to each deltoid muscle).

[12 Subjects]</td></tr>
</table>

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-1439 (005F) 100 mg tablet	[redacted]
HFUV MK-1439, 0.40 g / vial (PIV for reconstitution)	[redacted]
HSSV MK-1439, 3 mL Diluent (low PS80 content)	[redacted]

Endpoints and definitions	Primary endpoints	Part 1	Safety	Adverse events/experiences (AEs), in addition to laboratory safety tests, 12-lead electrocardiogram (ECGs), physical examinations, and vital signs. Incidence, frequency, and severity of AEs.
		Part 2	PK	AUC0-last, Cmax, Tmax, and t½
	Secondary endpoints	Part 2	Safety	AEs, clinical laboratory tests, 12-lead ECG, physical examination, vital signs measurements, in addition to monitoring of IM injection sites.
Trial status	[redacted]-20[redacted] to [redacted]-20[redacted]			
Initial Database lock	[redacted]-20[redacted]			
Final Database lock	[redacted]-20[redacted]			
RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol and Statistical Analysis Plan (SAP).			
SUBJECT DISPOSITION:	Subject disposition is summarized in the table below. Forty-two (42) subjects enrolled in Part 1. One subject withdrew from the study prior to Day 8 dosing in Part 1 due to personal reasons. The subject was not replaced. From the subjects completing Part 1, 36 subjects were enrolled into Part 2. No subject from Part 1 was excluded from participation in Part 2 due to safety or tolerability reasons. All subjects enrolled in Part 2 completed.			

Disposition of Subjects

NUMBER OF SUBJECTS	PART 1	PART 2
RANDOMIZED	N/A†	36‡
ENROLLED	42	36
Female (age range) Male (age range)	16 (22 – 58) 26 (24 – 57)	13 (23 – 58) 23 (24 – 57)
COMPLETED	41	36
DISCONTINUED	1	0
Withdrawal by Subject	1	N/A

N/A = Not Applicable
† Allocation of treatment (randomization) was not applicable for Part 1 of the study.
‡ 36 subjects were randomized into three treatment groups A, B, or C with 12 subjects in each treatment. Subjects in Part 2 also participated in Part 1.

Analysis description (Part 1)	**Primary Analysis:** Safety and tolerability of oral MK-1439 administered QD over a 14 day dosing period. An assessment of safety and tolerability was based primarily on the frequency and severity of AEs and other safety measurements. Incidence of the number of subjects with AEs was descriptively summarized and listed by treatment. The incidence of the number of subjects with drug-related AEs was descriptively summarized.
Analysis population and time point description:	Safety and tolerability were determined from the subjects in the Part 1 All Subjects As Treated (AST) dataset as defined in the protocol. All 42 subjects who received at least one dose of the 100 mg MK-1439 oral tablets were included in Part 1 AST dataset.
Summary	Multiple doses of 100 mg MK-1439 administered QD for 14 days were generally well tolerated. There were no clinically meaningful trends in laboratory safety measurements, vital signs, physical examinations, or ECGs reported. No subject was discontinued or withdrew participation from Part 1 of the study due to an AE. A total of 24 AEs were reported by 12 subjects (28.6%) following oral dosing of MK-1439, with eight (8) subjects (19.0%) reporting one or more drug-related AEs. All AEs were mild in severity, limited in duration, and resolved. The most common AE (reported by ≥2 subjects) was headache, reported by 3 subjects (7.1%). The most common drug-related AE was headache, reported by 2 subjects (4.8%). No other AEs (related or unrelated) were reported by more than one subject. MK-1439 was generally well tolerated in the study population and all were eligible, from a safety and tolerability perspective, for participation in Part 2.

Analysis description (Part 2)	**Primary Analysis:** Pharmacokinetics of fixed dose MK-1439 Long Acting Parenteral (LAP) intramuscular (IM) suspension Venous Plasma Samples (Direct Venipuncture): Individual values of the PK parameters (Cmax, AUC0-last, Tmax, and t½) of MK-1439 from venous plasma samples were listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation (SD), arithmetic percent coefficient of variation (CV) (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale). DBS Samples (Venous and Fingerstick): The measured drug concentrations of in-clinic venous and fingerstick DBS samples were compared to concentrations obtained from venous plasma samples. Individual subject MK-1439 concentration-time profiles were generated with the measured venous plasma and the converted plasma concentrations from the observed DBS concentration via the linear regression of DBS versus plasma concentration for the clinic venous and fingerstick data, separately. Actual sampling times were used. Mean concentration-time graphs were generated based on the measured venous plasma MK-1439 concentrations and the converted plasma concentrations from the observed DBS concentrations for the clinic venous (converted plasma concentration = DBS venous concentration – intercept / slope) and fingerstick (converted plasma concentration = DBS fingerstick concentration / slope) data. MK-1439 concentrations from DBS samples collected at home and in the clinic from venous DBS or fingerstick DBS were integrated into one concentration-time profile for each subject and visually inspected for fit. Individual values were listed for each DBS concentration by treatment and day and the following (non-model-based) descriptive statistics were provided: N (number of subjects with non-missing data), arithmetic mean, SD, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale). A linear mixed effect model, with all available post-dose timepoints containing both plasma and DBS samples collected in clinic, was performed to assess the correlation between the MK-1439 concentrations obtained from DBS (in clinic venous blood) and

	plasma, and between DBS (in clinic fingerstick blood) and plasma, for each treatment. The model included DBS concentration as the response, plasma concentration as the covariate, and random intercept and slope for the plasma concentration. Both the random intercept and slope were assumed to follow a bivariate normal distribution.
Analysis population and time point description	Primary analysis was conducted on subjects in the PP dataset. The PP dataset included data from Part 2 of the study only.
Summary	The plasma concentration-time profiles of MK-1439 following all three treatments demonstrated a rapid initial release of the drug product which resulted in an initial peak at approximately 4 days post-injection. This first peak was followed by a decline in plasma concentrations over the next approximately 6 days, with a subsequent increase in plasma concentrations reaching a second peak at approximately 24 to 36 days,corresponding to prolonged and sustained release of the drug product. Summary statistics are provided in the table below. Treatment A (200 mg MK-1439 20% suspension) had the highest exposure, along with the most delayed Tmax. Treatment B (200 mg MK-1439 30% suspension) had the lowest exposure, lowest Cmax, and longest t½. Treatment C (200 mg MK-1439 20% suspension administered as two injections) resulted in the highest peak concentrations with the shortest Tmax. Importantly, the apparent terminal t½ values for all three formulations were notably prolonged compared to oral administration (approximately 11-15 hours), with apparent terminal t½ (geometric mean) ranging from 46 to 58 days. In addition, most subjects showed measurable concentrations up to Day 183. Overall, concentrations measured by DBS (in clinic venous blood), and those measured by DBS (in clinic fingerstick blood), were each strongly, linearly, and positively correlated to the plasma concentrations measured by direct venipuncture. The slopes of the DBS venous and DBS fingerstick concentrations versus the plasma concentrations were 0.7015 and 0.7404, respectively.

Descriptive Statistics for Plasma MK-1439 Pharmacokinetics Following 200 mg Fixed Doses of Two Formulations of MK-1439 Long Acting Parenteral Injections Administered as Single Intramuscular or as Two Intramuscular Injections in Healthy Subjects

Parameter	*Trt*	*GeoMean*	*GCV%*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC0-last	**A**	4.22	24.8	4.34	1.12	25.7	3.90	3.02	6.46	12
(Day·nM)	**B**	3.03	28.2	3.14	0.824	26.3	3.18	2.02	4.32	12
	C	4.13	28.7	4.27	1.09	25.6	4.36	2.59	5.63	12
Cmax	**A**	67.6	40.4	72.5	28.3	39.1	66.8	40.6	119	12
(nM)	**B**	50.3	23.5	51.6	12.2	23.7	48.4	35.9	74.0	12
	C	73.5	31.6	76.8	23.2	30.2	72.6	44.6	112	12
Tmax	**A**	12.49	149.8	20.33	18.65	91.7	13.52	2.96	56.96	12
(Day)	**B**	8.58	145.0	14.84	15.91	107.2	4.98	3.03	43.01	12
	C	6.75	108.9	10.42	11.59	111.3	4.54	2.97	35.96	12
t½†	**A**	45.96	41.1	49.92	25.45	51.0	46.11	27.64	121.42	11
(Day)	**B**	58.27	56.4	67.29	44.14	65.6	54.57	30.74	176.59	11
	C	50.48	39.2	53.81	20.26	37.6	54.17	27.19	97.35	11

† Terminal elimination parameters were not selected for two subjects due to an upward trend in the terminal elimination phase to the last sampling time point; terminal elimination parameters were not selected one subject due to an insufficient number of data points in the elimination phase (one subject in each treatment).

GeoMean = Geometric Mean
GCV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale.
SD = Standard deviation
CV% = Coefficient of variation (100*SD/Mean)
N = Number of non-missing data

Treatment A: MK-1439 200 mg (1 mL of 20% suspension for IM injections)
Treatment B: MK-1439 200 mg (0.66 mL of 30% suspension for IM injections)
Treatment C: MK-1439 200 mg (2x0.5 mL of 20% suspension for IM injections)

Analysis Description (Part 2)	**Secondary Analysis**: Safety and tolerability of fixed dose MK-1439 LAP intramuscular (IM) suspension An assessment of safety and tolerability was based primarily on the frequency and severity of AEs and other safety measurements. Incidence of the number of subjects with AEs was descriptively summarized and listed by treatment. The incidence of the number of subjects with drug-related AEs was descriptively summarized In addition, intramuscular injection sites were inspected for injection site-related signs and symptoms. Descriptive statistics (arithmetic mean, SD, median, and minimum and maximum) of the scores of each injection-related safety parameter (pain, tenderness, erythema / redness, and swelling) on a 5-point scale were provided for each treatment at each time point.
Analysis population and time point description	Safety and tolerability were determined from the subjects in the Part 2 AST dataset as defined in the protocol. All 36 subjects who received the IM injection were included in the Part 2 AST dataset.
Summary	The administration of LAP IM injections of MK-1439 was generally well tolerated. No SAEs or deaths were reported and no subject discontinued due to an AE. Most AEs were mild in severity with the exception of two unrelated, moderately severe injection site pain AEs. A total of 81 AEs were reported by 26 subjects (72.2%) following IM injection of MK-1439 as follows: • Treatment A: 26 AEs reported by 11 of 12 (91.7%) subjects; • Treatment B: 15 AEs reported by 5 of 12 (41.7%) subjects; • Treatment C: 40 AEs reported by 10 of 12 (83.3%) subjects. Seventeen (17) subjects (47.2%) reported an injection site pain AE (41 events), of which none were considered drug-related and all of which resolved by study completion. A higher incidence of injection site pain was reported with Treatment C (eight [8] subjects [66.7%]) compared to Treatment A (six [6] subjects [50.0%]) and Treatment B (three [3] subjects [25.0%]). Furthermore, a higher mean score of pain was observed following Treatment C administration. An overall increase in the mean scores of both pain and tenderness was observed three and four days following the IM injections for all three treatments, with a maximum score of moderate intensity. The most common AEs, regardless of casuality, were as follows: five (5) subjects (13.9%) with decreased neutrophil count, five (5) subjects (13.9%) with decreased white blood cell (WBC) count AE, and five (5) subjects (13.9%) reported at least one headache AE. Eight (8) subjects (22.2%) reported one or more drug-related AEs. The most common drug-related AEs (seen in more than 2 subjects) were decreased neutrophil count, reported by four (4) subjects (11.1%),

	decreased WBC count, reported by four (4) subjects (11.1%), and headache, reported by four (4) subjects (11.1%). There were no clinically meaningful trends in laboratory safety measurements, vital signs, physical examinations, or ECGs.
CONCLUSIONS:	1. The pharmacokinetics of MK-1439 following an IM injection of all three LAP treatments was characterized by a two peak release profile corresponding to a rapid initial release of the drug product from the formulation within the first week post-injection, followed by a prolonged and sustained release of the drug for weeks post-injection. Apparent terminal t1/2 for all three treatments ranged from 46 to 58 days. In addition, most subjects showed measurable concentrations up to Day 183. 2. Multiple oral doses of 100 mg MK-1439 administered QD over a 14-day dosing period were generally well tolerated by the healthy subjects who participated in this study. 3. Single doses of 200 mg MK-1439 administered as one 1 mL (20% suspension) injection in one deltoid muscle, one 0.66 mL (30% suspension) injection in one deltoid muscle, or one 0.5 mL (20% suspension) injection in both deltoid muscles were generally well tolerated by the healthy subjects who participated in this study.
FINAL REPORT DATE:	[redacted]-20[redacted]

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC MK-1439, tablet Indication: human immunodeficiency virus (HIV) infections	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Relative Bioavailability Study to Compare the Pharmacokinetics of MK-1439 in Male and Female Subjects and Healthy Elderly and Young Adult Subjects #009-01

INVESTIGATOR/STUDY CENTER:
[redacted], D.O.
[redacted]

PUBLICATION(S): Not applicable

PRIMARY THERAPY PERIOD: 13 April 2012 – 12 June 2012
Frozen file date was 06-Aug-2012.

CLINICAL PHASE: I

DURATION OF TREATMENT: Subjects received one single administration of 100 mg MK-1439. Each treatment was given after an overnight fast of at least 8 hours.

OBJECTIVE(S):
Primary:

(1) To assess the relative bioavailability of MK-1439 between healthy elderly male and female subjects.

Hypothesis:
The pharmacokinetics of MK-1439 after administration of a single 100-mg tablet (Phase I formulation) to healthy elderly male and female subjects will be similar.

(2) To assess the relative bioavailability of MK-1439 between healthy elderly and young adult subjects

Hypothesis:
The pharmacokinetics of MK-1439 after administration of a single 100-mg tablet (Phase I formulation) to healthy elderly and young adult subjects will be similar.

Secondary: To assess the safety and tolerability of MK-1439 after administration of a single 100-mg dose of MK-1439 to healthy elderly male and female subjects and young adult female subjects.

STUDY DESIGN:
This was an open-label, 1-period, parallel-group study in healthy elderly male and female subjects and healthy young female subjects to identify gender- and age-related difference in the pharmacokinetics of MK-1439. Thirty-six (36) subjects, 12 subjects per group, were enrolled in the study. Subjects received a single oral 100-mg dose of MK-1439 (one Phase I tablet) with 240 mL of water after fasting overnight for at least 8 hours. Blood samples for determination of plasma MK-1439 concentrations were collected at pre-dose and at specified time points post-dose. Adverse experiences were recorded throughout the study. For PK analysis, additional data was used from 6 young male subjects obtained from MK-1439 Protocol 001.

SUBJECT DISPOSITION:
This study was conducted in healthy elderly male and female subjects and healthy young female subjects. Thirty-six (36) subjects, 12 subjects per group, were enrolled in the study.

DOSAGE/FORMULATION NOS.:

Drug	Potency	Formulation No.	Dosage Form	Control No.
MK-1439	100 mg	[redacted]	Tablet	[redacted]

DIAGNOSIS/INCLUSION CRITERIA:

Elderly male and female subjects (50% of either gender) of any race between the ages of 65 and 80 years, inclusive, or young female subjects of any race between the ages of 18 and 50 years having a body mass index (BMI) between 18 and 30, inclusive. BMI = weight (kg)/height $(m)^2$. Female subjects had to be postmenopausal, or surgically sterilized at 3 months prior to baseline. Female subjects of childbearing potential and non-vasectomized men were required to use specified birth control measures.

EVALUATION CRITERIA:

Pharmacokinetics: Blood samples for determination of plasma MK-1439 were obtained on Days 1 through 4, at designated time points to determine MK-1439 plasma concentrations. These plasma concentrations were used to calculate pharmacokinetic parameters including $AUC_{0-\infty}$, $AUC_{0\text{-last}}$, AUC_{0-24}, C_{max}, $t_{1/2}$ and T_{max} as well as C_{24hr}.

Safety: The safety and tolerability of MK-1439 was assessed by clinical evaluation including vital signs, 12-lead ECG, and laboratory safety evaluations (hematology, blood chemistry, and urinalysis) which were obtained at pre-specified time points throughout the study. Subjects have been monitored closely throughout the study for adverse experiences.

STATISTICAL PLANNING AND ANALYSIS:

Pharmacokinetics: The gender and age effects on MK-1439 pharmacokinetic parameters were addressed using the plasma $AUC_{0-\infty}$, C_{max} and C_{24hr} of MK-1439 in elderly male, elderly female and young female subjects obtained in the present study and that in young male subjects obtained from historical data in MK-1439 Protocol 001.

Past experience suggests that $AUC_{0-\infty}$ and C_{24hr} are lognormally distributed. Therefore, these variables were log transformed before analysis. The statistical model used was a one-way ANOVA model with population (elderly male, elderly female, young male and young female) as a fixed effect. The CIs for the means (mean differences) was constructed on the natural log scale and referenced the t-distribution. Exponentiating the means (mean differences) and lower and upper limits of these CIs yielded estimates for the population geometric means (population GMR) and CIs about the geometric means (GMRs) on the original scale.

Poolability of the pharmacokinetic data across two groups was assessed using the following criteria:

1) if the 90% CI of the GMR between the two groups constructed from the above model was contained within the bounds of (0.5, 2.0), and
2) the p-value of the comparisons between the 2 groups was >0.05.

If both criteria were satisfied, then the pharmacokinetic data from the two groups were pooled.

Data was examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods could be used if a serious departure from the assumptions of the models(s) was observed, or suitable data transformations could be applied.

Descriptive statistics was provided by population. Minimum, median and maximum was provided for all pharmacokinetic parameters. Arithmetic mean and standard deviation based on the raw scale were provided for $AUC_{0-\infty}$, C_{max} and C_{24hr}. In addition, the percent CV of $AUC_{0-\infty}$, C_{max} and C_{24hr} was provided and calculated according to the following formula: 100 x sqrt($\exp(s^2)$ - 1), where s^2 is the observed variance on the natural log-scale. Geometric mean and percent CV (as defined above) were provided for $t_{1/2}$ as well.

Gender/Age

If the pharmacokinetic data in the gender or age groups could be pooled together according to the above pooling criteria, the effects were evaluated between the pooled groups. The GMRs for MK-1439 $AUC_{0-\infty}$ and corresponding 90% CI were generated from the above ANOVA model. If the 90% CI for $AUC_{0-\infty}$ GMRs were contained within the pre-specified bounds of (0.5, 2.0), then the hypothesis that the plasma $AUC_{0-\infty}$ following administration of a single oral dose of 100-mg MK-1439 in one pooled group is similar to that obtained in the other pooled group was supported.

If the poolability could not be supported based on the above criteria, the GMRs and 90% CIs were reported within each age or gender group separately.

The plasma C_{24hr} and C_{max} of MK-1439 were analyzed in a similar fashion as outlined above for $AUC_{0-\infty}$. Ninety-five percent CIs will be provided for the geometric mean of $AUC_{0-\infty}$, C_{24hr} and C_{max} by population.

Safety: Summary statistics were generated for the number of adverse experiences, vital signs, ECG and results of laboratory safety tests.

RESULTS:

Pharmacokinetics:

Pharmacokinetic parameters of MK-1439 were investigated in healthy elderly male and female and young adult male and female subjects. As male subjects and female subjects could be pooled, the comparison for gender was performed on the pooled populations. The relative bioavailability and 90% CIs for $AUC_{0-\infty}$, C_{max} and C_{24hrs} GMR (female/male) for MK-1439 were 119.95%, [102.86, 139.88], 141.84%, [122.76, 163.87] and 101.72%, [83.63, 123.72], respectively. Since the 90% CIs for the GMRs of plasma $AUC_{0-\infty}$, and C_{24hrs} were all fully contained within the pre-specified bounds (0.5, 2.0), results indicate that the relative bioavailability of MK-1439 is similar in male and female subjects. Of note, in this study the observed $AUC_{0-\infty}$ and C_{max} responses for elderly female subjects were approximately 25% and 58% higher than the elderly male subject, respectively.

Since the poolability of pharmacokinetic data between the elderly female and elderly male groups could not be supported based on the pooling criteria ($p<0.050$) for MK-1439 pharmacokinetic parameters including $AUC_{0-\infty}$, C_{24hr} and C_{max}, the age effect on pharmacokinetic parameter was evaluated within each gender group separately (elderly male versus young male, and elderly female versus young female). The relative bioavailability and 90% CIs for $AUC_{0-\infty}$, C_{max} and C_{24hrs} GMR (elderly male/young male) for MK-1439 were 85.35%, [66.51, 109.53], 91.83%, [72.95, 115.59] and 81.20%, [59.15, 111.47], respectively. The relative bioavailability and 90% CIs for $AUC_{0-\infty}$, C_{max} and C_{24hrs} GMR (elderly female/young female) for MK-1439 were 96.98%, [79.35, 118.52], 118.05%, [97.82, 142.45] and 93.79%, [72.41, 121.47], respectively. Thus, the relative bioavailability is similar in elderly male compared to young adult male subjects and elderly female compared to young female subjects.

Safety:

After a single dose of MK-1439, 8 subjects (22.2%) reported at least one adverse experience. Of these, 7 subjects (19.4%) reported at least one adverse experience related to the study drug. There were no deaths and no serious adverse experiences. None of the subjects prematurely discontinued from the study due to adverse experiences. Almost all adverse experiences were of mild intensity; one was of moderate intensity. The adverse experiences were all resolved during the study. There were no clinically significant findings for laboratory safety values, vital signs or ECG data.

CONCLUSIONS:

1. The relative bioavailability of the MK-1439 100 mg tablet is similar between male and female, elderly and young male or elderly and young female subjects.

2. Based on the assessment of clinical and laboratory adverse experiences, single 100-mg doses of MK-1439 are generally well tolerated, independent of age or gender.